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THE UNITED STATES PHARMACOPEIAL CONVENTION
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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 2014 *USP 37–NF 32*, and its supplements, *Interim Revision Announcements (IRAs)* and *Revision Bulletins* to that edition, will be official until May 1, 2015, at which time the *USP 38–NF 33* becomes official.

Publication	Release Date	Official Date	Official Until
<i>USP 38–NF 33</i>	November 1, 2014	May 1, 2015	May 1, 2016 (except as superseded by supplements, IRAs, and Revision Bulletins)
<i>First Supplement to the USP 38–NF 33</i>	February 1, 2015	August 1, 2015	May 1, 2016 (except as superseded by Second Supplement, IRAs, and Revision Bulletins)
<i>Second Supplement to the USP 38–NF 33</i>	June 1, 2015	December 1, 2015	May 1, 2016 (except as superseded by IRAs and Revision Bulletins)
<i>USP 39–NF 34</i>	November 1, 2015	May 1, 2016	May 1, 2017 (except as superseded by supplements, IRAs, and Revision Bulletins)

The table below gives the details of the IRAs that will apply to *USP 38–NF 33*.

IRA	PF Posting Date	Comment Due Date	IRA Posting Date	IRA Official Date
41(1)	January 2, 2015	March 31, 2015	May 30, 2015	July 1, 2015
41(2)	March 3, 2015	May 31, 2015	July 31, 2015	September 1, 2015
41(3)	May 1, 2015	July 31, 2015	September 26, 2015	November 1, 2015
41(4)	July 1, 2015	September 30, 2015	November 26, 2015	January 1, 2016
41(5)	September 2, 2015	November 30, 2015	January 30, 2016	March 1, 2016
41(6)	November 3, 2015	January 31, 2016	March 27, 2016	May 1, 2016

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

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10 mL of water. Shake until the Tablet is disintegrated, and allow to stand for 16 h. Dilute with water to volume, and filter, discarding the first few mL of the filtrate. Dilute the resulting filtrate with 0.2 N sulfuric acid to obtain a solution containing nominally 120 µg/mL of codeine sulfate (trihydrate).

Spectrometric conditions

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

Mode: UV-Vis

Analytical wavelength: About 284 nm

Cell: 1 cm

Blank: 0.2 N sulfuric acid

Analysis

Samples: Standard solution, Sample solution, and Blank

Calculate the percentage of $(C_{18}H_{21}NO_3)_2 \cdot H_2SO_4 \cdot 3H_2O$ in the Tablet taken:

$$\text{Result} = (A_U/A_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

A_U = absorbance of the Sample solution

A_S = absorbance of the Standard solution

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

C_U = nominal concentration of codeine sulfate trihydrate in the Sample solution (µg/mL)

M_{r1} = molecular weight of codeine sulfate trihydrate, 750.87

M_{r2} = molecular weight of anhydrous codeine sulfate, 696.82

Acceptance criteria: Meet the requirements

IMPURITIES

Organic Impurities

• PROCEDURE

Diluent, Solution A, Solution B, Mobile phase, Standard solution, Sensitivity solution, Sample solution, Chromatographic system, and System suitability: Proceed as directed in the Assay.

Analysis

Samples: Standard solution and Sample solution

Calculate the percentage of each individual impurity in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

r_U = peak response of each individual impurity from the Sample solution

r_S = peak response of codeine sulfate from the Standard solution

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

C_U = concentration of codeine sulfate in the Sample solution (mg/mL)

F = relative response factor of the related compounds (see Impurity Table 1)

Acceptance criteria

Individual impurities: See Impurity Table 1.

Total impurities: NMT 0.5%

Impurity Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Codeine-N-oxide ^a	0.39	1.25	0.2
Codeine sulfate	1.00	—	—

^a 7,8-Didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol N-oxide.

^b 7,8-Didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-one.

Impurity Table 1 (Continued)

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Codeinone ^b	1.10	1.0	0.3
Individual unspecified degradant	—	—	0.2

^a 7,8-Didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol N-oxide.

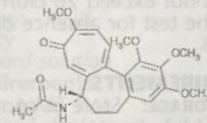
^b 7,8-Didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan-6α-one.

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in well-closed containers.

• **USP REFERENCE STANDARDS (11)**
USP Codeine Sulfate RS

Colchicine



$C_{22}H_{25}NO_6$ 399.44

Acetamide, N-(5,6,7,9-tetrahydro-1,2,3,10-tetramethoxy-9-oxobenzo[a]heptalen-7-yl)-, (S)-.

