preparation having a known concentration of about 1.7 mg of lidocaine per mL.

Assay preparation—Transfer an accurately measured volume of Injection, equivalent to about 100 mg of lidocaine hydrochloride, to a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Resolution preparation—Prepare a solution of methylparaben in *Mobile phase* containing about 220 µg per mL. Mix 2 mL of this solution and 20 mL of the *Standard preparation*.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 3.9-mm × 30-cm column that contains packing L1. The flow rate is about 1.5 mL per minute. Chromatograph about 20 µL of the *Resolution preparation,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between lidocaine and methylparaben is not less than 3.0. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 1.5%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Assay 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 lidocaine hydrochloride ($C_{14}H_{22}N_2O \cdot HCl$) in each mL of the Injection taken by the formula:

$$(270.80/234.34)(50)(C/V)(r_U / r_S)$$

in which 270.80 and 234.34 are the molecular weights of lidocaine hydrochloride and lidocaine, respectively; C is the concentration, in mg per mL, of USP Lidocaine RS in the *Standard preparation;* V is the volume, in mL, of Injection taken; and r_U and r_S are the lidocaine peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Assay for epinephrine—

Mobile phase—Mix 50 mL of glacial acetic acid and 930 mL of water, and adjust with 1 N sodium hydroxide to a pH of 3.40. Dissolve 1.1 g of sodium 1-heptanesulfonate in this solution, add 1.0 mL of 0.1 M edetate disodium, and mix. Mix about 9 volumes of this solution with 1 volume of methanol, so that the retention time of epinephrine is about 4 to 6 minutes. Pass through a membrane filter having a 1-µm or finer porosity, and degas.

Standard preparation—Dissolve an accurately weighed quantity of USP Epinephrine Bitartrate RS in *Mobile phase* to obtain a solution having a known concentration of about 9 µg of epinephrine bitartrate per mL. Pipet 10 mL of this solution into a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix to obtain a *Standard preparation* having a known concentration of about 1.8 µg of epinephrine bitartrate per mL.

Assay preparation—Transfer an accurately measured volume of Injection, equivalent to about 50 µg of epinephrine, to a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is fitted with a 3.9-mm × 30-cm stainless steel column that contains packing L1 and is equipped with an electrochemical detector held at a potential of +650 mV, a controller capable of regulating the background current, and a suitable recorder. The flow rate is about 1 mL per minute. Chromatograph the *Standard preparation* as directed for *Procedure:* the relative standard deviation of the peak responses of successive injections of the *Standard preparation* is not more than 1.5%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Assay preparation* and the *Standard preparation* into the chromatograph by means of a suitable microsyringe or sampling valve, adjusting the specimen size and other operating parameters so that satisfactory chromatography and peak responses are obtained. Record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in µg, of epinephrine ($C_9H_{13}NO_3$) in each mL of the Injection taken by the formula:

$$(183.20/333.29)(50)(C/V)(r_U / r_S)$$

in which 183.20 and 333.29 are the molecular weights of epinephrine and epinephrine bitartrate, respectively; C is the concentration, in µg per mL, of USP Epinephrine Bitartrate RS in the *Standard preparation;* V is the volume, in mL, of Injection taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Lidocaine and Prilocaine Cream

» Lidocaine and Prilocaine Cream contains not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of lidocaine ($C_{14}H_{22}N_2O$) and prilocaine ($C_{13}H_{20}N_2O$).

Packaging and storage—Preserve in collapsible tubes or in tight containers. Do not store above 30°. Do not freeze.

USP Reference standards ⟨11⟩—
USP Lidocaine RS
USP Prilocaine Hydrochloride RS
USP Prilocaine Related Compound B RS
(*RS*)-*N*-(4-Methylphenyl)-2-(propylamino)propanamide.
$C_{13}H_{20}N_2O$ 220.31

Identification—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.*

Microbial enumeration tests ⟨61⟩ **and Tests for specified microorganisms** ⟨62⟩—It meets the requirements of the tests for absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa.* The total aerobic microbial count does not exceed 100 cfu per g, and the total combined molds and yeasts count does not exceed 50 cfu per g.

