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Eighteenth Revision

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FIRST SUPPLEMENT

TO THE

PHARMACOPEIA OF THE UNITED STATES

EIGHTEENTH REVISION

(First U. S. P. XVIII Supplement)

Changes and additions listed herein constitute revisions in U. S. P. XVIII effective November 1, 1971, except where otherwise noted.

Unless otherwise indicated, page citations refer to the pages of U. S. P. XVIII.

Aluminum Sulfate, page 30—Change the definition to read:

Aluminum Sulfate contains an amount of $Al_2(SO_4)_3$ equivalent to not less than 97.0 percent and not more than 101.5 percent of $Al_2(SO_4)_3 . 14H_2O$.
(Official Jan. 1, 1971)

Amitriptyline Hydrochloride Injection, page 38—In the second sentence of the definition, change "not more than 115.0 percent" to:

not more than 110.0 percent
(Foregoing change official Sept. 1, 1970)

In the *Assay*, under *Procedure*, change "potassium periodate solution (1 in 50)" to:

periodic acid solution (1 in 50)

Ammonium Chloride Tablets, page 41—Delete the section, *Weight variation.*
(Official Sept. 1, 1970)

Antimony Potassium Tartrate, page 49—In the final sentence of the section, *Arsenic*, change "0.02 mg. of arsenic" to:

0.015 mg. of arsenic
(Official Jan. 1, 1971)

This Supplement includes the entire content of the first interim revision announcement, effective September 1, 1970, and the second announcement, effective January 1, 1971.

Interim revision announcements (of which two have been issued for U. S. P. XVIII to date) are issued to the pharmaceutical press to serve as advance notice of changes of relatively limited concern which will be included subsequently in a Supplement. Supplements, in turn, are mailed to all holders of the Pharmacopeia who have returned the Official Order Form.

Aspirin Tablets, page 54—In the second sentence of the definition, change "75-mg. size" to:

81-mg. size

In the section, *Non-aspirin salicylates,* in the third sentence of the second paragraph under *Procedure,* change "Pipet 10 ml. of this solution" to:

Pipet 5 ml. of this solution

In the second sentence of the section, *Packaging and storage,* change "75-mg. size" to:

81-mg. size
(Official Jan. 1, 1971)

Atropine Sulfate, page 56—Add the following, as *Identification test E.*

E: Prepare a solution of Atropine Sulfate and a solution of U. S. P. Atropine Sulfate Reference Standard as directed for *Standard preparation* in the *Assay* under *Atropine Sulfate Injection,* page 57, and proceed to obtain a chromatogram as directed under *Standard curve,* making up the solutions in only one of the four concentrations specified. The solution of Atropine Sulfate yields a chromatogram identical to that obtained with the corresponding solution prepared from the Reference Standard.
(Foregoing change official Sept. 1, 1970)

In the section, *Melting temperature,* change "not lower than 188°" to:

not lower than 187°
(Foregoing change official Jan. 1, 1971)

Atropine Sulfate Injection, page 57—Make the following changes in the *Assay.*

In the first sentence under *Assay preparation,* change "about 1 mg." to:

about 0.8 mg.

In the third sentence under *Standard curve,* change "100-mesh" to:

100- to 120-mesh

In the last sentence under *Procedure,* change "in mg. per ml." to:

in mg.
(Official Sept. 1, 1970)

Atropine Sulfate Ophthalmic Solution, page 58—Make the following changes in the first sentence of the *Assay.*

Change "*pH 9.0 Buffer*" to:

water

Change "about 1 mg." to:

about 0.8 mg.
(Official Sept. 1, 1970)

Bacitracin Ointment, page 61—Change the first sentence of the section, *Packaging and storage,* to read:

Preserve in well-closed containers containing not more than 60 g., unless labeled solely for hospital use, preferably in a cool place.
(Official Jan. 1, 1971)

Gamma Benzene Hexachloride Cream, page 71—Change the section, *pH,* to read:

pH, page 938: between 8.0 and 9.0, in a 1 in 5 dilution.
(Official Jan. 1, 1971)

Gamma Benzene Hexachloride Lotion, page 71—In the section, *pH,* change "8.0" to:

8.5
(Official Jan. 1, 1971)

Benztropine Mesylate Tablets, page 75—In the *Assay,* under *pH 4.0 Tartrate buffer,* change "14.2 ml. of 1 *N* sodium hydroxide" to:

