age of $C_{38}H_{69}NO_{13}$ in the portion of Clarithromycin taken by the formula:

$$50(C_S / W)(r_U / r_S)P$$

in which C_S is the concentration, in mg per mL, of USP Clarithromycin RS in the *Standard preparation; W* is the weight, in mg, of Clarithromycin taken to prepare the *Assay preparation;* r_U and r_S are the clarithromycin peak area responses obtained from the chromatograms of the *Assay preparation* and the *Standard preparation,* respectively; and *P* is the purity of USP Clarithromycin RS taken to prepare the *Standard preparation.*

Clarithromycin for Oral Suspension

» Clarithromycin for Oral Suspension is a dry mixture of Clarithromycin, dispersing agents, diluents, preservatives, and flavorings. It contains not less than 90.0 per cent and not more than 115.0 percent of the labeled amount of $C_{38}H_{69}NO_{13}$, the labeled amount being 25 mg or 50 mg per mL when constituted as directed in the labeling.

Packaging and storage—Preserve in tight containers.

USP Reference standards ⟨11⟩**—**
USP Clarithromycin RS

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

Uniformity of dosage units ⟨905⟩**—**

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

Deliverable volume ⟨698⟩**—**

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

pH ⟨791⟩**:** between 4.0 and 5.4, in the suspension constituted as directed in the labeling.

Loss on drying ⟨731⟩**—**Dry about 1 g of it in vacuum at a pressure not exceeding 5 mm of mercury at 60° for 3 hours: it loses not more than 2.0% of its weight.

Assay—

Mobile phase—Prepare a mixture of methanol and 0.067 M monobasic potassium phosphate (600:400), adjust with phosphoric acid to a pH of 3.5, pass through a filter having a 0.5-µm or finer porosity, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Quantitatively dissolve an accurately weighed quantity of USP Clarithromycin RS in methanol, shaking and sonicating if necessary to effect dissolution, to obtain a solution having a known concentration of about 2100 µg of clarithromycin ($C_{38}H_{69}NO_{13}$) per mL, taking into account the stated potency, in µg per mg, of USP Clarithromycin RS. Transfer 10.0 mL of this stock solution to a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix. Pass a portion of this solution through a filter having a 0.5-µm or finer porosity, and use the filtrate as the *Standard preparation.* This solution contains about 415 µg of clarithromycin per mL.

Assay preparation—Constitute Clarithromycin for Oral Suspension as directed in the labeling. Transfer an accurately measured volume of the constituted Oral Suspension, equivalent to about 1 to 2 g of clarithromycin, with the aid of about 330 mL of 0.067 M dibasic potassium phosphate, to a 1000-mL volumetric flask containing about 50 mL of 0.067 M dibasic potassium phosphate. Shake by mechanical means for 30 minutes, dilute with methanol to volume, and mix. Sonicate for about 30 minutes, and allow to cool. Dilute with methanol to volume, add a magnetic stirring bar, and stir for 60 minutes. Allow to settle, and transfer an accurately measured volume of the clear supernatant, equivalent to about 20 mg of clarithromycin, to a 50-mL volumetric flask, dilute with *Mobile phase* to volume, mix, and pass through a filter having a 0.5-µm or finer porosity. Use the filtrate as the *Assay preparation.*

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 210-nm detector, an optional guard column that contains packing L1, and a 4.6-mm × 15-cm analytical column that contains packing L1 and is maintained at a constant temperature of about 50 °. 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, determined from the clarithromycin peak, is not less than 2100 theoretical plates when calculated by the formula:

$$5.545(t/W_{h/2})^2$$

the tailing factor is not less than 1.0 and not more than 1.7; the capacity factor, k', is not less than 2.5 and not more than 6; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, and measure the areas for the major peaks. Calculate the quantity, in mg, of $C_{38}H_{69}NO_{13}$ in each mL of the constituted Oral Suspension taken by the formula:

$$50(C/Vv)(r_U / r_S)$$

in which *C* is the concentration, in µg per mL, of clarithromycin ($C_{38}H_{69}NO_{13}$) in the *Standard preparation; V* is the volume, in mL, of constituted Oral Suspension taken to prepare the *Assay preparation; v* is the volume, in mL, of clear supernatant taken to prepare the *Assay preparation;* and r_U and r_S are the clarithromycin peak area responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Clarithromycin Tablets

DEFINITION

Clarithromycin Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of $C_{38}H_{69}NO_{13}$.

IDENTIFICATION

- The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

- **PROCEDURE**

Mobile phase: Methanol and 0.067 M monobasic potassium phosphate (13:7). Adjust with phosphoric acid to a pH of 4.0, and pass through a suitable filter.

Standard stock solution: 625 µg/mL of clarithromycin from USP Clarithromycin RS dissolved in methanol. [NOTE—Shake and sonicate to facilitate dissolution.]

Standard solution: 125 µg/mL of clarithromycin from *Standard stock solution* in *Mobile phase*. Pass through a suitable filter.

System suitability stock solution: 625 µg/mL of USP Clarithromycin Related Compound A RS in methanol.

System suitability solution: 125 µg/mL of USP Clarithromycin RS from *Standard stock solution* and 125 µg/mL of USP Clarithromycin Related Compound A RS from *System suitability stock solution* in *Mobile phase*

Sample stock solution: Equivalent to 4 mg/mL of clarithromycin from finely powdered Tablets in methanol. [NOTE—Shake by mechanical means for 30 min to disperse and allow any insoluble matter to settle.]

