pH ⟨791⟩**:** between 6.0 and 9.0.

Globule size limits—The Injectable Emulsion meets the requirements of the limits specified in both *Method I* and *Method II* as directed under *Globule Size Distribution in Lipid Injectable Emulsions* ⟨729⟩.

Limit of oil droplet mean diameters (See *Method I—Light Scattering Method* under *Globule Size Distribution in Lipid Injectable Emulsions* ⟨729⟩)—Using the method of light scattering, determine the mean droplet diameter (MDD): the sample meets the requirements. The intensity-weighted mean droplet diameter (MDD) for the Injectable Emulsion must be ≤500 nm, or 0.5 µm, irrespective of the concentration of the dispersed lipid phase.

Limit of large globule volume-diameter (See *Method II—Light Obscuration or Extinction Method* under *Globule Size Distribution in Lipid Injectable Emulsions* ⟨729⟩)—Using the method of light obscuration, determine the size distribution of globules in the large-diameter tail of the dispersion (detection threshold ≥2.0 µm). Calculate the volume-weighted mass of lipid in the form of globules with diameters in excess of 5.0 µm per 100 mL of the Injectable Emulsion. The volume-weighted, large-diameter fat globule limits of the dispersed phase, expressed as the percentage of fat residing in globules larger than 5 µm (PFAT5) for a given Injectable Emulsion, is not to exceed 0.05%.

Limit of free fatty acid—

Solvent—Prepare a mixture of heptane, isopropanol, and water (400:400:200) in a separatory funnel. Allow the phases to separate, and discard the lower phase. Filter the upper phase (heptane solution) through 40 g of anhydrous sodium sulfate. Store in a tightly capped glass container, and use within 1 week.

Chromatographic column—Prepare a slurry of heptane and chromatographic silica gel having an average pore size of 6 nm, and activate at a temperature of 110° for not less than 1 hour prior to use. Transfer the slurry to a 2.3-cm chromatographic tube (see *Column Chromatography* under *Chromatography* ⟨621⟩), and pack to a bed height of between 5 cm and 6 cm. Wash the column with about 40 mL of heptane, and drain the heptane through the column to a level of about 0.5 cm above the silica gel bed.

Procedure—Transfer 20.0 mL of the Injectable Emulsion to a flask, freeze, and lyophilize. Dissolve the residue in 30 mL of *Solvent,* and transfer the solution to the column. Rinse the flask with three 30-mL portions of *Solvent,* and transfer the washings to the column, allowing each rinsing to drain to the top of the column bed before applying the next rinse. Collect a total of 120 mL of effluent. Add 10 drops of phenolphthalein TS to the effluent, bubble nitrogen through the solution, and titrate with 0.02 N alcoholic potassium hydroxide VS until the solution remains pale pink after mixing for 10 seconds. Titrate a blank using 120 mL of *Solvent.* Calculate the quantity, in mEq, of free fatty acids per g of oil in the Injectable Emulsion using the formula:

$$(V_U - V_B)N / 20C$$

in which V_U is the volume, in mL, of 0.02 N alcoholic potassium hydroxide consumed by the eluant; V_B is the volume, in mL, of 0.02 N alcoholic potassium hydroxide consumed by the blank; N is the normality of the 0.02 N alcoholic potassium hydroxide; and C is the labeled concentration, in g per mL, of the total oil(s) in the Injectable Emulsion: not more than 0.07 mEq of free fatty acids per g of oil is found.

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

Assay—

Mobile phase—Prepare a filtered and degassed mixture of isopropanol, ethyl acetate, and glacial acetic acid (179:20:1).

Standard preparation—Dissolve an accurately weighed portion of Soybean Oil (or other relevant oils used in the Emulsion) in *Mobile phase* to obtain a solution having a known concentration of about 8 mg per mL.

Assay preparation—Transfer an accurately measured portion of Emulsion, equivalent to about 800 mg of oil, to a 100-mL volumetric flask with the aid of additional portions of *Mobile phase.* Dilute with *Mobile phase* to volume, and mix to obtain a solution containing about 8 mg of oil per mL.

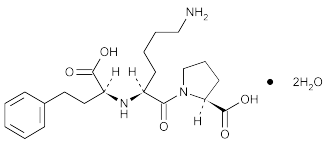
Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a refractive index detector and a 4.1-mm × 25-cm column that contains packing L21. The flow rate is about 1 mL per minute, adjusted so that the peak due to oil elutes at about 6.5 minutes. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the capacity factor, k', is not less than 1.0; the tailing factor for the oil peak is not more than 2.5; 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, record the chromatograms, and measure the peak responses. Calculate the quantity, in mg, of oil in the portion of Emulsion taken by the formula:

$$100C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of Soybean Oil or other relevant oils used in the Emulsion in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Lisinopril



$C_{21}H_{31}N_3O_5 \cdot 2H_2O$ 441.52

L-Proline, 1-[N^2-(1-carboxy-3-phenylpropyl)-L-lysyl]-, dihydrate, (*S*)-.

1-[N^2-[(*S*)-1-Carboxy-3-phenylpropyl]-L-lysyl]-L-proline dihydrate [83915-83-7].

» Lisinopril contains not less than 98.0 percent and not more than 102.0 percent of $C_{21}H_{31}N_3O_5$, calculated on the anhydrous basis.

Packaging and storage—Preserve in well-closed containers.

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

Identification—

A: *Infrared Absorption* ⟨197M⟩.

B: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that of the *Standard preparation* obtained as directed in the *Assay*.

Specific rotation ⟨781S⟩: between –115.3° and –122.5° (λ = 405 nm).