142 ml. of 1 *N* sodium hydroxide

Bishydroxycoumarin, page 79; **Bishydroxycoumarin Tablets,** page 80—Change the official title by substituting for "Bishydroxycoumarin" and "Bishydroxycoumarin Tablets," respectively, in the appropriate places throughout both monographs, the following:

Dicumarol
Dicumarol Tablets
(Official Apr. 1, 1972)

Butylparaben, page 84—In the section, *Identification,* change "between 212° and 214°" to:

between 212° and 217°
(Official Jan. 1, 1971)

Carbachol, page 98—In the section, *Melting range,* change "between 201° and 205°" to:

between 200° and 204°, with some decomposition
(Official Jan. 1, 1971)

Carbachol Ophthalmic Solution, page 98—Change the *Assay* to read:

Assay—
Hypochlorite reagent—Dilute 1 volume of sodium hypochlorite T.S. to 15 volumes with water, allow to stand for 30 minutes, then mix equal volumes of the resulting solution and sodium hydroxide T.S. Prepare fresh daily.
Standard preparation—Dissolve a suitable quantity of U. S. P. Carbachol Reference Standard, accurately weighed, in water, and dilute quantitatively and stepwise with water to obtain a solution having a known concentration of about 100 mcg. per ml.

Assay preparation—Dilute an accurately measured volume of Carbachol Ophthalmic Solution quantitatively and stepwise with water to obtain a solution containing about 100 mcg. per ml.

Procedure—Transfer 2-ml. portions each of the *Assay preparation* and the *Standard preparation*, and of water to provide a blank, to 50-ml. conical flasks. To each flask add 1.0 ml. of 0.1 *N* hydrochloric acid, and mix. Treat each as follows: Add 4.0 ml. of *Hypochlorite reagent*, rinsing the inner walls of the flask with small portions of water, mix, and allow to stand for 15 minutes, accurately timed. Add 2.0 ml. of a 1 in 200 solution of phenol in water, rinsing the walls of the flask with the solution and with additional small portions of water. Mix, and allow to stand for 5 minutes. Add 1.0 ml. of a 3 in 1000 solution of potassium iodide in water, mix, and allow to stand for 5 minutes. Add 5.0 ml. of a 1 in 500 solution of amylose, mix, transfer the solutions to 50-ml. volumetric flasks with the aid of several small portions of water, and dilute each solution with water to volume. Concomitantly determine the absorbances of the solutions from the *Assay preparation* and the *Standard preparation* in 1-cm. cells at the wavelength of maximum absorbance at about 590 mμ, with a suitable spectrophotometer, against the blank. Calculate the quantity, in mg., of $C_6H_{15}ClN_2O_2$ in each ml. of the Solution taken by the formula $0.001CD(A_U/A_S)$, in which C is the concentration, in mcg. per ml., of U. S. P. Carbachol Reference Standard in the *Standard preparation*, D is the dilution factor used in the *Assay preparation*, and A_U and A_S are the absorbances of the solutions from the *Assay preparation* and the *Standard preparation*, respectively.

Chlordiazepoxide Hydrochloride Capsules, page 114—Change the section, *Content uniformity*, to read:

Content uniformity, page 930—[NOTE—Use low-actinic glassware in this procedure.] Transfer the contents of 1 Capsule to a 200-ml. volumetric flask, dissolve in water, and add water to volume. Dilute a portion of this solution quantitatively and stepwise with dilute hydrochloric acid (1 in 100) to obtain a concentration of about 6 mcg. of chlordiazepoxide hydrochloride per ml. Dissolve a suitable quantity of U. S. P. Chlordiazepoxide Hydrochloride Reference Standard, accurately weighed, in dilute hydrochloric acid (1 in 100) to obtain a Standard solution having a known concentration of about 6 mcg. per ml. Concomitantly determine the absorbances of the two solutions in 1-cm. cells at the wavelength of maximum absorbance at about 245 mμ, with a suitable spectrophotometer, using dilute hydrochloric acid (1 in 100) as the blank. Calculate the quantity, in mg., of $C_{16}H_{14}ClN_3O.HCl$ in the Capsule by the formula $(T/D)C(A_U/A_S)$, in which T is the labeled quantity, in mg., of chlordiazepoxide hydrochloride in the Capsule, D is the concentration, in mcg. per ml., of chlordiazepoxide hydrochloride in the test solution (on the basis of the labeled quantity per Capsule and the extent of dilution), C is the concentration, in mcg. per ml., of U. S. P. Chlordiazepoxide Hydrochloride Reference Standard in the Standard solution, and A_U and A_S are the absorbances of the solution from the contents of the Capsule and the Standard solution, respectively. Chlordiazepoxide Hydrochloride Capsules meet the requirements for *Capsules*.