Sample solution: 120 µg/mL of clarithromycin from *Sample stock solution* in *Mobile phase*. Pass through a filter of 0.5- µm or finer pore size.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 210 nm
Column: 4.6-mm × 15-cm; packing L1
[NOTE—A guard column containing packing L1 may be added.]
Column temperature: 50°
Flow rate: 1 mL/min
Injection size: 20–50 µL
System suitability
Samples: *System suitability solution* and *Standard solution*
[NOTE—The relative retention times for clarithromycin and clarithromycin related compound A are 0.75 and 1.0, respectively.]
Suitability requirements
Resolution: NLT 2.0 between clarithromycin and clarithromycin related compound A, *System suitability solution*
Column efficiency: NLT 750 theoretical plates from the clarithromycin peak, *Standard solution*
Tailing factor: 0.9–1.5, *Standard solution*
Relative standard deviation: NMT 2.0%, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate percentage of label claim of $C_{38}H_{69}NO_{13}$ in the portion of Tablets 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 clarithromycin in the *Standard solution* (µg/mL)
C_U = nominal concentration of the *Sample solution* (µg/mL)
Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS
• **DISSOLUTION** ⟨**711**⟩
Buffer solution: Prepare a solution containing 13.61 mg/mL of sodium acetate trihydrate in water. Prepare another solution by diluting 5.7 mL of glacial acetic acid to 1 L with water. Combine portions of the two solutions to obtain a pH of 5.0.
Medium: *Buffer solution*, 900 mL
Apparatus 2: 50 rpm
Time: 30 min
Standard solution: Proceed as directed in the *Assay*.
Sample solution: Dilute with *Mobile phase* to yield a nominal concentration of 125 µg/mL of clarithromycin.
Mobile phase, System suitability solution, Chromatographic system, and **System suitability:** Proceed as directed for *Assay*.
Analysis
Samples: *Standard solution* and *Sample solution*
Determine the amount of $C_{38}H_{69}NO_{13}$ dissolved in the *Medium*, as directed in the *Assay*.
Calculate the percentage of clarithromycin dissolved:

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

r_U = peak area of the *Sample solution*
r_S = peak area of the *Standard solution*
C_S = concentration of the *Standard solution* (µg/mL)
C_U = nominal concentration of the *Sample solution* (µg/mL)
Tolerances: NLT 80% (Q) of the labeled amount of $C_{38}H_{69}NO_{13}$ is dissolved.

• **UNIFORMITY OF DOSAGE UNITS** ⟨**905**⟩**:** Meet the requirements

SPECIFIC TESTS
• **LOSS ON DRYING** ⟨**731**⟩**:** Dry a portion of powdered Tablets in vacuum at a pressure not exceeding 5 mm of mercury at 110° for 3 h: it loses NMT 6.0% of its weight.

ADDITIONAL REQUIREMENTS
• **PACKAGING AND STORAGE:** Preserve in tight containers.
• **USP REFERENCE STANDARDS** ⟨**11**⟩
USP Clarithromycin RS
USP Clarithromycin Related Compound A RS
6,11-Di-*O*-methylerythromycin A.
$C_{39}H_{71}NO_{13}$ 762.00

Clarithromycin Extended-Release Tablets

» Clarithromycin Extended-Release Tablets contain not less than 90.0 per cent and not more than 110.0 percent of the labeled amount of clarithromycin ($C_{38}H_{69}NO_{13}$).

Packaging and storage—Preserve in well-closed containers, protected from light. Store at 25 °, excursions permitted between 15° and 30°.

Labeling—When more than one *Dissolution Test* is given, the labeling states the *Dissolution Test* used only if *Test 1* is not used.

USP Reference standards ⟨11⟩**—**
USP Clarithromycin RS
USP Clarithromycin Related Compound A RS
6,11-Di-*O*-methylerythromycin A.
$C_{39}H_{71}NO_{13}$ 762.00

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

Dissolution ⟨711⟩**—**
TEST 1—
Medium: 0.3 M phosphate buffer, pH 6.0 (prepared by dissolving 816.5 g of monobasic potassium phosphate and 48 g of sodium hydroxide in about 4 L of water, mixing, and diluting with water to 20 L. Adjust with either concentrated phosphoric acid or 1 N sodium hydroxide to a pH of 6.0 ± 0.05); 900 mL.
Apparatus 2: 75 rpm.
Times: 30, 45, 60, and 120 minutes.
Determine the percentages of the labeled amount of clarithromycin ($C_{38}H_{69}NO_{13}$) dissolved using the following method.
Standard solutions—Prepare five solutions of USP Clarithromycin RS dissolved in acetonitrile and diluted in *Medium,* with known concentrations over the range of about 60 to 600 µg per mL.
Test solution—Use portions of the solution under test passed through a 35-µm polyethylene filter.
Chromatographic system—Proceed as directed in the *Assay.*
Procedure—Separately inject equal volumes (about 50 µL) of the five *Standard solutions* and the *Test solution* into the chromatograph, and measure the responses for the major peaks. Perform a linear regression analysis to generate a standard curve using the peak area of each *Standard solution* versus its concentration. Determine the amount of clarithromycin ($C_{38}H_{69}NO_{13}$) dissolved at each specified time interval, using the peak area of each *Test solution* and the linear regression statistics for the *Standard solutions.*