Minimum fill ⟨755⟩**:** meets the requirements.

pH ⟨791⟩**:** between 8.7 and 9.7, determined in a solution (1 in 10) or in the undiluted Cream.

Related compounds—

Solution A, Solution B, Mobile phase, System suitability solution, and *Chromatographic system*—Proceed as directed in the *Assay.*

Standard solution—Dissolve accurately weighed quantities of USP Lidocaine RS and USP Prilocaine Hydrochloride RS in *Solution A,* and dilute quantitatively, and stepwise if necessary, with *Solution A* to obtain a solution having a known concentration of about 0.002 mg per mL of each compound. Immediately store this solution at or below 10°.

Test solution—Use the *Assay preparation,* prepared as directed in the *Assay.*

Chromatographic system (see *Chromatography* ⟨621⟩)—Proceed as directed in the *Assay*. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are listed in *Table 1;* and the resolution, *R,* between prilocaine and prilocaine related compound B is not less than 1.4. Chromatograph the *Standard solution* a minimum of six times, and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 5.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of each related compound in the portion of the Cream taken by the formula:

$$100C(r_U / r_S)(V/W)(100/L)(1/F)(220.31/256.77)$$

in which C is the individual concentration, in mg per mL, of either USP Lidocaine RS or USP Prilocaine Hydrochloride RS in the *Standard solution;* r_U is the individual peak response of the impurities obtained from the *Test solution;* r_S is the individual peak response for either lidocaine or prilocaine obtained from the *Standard solution;* V is the volume, in mL, of the *Test solution;* W is the weight, in mg, of the Cream taken to prepare the *Test solution;* L is the individual label claim, in percent, for either lidocaine or prilocaine; F is the relative response factor for each related compound as listed in *Table 1;* and 220.31 and 256.77 are the molecular weights of prilocaine and prilocaine hydrochloride, respectively (these are used only for calculation involving prilocaine related compounds). The percentages of lidocaine related compounds and prilocaine related compounds are calculated using the concentration and peak response from USP Lidocaine RS and USP Prilocaine Hydrochloride RS, respectively. The designation of whether an impurity is a lidocaine related compound or prilocaine related compound is specified in *Table 1*. The percentage of any individual unknown related compound is determined using the concentration and peak response from USP Prilocaine Hydrochloride RS in the *Standard solution*.

Assay—

Solution A—Dissolve about 2.73 g of monobasic potassium phosphate in 630 mL of water, and adjust with 5 N sodium hydroxide to a pH of 7.20 ± 0.02. Dilute with acetonitrile to 1 L.

Solution B—Dissolve about 2.73 g of monobasic potassium phosphate in 900 mL of water, and adjust with 5 N sodium hydroxide to a pH of 7.20 ± 0.02. Dilute with acetonitrile to 1 L.

Mobile phase—Use variable mixtures of filtered and degassed *Solution A* and *Solution B* as directed for *Chromatographic system*. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve accurately weighed quantities of USP Lidocaine RS and USP Prilocaine Hydrochloride RS in *Solution A,* and dilute quantitatively, and stepwise if necessary, with *Solution A* to obtain a solution having a known concentration of about 0.2 mg per mL of each compound. Immediately store this solution at or below 10°.

System suitability solution—Dissolve an accurately weighed quantity of USP Prilocaine Related Compound B RS in the *Standard preparation,* and dilute quantitatively, and stepwise if necessary, with the *Standard preparation,* to obtain a solution having a known concentration of about 0.08 mg per mL of prilocaine related compound B.

Assay preparation—Transfer a portion of the Cream, equivalent to about 20 mg each of lidocaine and prilocaine, accurately weighed, to a 100-mL volumetric flask. Add 5 mL of 5 N sodium hydroxide to disperse the Cream, and mix. Add 5 mL of 5 N hydrochloric acid, and dilute with *Solution A* to volume, and mix. Pass a portion through a nylon filter having a 0.2-µm or finer porosity, discarding the first 1 mL, and use the filtrate. Immediately store this solution at or below 10°.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 232-nm detector and a 4.6-mm × 10-cm column that contains 3-µm packing L1. The flow rate is about 1.5 mL per minute. The column temperature is maintained at 40°. The samples are maintained at or below 10°. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	67	33	equilibration
0–11.0	67	33	isocratic
11.0–22.0	67→100	33→0	linear gradient
22.0–32.0	100	0	isocratic

Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are 1.00 for prilocaine, 1.09 for prilocaine related compound B, and 2.14 for lidocaine; and the resolution, *R,* between prilocaine and prilocaine related compound B is not less than 1.4. Chromatograph the *Standard preparation* a minimum of five times, and record the peak responses as directed for *Procedure:* the column efficiency is not less than 5000 theoretical plates, based on the prilocaine peak; the tailing factor is not more than 1.5, based on the prilocaine peak; 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 responses for the lidocaine and prilocaine peaks. Calculate the percentage of the label claim of lidocaine ($C_{14}H_{22}N_2O$) and prilocaine ($C_{13}H_{20}N_2O$) in the portion of Cream taken by the formula:

$$100C(r_U / r_S)(V/W)(100/L)(220.31/256.77)$$

in which C is the individual concentration, in mg per mL, of either USP Lidocaine RS or USP Prilocaine Hydrochloride RS in the *Standard preparation;* r_U and r_S are either the individual peak responses of lidocaine or prilocaine obtained from the *Assay preparation* and the *Standard preparation,* respectively; V is the

Table 1

Related Compound	Relative Retention Time[a]	Relative Response Factor (F)	Limit
o-Toluidine	0.38	2.3 (P)[b]	not more than 2.0%
n-Chloroacetyl-2,6-xylidine	0.54	1.0 (L)[c]	not more than 0.1%
2,6-Dimethylaniline	0.67	3.3 (L)[c]	not more than 0.1%
Prilocaine	1.00	—	—
2-Diethylaminoaceto-2,4-xylidine	1.33	0.8 (L)[c]	not more than 0.1%
Lidocaine	2.14	—	—
n-Dichloroacetyl-2,6-xylidine	2.98	2.2 (L)[c]	not more than 0.1%
Any other individual related compounds	—	1.0 (P)[b]	not more than 0.2%
Total related compounds, excluding *o*-toluidine	—	—	not more than 1.0%

[a] Relative to the prilocaine peak.

[b] P designates a prilocaine related compound.

[c] L designates a lidocaine related compound.

volume, in mL, of the *Assay preparation; W* is the weight, in mg, of the Cream taken to prepare the *Assay preparation; L* is the individual label claim, in percent, for either lidocaine or prilocaine; and 220.31 and 256.77 are the molecular weights of prilocaine and prilocaine hydrochloride, respectively (these are used only for calculating the percentage of prilocaine in the Cream).

Lime

CaO 56.08
Calcium oxide [1305-78-8].

» Lime, when freshly ignited to constant weight, contains not less than 95.0 percent of CaO.

Packaging and storage—Preserve in tight containers.

Identification—

A: Moisten it with water: heat is generated, and a white powder is obtained (calcium hydroxide or slaked lime). Mix the powder with 3 or 4 times its weight of water: a smooth magma of lime forms that is alkaline to litmus.

B: Slake 1 g with 20 mL of water, and add 6 N acetic acid until the lime is dissolved: the resulting solution responds to the test for *Calcium* 〈191〉.

Loss on ignition 〈733〉—Ignite a portion to constant weight in a tared platinum crucible at 1100 ± 50°: it loses not more than 10.0% of its weight.

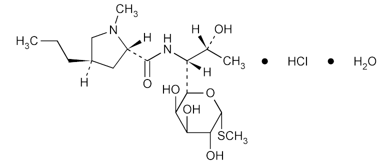
Insoluble substances—Slake 5.0 g, then mix with 100 mL of water, followed by hydrochloric acid, dropwise, with agitation, until solution takes place: the resulting solution after boiling and cooling is acid, and when filtered through a tared crucible, washed with water until free of chlorides, and dried at 105° for 1 hour yields not more than 50 mg of insoluble substances (1.0%).

Carbonate—Slake 1 g, mix with 50 mL of water, and decant the greater portion of the milky liquid: the addition of an excess of 3 N hydrochloric acid to the residue does not cause more than a slight effervescence.