Chloroquine Phosphate Tablets, page 121—In the section, *Identification*, change "the *Identification tests*" to:

Identification tests A and *B*
(Official Sept. 1, 1970)

Chlorpheniramine Maleate Elixir, page 122—Make the following changes in the *Assay*.

In the fourth sentence, change "Standard solution having a known concentration of about 50 mcg. per ml." to:

Standard solution having a known concentration of about 40 mcg. per ml.

In the final sentence, change the calculation formula to:

$0.01C(A_U/A_S)$

Cholestyramine Resin, page 132—In the section, *Exchange capacity,* in the final sentence under *Procedure,* change the calculation formula to:

$M(A_R - A_U)(W_S)/(A_R - A_S)W_U$

(Official Jan. 1, 1971)

Cyanocobalamin Injection, page 154—Delete the section, *pH.*

(Official Sept. 1, 1970)

Dexamethasone Sodium Phosphate Injection—Add the following monograph.

Dexamethasone Sodium Phosphate Injection

Dexamethasone Sodium Phosphate Injection is a sterile solution of dexamethasone sodium phosphate in water for injection. It contains not less than 90.0 percent and not more than 115.0 percent of the labeled amount of dexamethasone phosphate ($C_{22}H_{30}FO_8P$), present as the disodium salt.

Identification—Place 5 ml. of *Assay preparation* in a glass-stoppered, 50-ml. tube, and add 5 ml. of alkaline phosphatase solution, prepared by dissolving 50 mg. of alkaline phosphatase enzyme in 50 ml. of *pH 9 Buffer with magnesium* (see page 176). Allow to stand at 37° for 45 minutes, and extract with 25 ml. of methylene chloride. Evaporate 15 ml. of the methylene chloride extract on a steam bath to dryness, and dissolve the residue in 1 ml. of methylene chloride. On a suitable, thin-layer chromatographic plate, coated with a 0.25-mm. layer of chromatographic silica gel, spot 5 µl. of this solution and 5 µl. of a solution of U. S. P. Dexamethasone Reference Standard in methylene chloride containing 300 mcg. per ml. Allow the spots to dry, and develop the chromatogram in a tank completely lined with a strip of filter paper, using a solvent system consisting of 50 parts of chloroform, 50 parts of acetone, and 1 part of water, until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing tank, mark the solvent front, and allow the spots to dry. Spray the plate with dilute sulfuric acid (1 in 2), and heat at 105° until brown or black spots appear. The R_f value of the main spot obtained from the sample corresponds to that obtained with the Reference Standard.

pH, page 938: between 7.5 and 8.5.

Other requirements—It meets the requirements under *Injections,* page 797.

Assay—

pH 9 Buffer with magnesium—Prepare as directed in the *Assay* under *Dexamethasone Sodium Phosphate,* page 175.

Alkaline phosphatase solution—Transfer 250 mg. of alkaline phosphatase enzyme to a 25-ml. volumetric flask, and dissolve by diluting with *pH 9 Buffer with magnesium* to volume. Prepare this solution fresh daily.

Standard preparation—Place in a 100-ml. volumetric flask about 50 mg. of U. S. P. Dexamethasone Phosphate Reference Standard, accurately weighed, add about 5 ml. of water, then add 2 drops of sodium hydroxide solution (1 in 10), dilute with water to volume, and mix. Pipet 10 ml. of this solution into a 50-ml. volumetric flask, and add water to volume.

Assay preparation—Pipet a volume of Dexamethasone Sodium Phosphate Injection, equivalent to 20 mg. of dexamethasone phosphate, into a 200-ml. volumetric flask, add water to volume, and mix. Pipet 10 ml. of this solution into a 125-ml. separator, and wash with two 25-ml. portions of methylene chloride, discarding the washings.

Procedure—Pipet 3 ml. of the *Assay preparation* and 3 ml. of the *Standard preparation* into separate, 125-ml. separators each containing 8.0 ml. of *Alkaline phosphatase solution,*

and treat each solution as follows: Allow to stand at room temperature for 2 hours. Extract with two 25-ml. portions of methylene chloride, filtering the extracts through methylene chloride–washed cotton into a small beaker. Evaporate the methylene chloride on a steam bath just to dryness, cool, and dissolve the residue in 25.0 ml. of alcohol.

Prepare a blank by evaporating 50 ml. of methylene chloride to dryness and dissolving the residue in 25 ml. of alcohol.

