200-mL volumetric flask. Add dilute hydrochloric acid (1 in 120) to volume, and mix.

Procedure—Concomitantly determine the absorbances of the *Assay preparation* and the *Standard preparation,* in 1-cm cells at the wavelength of maximum absorbance at about 264 nm, with a suitable spectrophotometer, using dilute hydrochloric acid (1 in 120) as the blank. Calculate the quantity, in mg, of $C_{16}H_{19}BrN_2 \cdot C_4H_4O_4$ in the portion of Tablets taken by the formula:

$$0.2C(A_U / A_S)$$

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

Brompheniramine Maleate and Pseudoephedrine Sulfate Oral Solution

» Brompheniramine Maleate and Pseudoephedrine Sulfate Oral Solution contains not less than 90.0 percent and not more than 110.0 per cent of the labeled amounts of brompheniramine maleate ($C_{16}H_{19}BrN_2 \cdot C_4H_4O_4$) and pseudoephedrine sulfate [$(C_{10}H_{15}NO)_2 \cdot H_2SO_4$].

USP Reference standards ⟨11⟩—
USP Brompheniramine Maleate RS
USP Pseudoephedrine Sulfate RS

Identification—

A: The retention times of the major peaks in the chromatogram of the *Assay preparation* correspond to those in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

B: A solution of it meets the requirements of the test for *Sulfate* ⟨191⟩.

C: Transfer a volume of Oral Solution, equivalent to about 6 mg of brompheniramine maleate, to a separator, add 0.5 mL of ammonium hydroxide and 5 mL of methylene chloride, shake for 1 minute, and allow the layers to separate. Use the clear, lower layer as the test solution. Prepare separate Standard solutions in methanol containing, respectively, 1.2 mg of USP Brompheniramine Maleate RS and 9 mg of USP Pseudoephedrine Sulfate RS per mL. Separately apply 5 µL of each solution to a suitable thin-layer chromatographic plate (see *Chromatography* ⟨621⟩) coated with a 0.25-mm layer of chromatographic silica gel mixture. Allow the spots to dry, and develop the chromatogram in a solvent system consisting of a mixture of ethyl ether, methanol, and ammonium hydroxide (16:3:1) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Locate the spots on the plate by examination under short-wavelength UV light: the R_F values of the two principal spots obtained from the test solution correspond to those obtained from the Standard solutions.

Uniformity of dosage units ⟨905⟩—

FOR ORAL SOLUTION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.

Deliverable volume ⟨698⟩—

FOR ORAL SOLUTION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.

Assay—

Mobile phase—Prepare a mixture of water, acetonitrile, methanol, and tetrahydrofuran (550:320:80:50). Transfer 1.0 mL of phosphoric acid, followed by 4.33 g of dodecyl sulfate sodium to this mixture, and mix. Adjust with ammonium hydroxide to a pH of 3.50 ± 0.05, filter, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩). [NOTE—The pH of the *Mobile phase* is critical and may cause 1 to 4 minutes of differences in the retention times of internal standard and brompheniramine maleate.]

Internal standard solution—Transfer about 50 mg of naphazoline hydrochloride to a 100-mL volumetric flask, add *Mobile phase* to volume, and mix.

Standard preparation—Dissolve an accurately weighed quantity of USP Brompheniramine Maleate RS in *Mobile phase,* and quantitatively dilute with *Mobile phase* to obtain a solution having a known concentration of about 6000 *J* µg per mL, *J* being the ratio of the labeled amount, in mg, of brompheniramine maleate to the labeled amount, in mg, of pseudoephedrine sulfate per mL *(Solution P).* Transfer about 30 mg of USP Pseudoephedrine Sulfate RS, accurately weighed, to a 25-mL volumetric flask, add 5.0 mL each of *Solution P* and *Internal standard solution,* dilute with *Mobile phase* to volume, and mix to obtain a *Standard preparation* having known concentrations of about 1200*J* µg of USP Brompheniramine Maleate RS per mL and about 1.2 mg of USP Pseudoephedrine Sulfate RS per mL.

Assay preparation—Using a "To contain" pipet transfer an accurately measured volume of Oral Solution, equivalent to about 30 mg of pseudoephedrine sulfate, to a 25-mL volumetric flask. Rinse the pipet with about 5 mL of *Mobile phase,* collecting the rinse in the volumetric flask. Add 5.0 mL of *Internal standard solution,* dilute with *Mobile phase* to volume, and mix.