Test solution: 10 mg per mL, in 0.25 M zinc acetate. Prepare the 0.25 M zinc acetate solution as follows. Mix 600 mL of water with 150 mL of glacial acetic acid and 54.9 g of zinc acetate, and stir to dissolve the zinc acetate. While stirring, add 150 mL of ammonium hydroxide, cool to room temperature, and adjust with ammonium hydroxide to a pH of 6.4. Transfer the solution to a 1000-mL volumetric flask, dilute with water to volume, and mix.

Water, *Method I* ⟨921⟩: between 8.0% and 9.5%.

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

Heavy metals, *Method II* ⟨231⟩: 0.001%.

Assay—

Phosphate solution—Dissolve 2.76 g of monobasic sodium phosphate in about 900 mL of water in a 1000-mL volumetric flask, and adjust with 1 N sodium hydroxide to a pH of 5.0. Dilute with water to volume, and mix.

Mobile phase—Prepare a filtered and degassed mixture of *Phosphate solution* and acetonitrile (96:4). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Lisinopril RS in water, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about 0.3 mg per mL.

Assay preparation—Transfer about 30 mg of Lisinopril, accurately weighed, to a 100-mL volumetric flask, dissolve in water, dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 210-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L7 and is maintained at a temperature of 50°. The flow rate is about 1 mL per minute. Chromatograph the *Standard preparation*, and record the peak responses as directed under *Procedure:* the column efficiency determined from the analyte peak is not less than 180 theoretical plates, the tailing factor for the analyte peak is not more than 1.7, and the relative standard deviation for replicate injections is not more than 1.0%.

Procedure—Separately inject equal volumes (about 20 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 $C_{21}H_{31}N_3O_5$ in the portion of Lisinopril taken by the formula:

$$100C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Lisinopril RS in the *Standard preparation*, calculated on the anhydrous basis; and r_U and r_S are the lisinopril peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively.

Lisinopril Tablets

» Lisinopril Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{21}H_{31}N_3O_5$.

Packaging and storage—Preserve in tight containers.

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

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

Dissolution ⟨711⟩**—**

Medium: 0.1 N hydrochloric acid; 900 mL.

Apparatus 2: 50 rpm.

Time: 30 minutes.

Determine the amount of lisinopril dissolved using the following method.

Mobile phase and *Chromatographic system*—Prepare as directed in the *Assay.*

Determine the amount of lisinopril dissolved by one of the following procedures.

PROCEDURE FOR POOLED SAMPLE—Proceed as directed for *Procedure* in *Apparatus 1 and Apparatus 2, Immediate-Release Dosage Forms* under *Dissolution* ⟨711⟩. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution. Inject a volume of the pooled sample into the chromatograph, record the chromatogram, and measure the response for the major peak. Calculate the quantity of $C_{21}H_{31}N_3O_5$ dissolved in comparison with a Standard solution having a known concentration of USP Lisinopril RS in the same *Medium* and similarly chromatographed.

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{21}H_{31}N_3O_5$ in the Tablets is dissolved in 30 minutes: the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying *Acceptance Table for a Pooled Sample*. Continue testing through the three stages unless the results conform at either S_1 or S_2. The quantity, *Q*, is the amount of dissolved active ingredient specified, expressed as a percentage of the labeled content.

Acceptance Table for a Pooled Sample

Stage	Number Tested	Acceptance Criteria
S_1	6	Average amount dissolved is not less than Q + 10%.
S_2	6	Average amount dissolved (S_1 + S_2) is equal to or greater than Q + 5%.
S_3	12	Average amount dissolved (S_1 + S_2 + S_3) is equal to or greater than Q.

PROCEDURE FOR UNIT SAMPLE—Proceed as directed for *Procedure* in *Apparatus 1 and Apparatus 2, Immediate-Release Dosage Forms* under *Dissolution* ⟨711⟩. Inject a volume of a filtered portion of the solution under test into the chromatograph, record the chromatogram, and measure the response for the major peak. Calculate the amount of $C_{21}H_{31}N_3O_5$ dissolved in comparison with a Standard solution having a known concentration of USP Lisinopril RS in the *Medium* and similarly chromatographed.

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{21}H_{31}N_3O_5$ is dissolved in 30 minutes.

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

Procedure for content uniformity—

Phosphate solution, Mobile phase, and Chromatographic system—Prepare as directed in the *Assay*.

Diluent—Dissolve 2.72 g of monobasic potassium phosphate in 800 mL of water, adjust with phosphoric acid to a pH of 4.0, dilute with water to 1000 mL, and mix.

Standard preparation—Dissolve an accurately weighed quantity of USP Lisinopril RS in *Diluent* to obtain a solution having a known concentration of about 0.2 mg per mL.

Test preparation—Place one Tablet in a volumetric flask of appropriate size, based on the labeled quantity, in mg, of lisinopril in the Tablet, to obtain a solution containing 0.2 mg of lisinopril per mL. Fill the flask to about 50% volume with *Diluent*, sonicate for 5 minutes, and shake by mechanical means for 20 minutes. Dilute with *Diluent* to volume, mix, and filter.

Procedure—[NOTE—Use peak areas where peak responses are indicated.] Separately inject equal volumes (about 20 µL) of the *Test preparation* and the *Standard preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{21}H_{31}N_3O_5$ in the Tablet taken by the formula:

$$(TC / D)(r_U / r_S)$$

in which T is the labeled quantity, in mg, of lisinopril in the Tablet; C is the concentration, in mg per mL, calculated on the anhydrous basis, of USP Lisinopril RS in the *Standard preparation; D* is the concentration, in mg per mL, of lisinopril in the *Test preparation*, based upon the labeled quantity per Tablet and the extent of dilution; and r_U and r_S are the lisinopril peak responses obtained from the *Test preparation* and the *Standard preparation,* respectively.