Pipet 20 ml. each of the treated *Assay preparation, Standard preparation,* and blank solution into separate, glass-stoppered flasks, and proceed as directed for *Procedure* under *Total Steroids Assay*, page 912, beginning with "add 2.0 ml. of a solution prepared by dissolving 50 mg. of blue tetrazolium." Calculate the quantity, in mg., of $C_{22}H_{30}FO_8P$ in each ml. of the Injection taken by the formula $0.2(C/V)(A_U/A_S)$, in which C is the concentration, in mcg. per ml., of U. S. P. Dexamethasone Phosphate Reference Standard in the *Standard preparation*, V is the volume, in ml., of Injection taken, and A_U and A_S are the absorbances of the solutions from the *Assay preparation* and *Standard preparation*, respectively.

Packaging and storage—Preserve in single-dose or in multiple-dose containers, preferably of Type I glass.

Injection available—Injection usually available contains the equivalent of the following amount of dexamethasone phosphate: 4 mg. in 1 ml.

CATEGORY and DOSE: See *Dexamethasone Sodium Phosphate.*

Diethylstilbestrol, page 187—Make the following changes in the *Assay.*

In lines 5, 10, and 14 under *Standardization of irradiation procedure,* change "tubes" to:

vessels

Change the *Procedure* to read:

Procedure—Transfer identical volumes of the *Standard preparation* and the *Assay preparation*, respectively, to vessels selected as described under *Standardization of irradiation procedure,* simultaneously irradiate the solutions under the optimum conditions therein established, and measure the absorbances of the solutions in 1-cm. cells at the maximum at 418 mμ, with a suitable spectrophotometer. Concomitantly determine the absorbances of the *Assay preparation* and *Standard preparation* in 1-cm. cells at 418 mμ, using water as the blank, and subtract these values from those for the respective irradiated solutions to obtain the corrected absorbances. Calculate the quantity, in mcg., of $C_{18}H_{20}O_2$ in each ml. of the *Assay preparation* by the formula $10(A_U/A_S)$, in which A_U and A_S are the corrected absorbances of the irradiated *Assay preparation* and *Standard preparation*, respectively.

Diethylstilbestrol Injection, page 188—Delete the last seven sentences of the *Assay,* and substitute therefor the following:

Filter the extracts into a 100-ml. volumetric flask through a chloroform-wetted pledget of cotton, washing the filter with several small portions of chloroform to adjust the solution to volume. If necessary, dilute the solution quantitatively and stepwise with chloroform so that it contains about 10 mcg. of diethylstilbestrol per ml. Transfer 20 ml. of the solution to a 50-ml. conical flask, and evaporate it to about 5 ml., with the aid of gentle heating in a current of air. Complete the evaporation of the solvent in the air current without further application of heat. Dissolve the residue in 10.0 ml. of alcohol, add 10.0 ml. of dibasic potassium phosphate solution (1 in 55), and mix. Using this clear solution as the *Assay preparation,* proceed as directed in the *Assay* under *Diethylstilbestrol,* page 187.

Diethylstilbestrol Suppositories, page 188—Delete the last six sentences of the first paragraph of the *Assay,* and substitute therefor the following:

Filter the extracts into a 250-ml. conical flask through a chloroform-wetted pledget of cotton, washing the filter with several small portions of chloroform. Evaporate the solvent to about 10 ml., with the aid of gentle heating in a current of air. Complete the evaporation of the solvent in the air current without further application of heat. Dissolve the residue in 25.0 ml. of alcohol, add 25.0 ml. of dibasic potassium phosphate solution (1 in 55), and mix. Using this clear solution as the *Assay preparation*, proceed as directed in the *Assay* under *Diethylstilbestrol*, page 187.

Diethylstilbestrol Tablets, page 189—In the next-to-last sentence of the section, *Content uniformity*, change "maximum absorbances" to:

corrected absorbances

Make the following changes in the *Assay*.

Change the second sentence to read:

Weigh accurately not less than 200 mg. of the powder, equivalent to not less than 200 mcg. of diethylstilbestrol, and transfer to a small beaker.

Delete the last six sentences (in lines 9–16 on page 190), and substitute therefor the following:

Transfer a portion of this solution, equivalent to about 200 mcg. of diethylstilbestrol, to a 50-ml. conical flask, and evaporate to about 5 ml. with the aid of gentle heating in a current of air. Proceed as directed in the *Assay* under *Diethylstilbestrol Injection*, page 6 of this Supplement, beginning with "Complete the evaporation of the solvent in the air current."