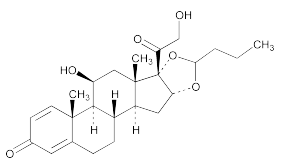
Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4-mm × 30-cm column that contains packing L11. The flow rate is about 1.5 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative retention times are about 1.0 for pseudoephedrine sulfate, 1.5 for naphazoline hydrochloride, and 2.5 for brompheniramine maleate; the resolution, R, between the pseudoephedrine sulfate and naphazoline hydrochloride peaks is not less than 3, and between the brompheniramine maleate and naphazoline hydrochloride peaks is not less than 3; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of brompheniramine maleate ($C_{16}H_{19}BrN_2 \cdot C_4H_4O_4$) in each mL of the Oral Solution taken by the formula:

$$25CV(R_U / R_S)$$

in which C is the concentration, in mg per mL, of USP Brompheniramine Maleate RS in the *Standard preparation; V* is the volume, in mL, of Oral Solution taken; and R_U and R_S are the peak response ratios obtained for brompheniramine maleate and naphazoline hydrochloride from the *Assay preparation* and the *Standard preparation,* respectively. Calculate the quantity, in mg, of pseudoephedrine sulfate $(C_{10}H_{15}NO)_2 \cdot H_2SO_4$ in each mL of the Oral Solution taken by the same formula, changing the terms to refer to pseudoephedrine sulfate.

Budesonide



$C_{25}H_{34}O_6$ 430.53

Pregna-1,4-diene-3,20-dione, 16α,17-[1*R*-butylidenebis(oxy)]-11β,21-dihydroxy and pregna-1,4-diene-3,20-dione,16α,17-[1*S*-butylidenebis(oxy)]-11β,21-dihydroxy;
(*RS*)-11β,16α,17,21-Tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with butyraldehyde [51372-29-3; 51372-28-2; 51333-22-3].

DEFINITION

Change to read:

Budesonide is a mixture of two epimeric forms, epimer A(C-22S) and epimer B(C-22R). It contains NL T •40.0%• (RB 1-Jun-2011) and NMT 51.0% of epimer A, and the sum of both epimers is NLT 98.0% and NMT 102.0% of $C_{25}H_{34}O_6$, calculated on the dried basis.

[NOTE—Protect all solutions containing budesonide from light.]

IDENTIFICATION

- **A. INFRARED ABSORPTION** ⟨197K⟩
- **B. ULTRAVIOLET ABSORPTION** ⟨197U⟩

Sample solution: 25 µg/mL
Medium: Methanol
Acceptance criteria: Meets the requirements

ASSAY

Change to read:

- **PROCEDURE**

Buffer: 3.17 mg/mL of monobasic sodium phosphate and 0.23 mg/mL of phosphoric acid. The pH is 3.2 ± 0.1.
Mobile phase: Acetonitrile and *Buffer* (32:68)
Standard solution: Dissolve a quantity of USP Budesonide RS in acetonitrile, and dilute quantitatively with *Buffer* to obtain a solution having a concentration of 0.5 mg/mL, keeping the proportion of acetonitrile in this solution to NMT 30%.
Sample solution: Dissolve 25 mg of Budesonide in 15 mL of acetonitrile in a 50-mL volumetric flask, and dilute with *Buffer* to volume.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 254 nm
Column: 4.6-mm × 15-cm; 5-µm packing L1
Flow rate: 1.5 mL/min
Injection size: 20 µL
System suitability
Sample: *Standard solution*
[NOTE—The relative retention time for epimer A is 1.1, with respect to epimer B.]
Suitability requirements
Resolution: NLT 1.5 between the two budesonide epimer peaks
Column efficiency: NLT 5500 theoretical plates, determined from the budesonide epimer B peak
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of epimer A ($C_{25}H_{34}O_6$) in the portion of Budesonide taken:

$$\text{Result} = [r_{UA}/(r_{UA} + r_{UB})] \times 100$$

r_{UA} = peak area of epimer A from the *Sample solution*
r_{UB} = peak area of epimer B from the *Sample solution*