Colchicine [64-86-8].

» Colchicine is an alkaloid contained in various species of *Colchicum* and in other genera. It contains not less than 94.0 percent and not more than 101.0 percent of $C_{22}H_{25}NO_6$, calculated on the anhydrous, solvent-free basis.

Caution—Colchicine is extremely poisonous.

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

USP Reference standards (11)—

USP Colchicine RS

Identification, Infrared Absorption (177K)—[NOTE—Disregard any peak occurring at 1735 cm^{-1} .]

Specific rotation (781S): between -240° and -250° , calculated on the anhydrous, solvent-free basis.

Test solution: 10 mg per mL, in alcohol.

Water, Method I (921): not more than 2.0%.

Limit of colchicine—To 5 mL of a solution (1 in 100) add 2 drops of ferric chloride TS: no definite green color is produced.

Limit of ethyl acetate—

Internal standard solution—Dilute 0.5 mL of *n*-propyl alcohol with water to 100.0 mL.

Standard solution—Pipet 1 mL of ethyl acetate and 0.5 mL of *n*-propyl alcohol into a 1000-mL volumetric flask, add water to volume, and mix. Each mL of Standard solution contains 0.90 mg of ethyl acetate.

Test solution—Place about 250 mg of Colchicine, accurately weighed, in a 10-mL volumetric flask, dissolve in about 8 mL of water, and add 1.0 mL of Internal standard solution. Add water to volume, and mix.

Procedure—Determine appropriate sensitivity settings on a gas chromatograph (see *Chromatography* (621)) fitted with a 4-mm $\times$ 1.5-m column packed with 20% (w/v) phase G14

on support S1, maintaining the column temperature at 75°, using nitrogen as the carrier gas, and using a flame-ionization detector. Inject the *Standard solution* and the *Test solution*, determine the peak height for ethyl acetate relative to the peak height for *n*-propyl alcohol, and calculate the percentage, by weight, of ethyl acetate in the portion of Colchicine taken: not more than 8.0% is found.

Chromatographic purity—The sum of the responses of any peaks other than that due to colchicine, eluting within 1.5 times the retention time for colchicine, is not more than 5.0% of the sum of all responses, obtained as directed in the Assay.

Residual solvents (467): meets the requirements, except that the limit of chloroform is 100 ppm.

Assay—[NOTE—Perform all dilutions in low-actinic glassware.]

Mobile phase—Dilute 45 mL of 0.5 M monobasic potassium phosphate with water to 450 mL. Add about 530 mL of methanol, cool to room temperature, and add methanol to bring the volume to 1000 mL. Adjust with 0.5 M phosphoric acid to a pH of 5.5 ± 0.05 , and pass through a 0.45- μ m membrane filter.

Standard preparation—Dissolve an accurately weighed quantity of USP Colchicine RS in a mixture of methanol and water (1:1), and dilute quantitatively and stepwise with the same mixture to obtain a solution having a known concentration of about 6 μ g per mL. This solution is stable for 4 months when stored tightly stoppered and in the dark.

Assay preparation—[NOTE—Prepare immediately before use.] Transfer about 60 mg of Colchicine, accurately weighed, to a 500-mL volumetric flask, dissolve in a mixture of methanol and water (1:1), dilute with the same mixture to volume, and mix. Pipet 5 mL of this solution into a 100-mL volumetric flask, dilute with the same mixture to volume, and mix.

Chromatographic system (see Chromatography (621))—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm $\times$ 25-cm column that contains packing L7. The flow rate is about 1 mL per minute. Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure*: the column efficiency is not less than 4500 theoretical plates, the retention time for colchicine is between 5.5 and 9.5 minutes, and the relative standard deviation for replicate injections is not more than 2%.

Procedure—Separately inject equal volumes (about 20 μ L) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for all peaks recorded during 1.5 times the retention time for colchicine. Calculate the quantity, in mg, of $C_{22}H_{25}NO_6$ in the Colchicine taken by the formula:

$$10C(r_u / r_s)$$

in which *C* is the concentration, in μ g per mL, of the *Standard preparation*; and r_u and r_s are the colchicine peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively.

Colchicine Injection

» Colchicine Injection is a sterile solution of $C_{22}H_{25}NO_6$ in Water for Injection, prepared from Colchicine with the aid of Sodium Hydroxide. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{22}H_{25}NO_6$.

Caution—Colchicine is extremely poisonous.

Packaging and storage—Preserve in single-dose containers, preferably of Type I glass, protected from light.