Digitoxin, page 194—In the *Assay*, make the following changes in the second paragraph under *Procedure*.

In the third sentence, change "pipet 10 ml. of alcohol" to:

pipet 5 ml. of alcohol

In the fourth sentence, change "Pipet 10 ml. of alcohol" to:

Pipet 5 ml. of alcohol
(Official Jan. 1, 1971)

Digitoxin Tablets, page 195—Change the section, *Content uniformity*, to read:

Content uniformity, page 930—Place 1 Tablet in a small beaker, add 5 to 10 drops of water, and allow to disintegrate, then add 5 ml. of acetonitrile that recently has been distilled in glass. Cover the beaker with a watch glass, and heat on a steam bath for 5 minutes. Cool, transfer the solution to a separator with 30 ml. of chloroform and 20 ml. of water, and shake the separator. Separate the chloroform layer, wash in a second separator containing 5 ml. of sodium bicarbonate solution (1 in 100), and filter through a pledget of cotton previously moistened with chloroform into a suitable container. Repeat the extraction and washing, using two 30-ml. portions of chloroform. Evaporate the combined extracts on a steam bath, with the aid of a current of air, to dryness. Dissolve the residue in 80 percent alcohol by shaking for 20 minutes, to obtain a solution having a concentration of about 5 mcg. per ml. Dissolve an accurately weighed quantity of U. S. P. Digitoxin Reference Standard in 80 percent alcohol, and dilute quantitatively and stepwise with 80 percent alcohol to obtain a Standard solution having a known concentration of about 5 mcg. per ml. Pipet into three separate glass-stoppered, 25-ml. flasks 2 ml. of the Standard solution, 2 ml. of the solution from the Tablet, and 2 ml. of 80 percent alcohol

to provide the reagent blank, respectively. Treat each flask as follows: Add 10 ml. of a solution freshly prepared by dissolving 35 mg. of ascorbic acid in 25 ml. of methanol and cautiously adding the solution to 100 ml. of hydrochloric acid. Mix, and add 1 ml. of a solution freshly prepared by diluting 1 ml. of 30 percent hydrogen peroxide with water to 500 ml. and diluting 1 volume of the resulting solution with 20 volumes of water. Allow to stand for 30 minutes. Treating the flasks individually, concomitantly determine the fluorescence readings of the solution from the Tablet and the Standard solution in a suitable fluorometer, against the reagent blank, arranged to deliver activation radiation at 395 mμ and to measure the resultant fluorescence at the emission peak at about 580 mμ. Calculate the quantity, in mg., of $C_{41}H_{64}O_{13}$ in the Tablet by the formula $0.2TC(F_A/F_S)$, in which T is the labeled quantity, in mg., of digitoxin in the Tablet, C is the concentration, in mcg. per ml., of U. S. P. Digitoxin Reference Standard in the Standard solution, and F_A and F_S are the measurements of fluorescence of the solution from the Tablet and the Standard solution, respectively. Digitoxin Tablets meet the requirements for *Tablets*.

Dioctyl Sodium Sulfosuccinate, page 206—Change the definition to read:

Dioctyl Sodium Sulfosuccinate contains not less than 98.5 percent and not more than 100.5 percent of $C_{20}H_{37}NaO_7S$, calculated on the dried basis.

In the section, *Loss on drying*, change "not more than 3 percent" to:

not more than 2 percent

In the section, *Residue on ignition*, change "not more than 16.3 percent" to:

not more than 16.2 percent

Add the following:

Bis(2-ethylhexyl) maleate—Place 11.3 g., accurately weighed, in a 100-ml. volumetric flask. Pipet 20 ml. of pH 10 alkaline borate buffer (see page 939) into the flask, and add about 70 ml. of alcohol. Swirl the flask and contents, with gentle warming, until the solid dissolves. Cool, and add alcohol to volume. Transfer a portion of this test solution to a polarographic cell that is immersed in a water bath regulated at 25 ± 0.5°, and de-aerate by bubbling through the solution, for 10 minutes, purified nitrogen that previously has been passed through a solution prepared by mixing 4 volumes of alcohol and 1 volume of water. Insert the dropping mercury electrode of a suitable polarograph, and record the polarogram from −0.5 volt to −1.6 volts, using a saturated calomel electrode as the reference electrode (see *Polarography*, page 816). Determine the height of the diffusion current at the half-wave potential at about −1.32 volts. To a separate 50-ml. portion of the solution add 25 mg. of bis(2-ethylhexyl) maleate, accurately weighed, and when solution is complete, de-aerate a portion of the resulting solution, and record the polarogram, as directed in the foregoing. The diffusion current for the test solution of Dioctyl Sodium Sulfosuccinate is not greater than that for the solution containing the added bis(2-ethylhexyl) maleate [not more than 0.4 percent of bis(2-ethylhexyl) maleate].