Calculate the percentage of $C_{25}H_{34}O_6$ in the portion of Budesonide taken:

$$\text{Result} = [(r_{UA} + r_{UB})/(r_{SA} + r_{SB})] \times (C_S/C_U) \times 100$$

r_{UA} = peak area of epimer A from the *Sample solution*
r_{UB} = peak area of epimer B from the *Sample solution*
r_{SA} = peak area of epimer A from the *Standard solution*
r_{SB} = peak area of epimer B from the *Standard solution*
C_S = concentration of USP Budesonide RS in the *Standard solution* (mg/mL)
C_U = concentration of Budesonide in the *Sample solution* (mg/mL)

Acceptance criteria
Epimer A: •40.0%• (RB 1-Jun-2011)–51.0% on the dried basis
Both epimers: 98.0%–102.0% on the dried basis

IMPURITIES

- **PROCEDURE 1: LIMIT OF 21-ACETATE OF BUDESONIDE**

Buffer: 3.17 mg/mL of monobasic sodium phosphate and 0.23 mg/mL of phosphoric acid. The pH is 3.2 ± 0.1.
Mobile phase: Acetonitrile and *Buffer* (45:55)
Standard solution: Dissolve a quantity of USP Budesonide RS in acetonitrile, and dilute quantitatively with *Buffer* to obtain a solution having a concentration of 0.5 mg/mL, keeping the proportion of acetonitrile in this solution to NMT 30%.
Sample solution: Dissolve 25 mg of Budesonide in 15 mL of acetonitrile in a 50-mL volumetric flask, and dilute with *Buffer* to volume.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 254 nm
Column: 4.6-mm × 15-cm; 5-µm packing L1
Flow rate: 1.5 mL/min
Injection size: 20 µL
System suitability
Sample: *Standard solution*
[NOTE—The relative retention times for the first eluted epimer of the 21-acetate of budesonide, the second eluted epimer of the 21-acetate of budesonide, the first eluted epimer of budesonide (epimer B), and the second eluted epimer of budesonide (epimer A) are 3.1, 3.2, 1.0, and 1.1, respectively.]
Suitability requirements
Column efficiency: NLT 5500 theoretical plates, determined from the budesonide epimer B peak
Analysis
Sample: *Sample solution*
Calculate the percentage of the 21-acetate of budesonide in the portion of Budesonide taken:

$$\text{Result} = (r_{T1}/r_{T2}) \times 100$$

r_{T1} = sum of the peak areas for the two epimers of the 21-acetate of budesonide
r_{T2} = sum of the peak areas of the two budesonide peaks

Acceptance criteria: NMT 0.10% of the 21-acetate of budesonide is found.

- **PROCEDURE 2: LIMIT OF 11-KETOBUDESONIDE**

Buffer: 3.17 mg/mL of monobasic sodium phosphate and 0.23 mg/mL of phosphoric acid. The pH is 3.2 ± 0.1.
Mobile phase: Acetonitrile, isopropanol, and *Buffer* (26:9:65)
Standard solution: Dissolve a quantity of USP Budesonide RS in acetonitrile, and dilute quantitatively with *Buffer* to obtain a solution having a concentration of 0.5 mg/mL, keeping the proportion of acetonitrile in this solution to NMT 30%.
Sample solution: Dissolve 25 mg of Budesonide in 15 mL of acetonitrile in a 50-mL volumetric flask, and dilute with *Buffer* to volume.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)

Mode: LC
Detector: UV 254 nm
Column: 4.6-mm × 15-cm; 3.5-µm packing L1
Column temperature: 50°
[NOTE—Preheat the *Mobile phase* to 50°.]
Flow rate: 1.5 mL/min
Injection size: 20 µL
System suitability
Sample: *Standard solution*
[NOTE—The relative retention times for the two epimers of 11-ketobudesonide are 0.73 and 0.78, respectively; the relative retention times for 21-dehydrobudesonide, 14,15-dehydrobudesonide, and the first eluted epimer of budesonide (epimer B) are 0.68, 0.84, and 1.0, respectively.]
Suitability requirements
Column efficiency: NLT 5500 theoretical plates, determined from the budesonide epimer B peak
Analysis
Sample: *Sample solution*
Calculate the percentage of 11-ketobudesonide in the portion of Budesonide taken:

$$\text{Result} = (r_{T1}/r_{T2}) \times 100$$

r_{T1} = sum of the peak areas for the two ketobudesonide peaks
r_{T2} = sum of the peak areas of the two budesonide peaks

Acceptance criteria: NMT 0.2% of 11-ketobudesonide is found.