Magnesium and alkali salts—Dissolve 500 mg in 30 mL of water and 15 mL of 3 N hydrochloric acid. Neutralize the solution with 6 N ammonium hydroxide, heat to boiling, and add ammonium oxalate TS to precipitate the calcium completely. Heat the mixture on a steam bath for 1 hour, cool, dilute with water to 100 mL, mix, and filter. To 50 mL of the filtrate add 0.5 mL of sulfuric acid, evaporate to dryness, and ignite in a tared platinum crucible to constant weight. The weight of the residue does not exceed 9 mg.

Assay—Ignite about 1 g of Lime in a muffle furnace to constant weight, cool, weigh accurately, and dissolve in 20 mL of 3 N hydrochloric acid. Cool the solution, transfer to a 500-mL volumetric flask with the aid of water, dilute with water to volume, and mix. Transfer 50.0 mL to a suitable container, add 100 mL of water, 15 mL of 1 N sodium hydroxide, and 300 mg of hydroxy naphthol blue, and titrate with 0.05 M edetate disodium VS until the solution is deep blue in color. Each mL of 0.05 M edetate disodium is equivalent to 2.804 mg of CaO.

Lincomycin Hydrochloride



$C_{18}H_{34}N_2O_6S \cdot HCl \cdot H_2O$ 461.02
D-*erythro*-α-D-*galacto*-Octopyranoside, methyl 6,8-dideoxy-6-[[(1-methyl-4-propyl-2-pyrrolidinyl)carbonyl]amino]-1-thio-, monohydrochloride, monohydrate, (2*S*-*trans*)-.
Methyl 6,8-dideoxy-6-(1-methyl-*trans*-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-D-*erythro*-α-D-*galacto*-octopyranoside monohydrochloride monohydrate [7179-49-9].
Anhydrous 443.01 [859-18-7].

» Lincomycin Hydrochloride has a potency equivalent to not less than 790 µg of lincomycin ($C_{18}H_{34}N_2O_6S$) per mg.

Packaging and storage—Preserve in tight containers.

Labeling—Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms.

USP Reference standards 〈11〉—
USP Endotoxin RS
USP Lincomycin Hydrochloride RS

Identification, *Infrared Absorption* 〈197M〉.

Specific rotation 〈781S〉: between +135° and +150°.

Test solution: 20 mg per mL, in water.

Crystallinity 〈695〉: meets the requirements.

pH 〈791〉: between 3.0 and 5.5, in a solution (1 in 10).

Water, *Method I* 〈921〉: between 3.0% and 6.0%.

Limit of lincomycin B—Use the chromatogram obtained from the *Assay preparation* in the *Assay:* the area of the lincomycin B peak is not greater than 5.0% of the sum of the areas of the lincomycin B peak and the lincomycin peak.

Other requirements—Where the label states that Lincomycin Hydrochloride is sterile, it meets the requirements for *Sterility* and *Bacterial endotoxins* under *Lincomycin Injection*. Where the label states that Lincomycin Hydrochloride must be subjected to further processing during the preparation of injectable dosage forms, it meets the requirements for *Bacterial endotoxins* under *Lincomycin Injection*.

Assay—

Mobile phase—Add 13.5 mL of phosphoric acid to 1000 mL of water, and adjust with ammonium hydroxide to a pH of 6.0. Prepare a filtered and degassed mixture of this solution, acetonitrile, and methanol (780:150:150). Make adjustments if necessary (see *System Suitability* under *Chromatography* 〈621〉).

Standard preparation—Dissolve an accurately weighed quantity of USP Lincomycin Hydrochloride RS in *Mobile phase* to obtain a solution having a known concentration of about 1.2 mg per mL, using sonication if necessary to effect solution.

Assay preparation—To about 12 mg of Lincomycin Hydrochloride, accurately weighed, add 10.0 mL of *Mobile phase.* Shake by mechanical means for 5 minutes, and sonicate if necessary to effect solution.

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 46°. The flow rate is about 1 mL per minute. Chromatograph the *Standard preparation*, and record the responses as directed for *Procedure:* the tailing factor for the main lincomycin peak is not more than 1.3; the column