USP Reference standards (11)—

USP Colchicine RS

USP Endotoxin RS

Identification—

A: Transfer a volume of Injection, equivalent to about 2 mg of colchicine, to a separator. Add 5 mL of water, and extract with 15 mL of chloroform. Evaporate the chloroform extract, using mild heat, to dryness: the IR absorption spectrum of a potassium bromide dispersion of the residue so obtained exhibits maxima only at the same wavelengths as that of a similar preparation of USP Colchicine RS.

B: The UV absorption spectrum of the Injection, diluted with water to a concentration of about 10 μ g of colchicine per mL, exhibits maxima and minima at the same wavelengths as that of a similar solution of USP Colchicine RS, concomitantly measured.

Bacterial endotoxins (85)—It contains not more than 166.7 USP Endotoxin Units per mg of colchicine.

pH (791): between 6.0 and 7.2, in a solution of Injection containing 1.0 mg of potassium chloride in each mL.

Other requirements—It meets the requirements under *Injections* (1).

Assay—[NOTE—Perform all dilutions in low-actinic glassware.]

Mobile phase, Standard preparation, and Chromatographic system—Prepare as directed in the Assay under Colchicine.

Assay preparation—[NOTE—Prepare immediately before use.] Transfer an accurately measured volume, *V* mL, of Injection, equivalent to about 1 mg of colchicine, to a 50-mL volumetric flask, dilute with a mixture of methanol and water (1:1) to volume, and mix. Pipet 30 mL of this solution into a 100-mL volumetric flask, dilute with the same mixture to volume, and mix.

Procedure—Proceed as directed for *Procedure* in the Assay under Colchicine, and measure the responses for the colchicine peaks. Calculate the quantity, in mg, of $C_{22}H_{25}NO_6$ in each mL of the Injection taken by the formula:

$$(C / 6V)(r_u / r_s)$$

in which *C* is the concentration, in μ g per mL, of the *Standard preparation*; and r_u and r_s are the peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively.

Colchicine Tablets

» Colchicine Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{22}H_{25}NO_6$.

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

USP Reference standards (11)—

USP Colchicine RS

Identification—Weigh a portion of ground Tablets, equivalent to about 20 mg of colchicine, triturate with 20 mL of water, allow the solids to settle, and filter the supernatant into a separator. Extract with 30 mL of chloroform. Evaporate the chloroform extract, using mild heat, to dryness: the IR absorption spectrum of a potassium bromide dispersion of the residue so obtained exhibits maxima only at the same wavelengths as that of a similar preparation of USP Colchicine RS.

Dissolution. *Procedure for a Pooled Sample* (711)—[NOTE—Conduct this procedure without delay, under subdued light, and using low-actinic glassware.]

Medium: water; 500 mL.

Apparatus 1: 100 rpm.

Time: 30 minutes.

Procedure—Determine the amount of $C_{22}H_{25}NO_6$ dissolved, employing the procedure set forth in the Assay under Colchicine, making any necessary modifications.

Tolerances—Not less than 75% (Q) of the labeled amount of $C_{22}H_{25}NO_6$ is dissolved in 30 minutes.

Uniformity of dosage units (905): meet the requirements.

Assay—[NOTE—Perform all dilutions in low-actinic glassware.]

Mobile phase, Standard preparation, and Chromatographic system—Prepare as directed in the Assay under Colchicine.

Assay preparation—[NOTE—Prepare immediately before use.] Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 0.6 mg of colchicine, to a 100-mL volumetric flask, add about 50 mL of a mixture of methanol and water (1:1), and shake by mechanical means for 15 minutes, rinsing down the walls of the flask at about 8 minutes. Dilute with the same mixture to volume, and pass through a 0.45- μ m membrane filter.

Procedure—Proceed as directed for Procedure in the Assay under Colchicine, and measure the responses for the colchicine peaks. Calculate the quantity, in mg, of $C_{22}H_{25}NO_6$ in the portion of Tablets taken by the formula:

$$0.1 C(r_u / r_s)$$

in which C is the concentration, in μ g per mL, of the Standard preparation; and r_u and r_s are the peak responses obtained from the Assay preparation and the Standard preparation, respectively.

Colestipol Hydrochloride

» Colestipol Hydrochloride is an insoluble, high molecular weight basic anion-exchange copolymer of diethylenetriamine and 1-chloro-2,3-epoxypropane with approximately one out of five amino nitrogens protonated. Each g binds not less than 1.1 mEq and not more than 1.6 mEq of sodium cholate, calculated as cholate binding capacity.