- **PROCEDURE 3**

Buffer: 3.17 mg/mL of monobasic sodium phosphate and 0.23 mg/mL of phosphoric acid. The pH is 3.2 ± 0.1.
Mobile phase: Acetonitrile and *Buffer* (32:68)
Standard solution: Dissolve a quantity of USP Budesonide RS in acetonitrile, and dilute quantitatively with *Buffer* to obtain a solution having a concentration of 0.5 mg/mL, keeping the proportion of acetonitrile in this solution to NMT 30%.
Sample solution: Dissolve 25 mg of Budesonide in 15 mL of acetonitrile in a 50-mL volumetric flask, and dilute with *Buffer* to volume.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 254 nm
Column: 4.6-mm × 15-cm; 5-µm packing L1
Flow rate: 1.5 mL/min
Injection size: 20 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Column efficiency: NLT 5500 theoretical plates, determined from the budesonide epimer B peak
Analysis
Sample: *Sample solution*
Calculate the percentage of each impurity in the portion of Budesonide taken:

$$\text{Result} = (r_U/r_T) \times 100$$

r_U = peak area for each impurity
r_T = sum of the areas of all of the peaks

Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
16α-Hydroxyprednisolone[a]	0.11	0.2
D-Homobudesonide[b]	0.36	0.10
21-Dehydrobudesonide (epimers)[c]	0.61; 0.66	0.07[d]
14,15-Dehydrobudesonide[e]	0.86	0.10
Total specified impurities	—	0.4[f]
Any other individual impurity	—	0.10
Total unspecified impurities	—	0.4

[a] 11β,16α,17,21-Tetrahydroxypregna-1,4-diene-3,20-dione.
[b] 16α,17-[(1*RS*)-Butylidenebis(oxy)]-11β-hydroxy-17-(hydroxymethyl)-D-homoandrosta-1,4-diene-3,17a-dione.
[c] 16α,17-[(1*RS*)-Butylidenebis(oxy)]-11β-hydroxy-3,20-dioxopregna-1,4-dien-21-al.
[d] Limit includes both epimers.
[e] 16α,17-[(1*RS*)-Butylidenebis(oxy)]-11β,21-dihydroxypregna-1,4,14-triene-3,20-dione.
[f] Total specified impurities includes 11-ketobudesonide obtained in the test for *Limit of 11-Ketobudenoside* and the impurities listed above.

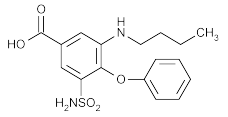
SPECIFIC TESTS

- **MICROBIAL ENUMERATION TESTS** ⟨**61**⟩ and **TESTS FOR SPECIFIED MICROORGANISMS** ⟨**62**⟩**:** The total aerobic microbial count is NMT 10^3 cfu/g, and the total combined molds and yeast count is NMT 10^2 cfu/g.
- **LOSS ON DRYING** ⟨**731**⟩**:** Dry a sample at 105 ° to constant weight: it loses NMT 0.3% of its weight.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers. Store at controlled room temperature.
- **USP REFERENCE STANDARDS** ⟨**11**⟩
USP Budesonide RS

Bumetanide



$C_{17}H_{20}N_2O_5S$ 364.42
Benzoic acid, 3-(aminosulfonyl)-5-(butylamino)-4-phenoxy-.
3-(Butylamino)-4-phenoxy-5-sulfamoylbenzoic acid [28395-03-1].

» Bumetanide contains not less than 98.0 per cent and not more than 102.0 per cent of $C_{17}H_{20}N_2O_5S$, calculated on the dried basis.

Packaging and storage—Preserve in tight, light-resistant containers. Store at 25 °, excursions permitted between 15 ° and 30°.

USP Reference standards ⟨11⟩**—**
USP Bumetanide RS
USP Bumetanide Related Compound A RS
3-Amino-4-phenoxy-5-sulfamoylbenzoic acid.
$C_{13}H_{12}N_2O_5S$ 308.31
USP Bumetanide Related Compound B RS
3-Nitro-4-phenoxy-5-sulfamoylbenzoic acid.
$C_{13}H_{10}N_2O_7S$ 338.29