In the *Assay*, change the first sentence under *Dioctyl sodium sulfosuccinate solution* to read:

Transfer about 3 g. of Dioctyl Sodium Sulfosuccinate, accurately weighed and with correction made for moisture content, to a 400-ml. beaker, add 50 ml. of hot water, and stir until a paste is formed.

(Official Sept. 1, 1970)

Diphenhydramine Hydrochloride Capsules, page 208—Insert after the third sentence of the *Assay* (in the fifth line) the following:

Extract the ether layer with 10 ml. of 0.1 *N* sulfuric acid, and add the acid extract to the main aqueous layer.
(Official Sept. 1, 1970)

Diphenhydramine Hydrochloride Elixir, page 208—Change the section, *Identification,* to read:

Identification—To 20 ml. of Elixir in a separator add 0.5 ml. of diluted hydrochloric acid, and extract with three 15-ml. portions of ether, discarding the extracts. Add 5 ml. of water. In a second separator dissolve 50 mg. of U. S. P. Diphenhydramine Hydrochloride Reference Standard in 25 ml. of water. Treat each solution as follows: Add 2 ml. of sodium hydroxide T.S., and extract with three 20-ml. portions of *n*-heptane. Wash the *n*-heptane extracts with 10 ml. of water, evaporate the extracts to dryness, and dissolve the residue in 4 ml. of carbon disulfide. Filter through a dry filter to clarify the solution, if necessary. Without delay, determine the absorption spectra in 1-mm. cells between 7 μ and 15 μ, with a suitable infrared spectrophotometer, using carbon disulfide in a matched cell as the blank. The spectrum of the solution prepared from the sample shows all of the significant absorption bands present in the spectrum of the solution prepared from the Reference Standard.

Delete the second and third sentences of the *Assay,* and substitute therefor the following:

Add 1 ml. of diluted sulfuric acid, and extract with two 25-ml. portions of ether. Combine the ether extracts, and wash them with 10 ml. of 0.1 *N* sulfuric acid, adding the washing to the main aqueous solution. Add 5 ml. of sodium hydroxide T.S., extract with four 25-ml. portions of ether, and combine the ether extracts.
(Official Sept. 1, 1970)

Diphenhydramine Hydrochloride Injection, page 209—Change the second and third sentences of the *Assay* to read:

Wash with two 20-ml. portions of ether, then extract the combined ether washings with 10 ml. of 0.1 *N* sulfuric acid, and add the acid extract to the main aqueous solution. Discard the ether, make the aqueous solution distinctly alkaline with sodium hydroxide T.S., and extract with three 20-ml. portions of ether.
(Official Sept. 1, 1970)

Emetine Hydrochloride Injection, page 224—Change the second sentence of the definition to read:

It contains an amount of anhydrous emetine hydrochloride ($C_{29}H_{40}N_2O_4 \cdot 2HCl$) equivalent to not less than 84.0 percent and not more than 94.0 percent of the labeled amount of emetine hydrochloride.
(Official Jan. 1, 1971)

Ephedrine Sulfate, page 224—In the section, *Specific rotation,* change "not less than $-30.0°$ and not more than $-32.0°$" to:

not less than $-30.5°$ and not more than $-32.5°$
(Official Sept. 1, 1970)

Ergonovine Maleate, page 232—Change the section, *Identification and purity,* to read:

Identification and purity—[NOTE—Conduct this test without exposure to daylight, and with the minimum necessary exposure to artificial light.]

Mobile solvent—Mix 10 volumes of chloroform with 1 volume of methanol.

Standard solutions—Dissolve 20 mg. of U. S. P. Ergonovine Maleate Reference Standard in 5 ml. of alcohol (*Standard solution A*). Dilute 3 ml. of *Standard solution A* with alcohol to 100 ml. (*Standard solution B*).