Packaging and storage—Preserve in tight containers.

USP Reference standards (11)—

USP Colestipol Hydrochloride RS

Identification—**Infrared Absorption** (197K)—Prepare the test specimen and the Standard specimen by mixing about 3 to 4 mg of Colestipol Hydrochloride and of USP Colestipol Hydrochloride RS, respectively, with about 150 mg of potassium bromide.

pH (791)—Prepare a 10% (w/w) suspension of it in deionized water in a clean vial. Insert the stopper, shake at approximately 10-minute intervals for 1 hour, and centrifuge. Transfer a portion of the clear supernatant to a suitable container, and record the pH as soon as the reading has stabilized: the pH is between 6.0 and 7.5.

Loss on drying (731)—Dry it in vacuum at a pressure of about 5 mm of mercury at 75° for 16 hours: it loses not more than 1.0% of its weight.

Residue on ignition (281): not more than 0.3%.

Delete the following:

• **Heavy metals, Method II** (231): not more than 0.002%.

• (Official 1-Dec-2015)

Content of chloride—

Test preparation—Using about 20 mg of Colestipol Hydrochloride, accurately weighed, proceed as directed under Oxygen Flask Combustion (471), 10 mL of 0.05 N sodium hydroxide being used as the absorbing liquid. Do not allow the paper specimen wrapper to come in contact with the liquid, and ignite the paper with an IR igniter. After combustion is complete, shake the flask vigorously, and allow to stand, with frequent shaking, for about 40 minutes or until no cloudiness is present. Transfer the solution to a 50-mL beaker. Wash the flask with two 5-mL portions of water and two 10-mL portions of alcohol, adding each washing to the beaker, and add 0.2 mL of nitric acid.

Reagent blank preparation—Using a paper specimen wrapper, complete the combustion, and allow the mixture to stand for about 40 minutes or until no cloudiness is present, as directed under Test preparation. Transfer the solution so obtained to a 50-mL beaker. Wash the combustion flask with two 5-mL portions of water and two 10-mL portions of alcohol, adding the washings to the beaker, and add 0.2 mL of nitric acid.

Procedure—Titrate the Test preparation and the Reagent blank preparation with 0.05 N silver nitrate VS, determining the endpoint potentiometrically, using a silver-silver chloride electrode and a glass reference electrode (see Titrimetry (541)). Determine the volume of 0.05 N silver nitrate VS consumed by the test specimen taken by the formula:

$$V - V_B$$

in which V and V_B are the volumes, in mL, of titrant used for the Test preparation and the Reagent blank preparation, respectively. Each mL of 0.05 N silver nitrate is equivalent to 1.773 mg of Cl: the chloride content is between 6.5% and 9.0%, calculated on the dried basis.

Water absorption—Transfer about 5 g of Colestipol Hydrochloride, accurately weighed, to a dry, 100-mL plastic container, and add about 80 g of water, accurately weighed. Cover the container, and allow the suspension to equilibrate for 72 hours. With the aid of vacuum, filter the slurry transferred to a medium-porosity, fritted-glass funnel, and collect the filtrate in a tared plastic container. Disconnect the vacuum 2 minutes after the collection of the last portion of the filtrate. Weigh the container and the filtrate, and determine the weight, in g, of the filtrate. Determine the amount of water absorbed by subtracting the weight of the filtrate from the weight of water taken for the test, and divide the weight, in g, of the absorbed water by the weight, in g, of Colestipol Hydrochloride taken: each g absorbs between 3.3 g and 5.3 g of water.

Cholate binding capacity—

Cholate solution—Dissolve accurately weighed quantities of sodium cholate and sodium chloride in water, and quantitatively dilute with water to obtain a solution having known concentrations of 10.0 mg of sodium cholate per mL and 9.0 mg of sodium chloride per mL. Adjust the solution by the dropwise addition of hydrochloric acid to a pH of 6.4 $\pm$ 0.1.

Test preparation—Transfer 1.0 $\pm$ 0.01 g of Colestipol Hydrochloride to a glass-stoppered, 125-mL conical flask. Add 100.0 mL of Cholate solution, insert the stopper securely in the flask, shake vigorously for 90 minutes with the flask positioned horizontally on a platform shaker, remove the flask from the shaker, and allow the solids to settle for 5 minutes.

Procedure—Transfer 20.0 mL of supernatant from the Test preparation to a 40-mL beaker, transfer 20.0 mL of Cholate