Procedure—Arrange a suitable chromatographic chamber for thin-layer chromatography. Place sufficient *Mobile solvent* to develop the chromatograms and a beaker containing 25 ml. of stronger ammonia water in the chromatographic chamber, and equilibrate for 30 minutes. On a suitable thin-layer chromatographic plate (see page 796), coated with a 0.25-mm. layer of chromatographic silica gel mixture, spot 0.025-ml. portions of a 1 in 250 solution of Ergonovine Maleate in alcohol and of *Standard solutions A* and *B*. Insert the plate into the chromatographic chamber, and seal. When the *Mobile solvent* has moved 10 cm., remove the plate and dry it in air in a hood. Examine with long-wavelength ultraviolet light (about 365 mμ), and spray the plate with a reagent prepared by dissolving 800 mg. of *p*-dimethylaminobenzaldehyde in a mixture of 80 g. of alcohol and 20 g. of sulfuric acid: the chromatogram of the sample exhibits its principal fluorescent spot and principal blue spot at the same R_f as the principal spot of *Standard solution A*, and no other blue fluorescent spot or blue-colored spot is more intense than that from *Standard solution B*.

(Official Sept. 1, 1970)

Ergonovine Maleate Injection, page 233—Change the second sentence of the section, *Identification and purity,* to read:

Evaporate the combined extracts with the aid of a current of air, but without heat, to dryness: the residue obtained, when dissolved in 0.5 ml. of alcohol, responds to the test for *Identification and purity* under *Ergonovine Maleate*, page 232, a 0.050-ml. portion of this solution being spotted on the thin-layer chromatographic plate.

(Official Sept. 1, 1970)

Ergonovine Maleate Tablets, page 234—Change the second sentence of the section, *Identification and purity,* to read:

Evaporate the combined extracts with the aid of a current of air, but without heat, to dryness: the residue obtained, when dissolved in 0.5 ml. of alcohol, responds to the test for *Identification and purity* under *Ergonovine Maleate*, page 232, a 0.050-ml. portion of this solution being spotted on the thin-layer chromatographic plate.

In the *Assay,* delete the first sentence under *Procedure*, and substitute therefor the following:

Pipet 5 ml. each of the *Standard preparation* and the *Assay preparation* into suitable test tubes. In turn, place each tube in an ice bath, and swirl continuously while adding, dropwise, 10.0 ml. of *p*-dimethylaminobenzaldehyde T.S. Allow to stand in subdued light for 1 hour, and concomitantly determine the absorbances of both solutions at the wavelength of maximum absorbance at about 550 mμ, with a suitable spectrophotometer, against a reagent blank.

(Official Sept. 1, 1970)

Ergotamine Tartrate Injection, page 236—Make the following changes in the *Assay.*

Under *Standard preparation,* change "50 ml. of tartaric acid solution (1 in 100)" to:

50 ml. of diluted alcohol

Change the fourth sentence under *Procedure* to read:

Allow to stand in subdued light at room temperature for not less than 90 minutes and not more than 2 hours.

In the last sentence under *Procedure*, change "at about 550 mμ" to:

at about 545 mμ
(Official Sept. 1, 1970)

Ergotamine Tartrate Tablets, page 237—In the *Assay*, in the third sentence under *Procedure*, change "in subdued light for 1 hour" to:

in subdued light at room temperature for not less than 90 minutes and not more than 2 hours
(Official Sept. 1, 1970)

Conjugated Estrogens, page 242—Change the second line of the *Usual dose* statement to read:

Intramuscular or intravenous, 25 mg.

Change the second line of the *Usual dose range* statement to read:

Intramuscular or intravenous, 25 to 50 mg. daily.
(Official Sept. 1, 1970)

Conjugated Estrogens for Injection, page 245—In the section, *Size available*, change "20 mg." to:

25 mg.
(Official Sept. 1, 1970)

Esterified Estrogens, page 246—Delete the third sentence of the definition, and substitute therefor the following as a second paragraph:

Esterified Estrogens contains not less than 75.0 percent and not more than 85.0 percent of sodium estrone sulfate, and not less than 6.5 percent and not more than 15.0 percent of sodium equilin sulfate, in such proportion that the total of these two components is not less than 90.0 percent, all percentages being calculated on the basis of the total esterified estrogens content.
(Official Sept. 1, 1970)

Ethinyl Estradiol, page 250—In the *Assay*, change the subsection, *Standard preparation*, to read:

Standard preparation—Dissolve about 20 mg. of U. S. P. Ethinyl Estradiol Reference Standard, accurately weighed, in anhydrous methanol contained in a 50-ml. volumetric flask, add anhydrous methanol to volume, and mix. Pipet 5 ml. of this solution into a 100-ml. volumetric flask, add isooctane to volume, and mix. Pipet 5 ml. of the resulting solution into a 50-ml. volumetric flask, add isooctane to volume, and mix.
(Official Jan. 1, 1971)

Ethinyl Estradiol Tablets, page 251—Change the *Assay* to read:

Assay—[NOTE—Observe the precautions with respect to the apparatus and the isooctane set forth in the *Assay* under *Ethinyl Estradiol,* page 250.]

Sulfuric acid–methanol—Prepare as directed in the *Assay* under *Ethinyl Estradiol,* page 250.

Standard preparation—Dissolve about 30 mg. of U. S. P. Ethinyl Estradiol Reference Standard in anhydrous methanol, and dilute the solution with anhydrous methanol to 50 ml. Pipet 5 ml. of this solution into a 100-ml. volumetric flask, add isooctane to volume, and mix. Pipet 5 ml. of the resulting solution into a 50-ml. volumetric flask, add isooctane to volume, and mix.

Assay preparation—Weigh and finely powder not less than 20 Ethinyl Estradiol Tablets. Weigh accurately a portion of the powder, equivalent to about 150 mcg. of ethinyl estradiol, transfer to a 125-ml. conical flask, and add 5 ml. of water. Heat the mixture on a steam bath for 5 minutes, with occasional stirring. Add about 70 ml. of methanol to the warm mixture, insert the stopper in the flask, and shake mechanically for 10 minutes. Filter the mixture into a 100-ml. volumetric flask, rinsing the flask and the filter with several small portions of methanol, dilute the filtrate with methanol to volume, and mix. Transfer 10.0 ml. of the solution to a 30-ml. beaker, and evaporate on a steam bath with the aid of a stream of nitrogen nearly to dryness. Transfer the residue to a 125-ml. separator with three 1-ml. portions of sodium hydroxide T.S. Rinse the beaker with 2 ml. of dilute sulfuric acid (1 in 4), and add the rinsing to the separator. Rinse the beaker with three 25-ml. portions of a 1 in 50 mixture of chloroform in isooctane, successively extracting the aqueous solution with each portion for 2 minutes. Combine the extracts in a second 125-ml. separator through a cotton-pledget filter, and wash the filter with 5 ml. of isooctane.

Procedure—Pipet 5 ml. of the *Standard preparation* into a 125-ml. separator, add 75 ml. of a 1 in 50 mixture of chloroform in isooctane, and mix. Pipet 5 ml. of *Sulfuric acid–methanol* into the separator containing the *Standard preparation* and 5 ml. into that containing the *Assay preparation,* allowing the pipet to drain for not less than 2 minutes. Treat each separator as follows: Shake for 2 minutes, allow to separate completely, and transfer 4.0 ml. of the fluorescent pink phase to a glass-stoppered, 15-ml. centrifuge tube containing 0.50 ml. of methanol. Insert the stopper, mix vigorously, and centrifuge to dispel air bubbles.

Concomitantly determine the absorbances of both solutions in 1-cm. cells at the wavelength of maximum absorbance at about 538 mμ, with a suitable spectrophotometer, using water as the blank. Calculate the quantity, in mcg., of $C_{20}H_{24}O_2$ in the portion of the Tablets taken by the formula $50C(A_U/A_S)$, in which C is the concentration, in mcg. per ml., of U. S. P. Ethinyl Estradiol Reference Standard in the *Standard preparation,* and A_U and A_S are the absorbances of the solutions from the *Assay preparation* and *Standard preparation,* respectively.

Fluorouracil, page 267—In the second sentence of the *Assay,* change "titrate with 0.1 *N* tetrabutylammonium hydroxide in dimethylformamide" to:

titrate with 0.1 *N* tetrabutylammonium hydroxide

(Official Jan. 1, 1971)

Gelatin, page 277—Change the section, *Microbial limits,* to read:

Microbial limits, page 846 and page 33 of this Supplement—The total bacterial count does not exceed 5000 per g., and the tests for *Salmonella* species and *Escherichia coli* are negative.

Chorionic Gonadotropin, page 289—In the section, *Water,* change "0.5 percent" to:

5 percent

Guanethidine Sulfate Tablets, page 293—Make the following changes in the *Assay.*

In the first paragraph, delete the words, "and *Standard preparation.*"

Add the following:

Standard preparation—Dissolve a suitable quantity of U. S. P. Guanethidine Sulfate Reference Standard, previously dried at 105° for 4 hours and accurately weighed, in dilute sulfuric acid (1 in 35) to obtain a solution having a known concentration of about 500 mcg. per ml.

(Official Jan. 1, 1971)

Histamine Phosphate Injection, page 299—In the section, *pH*, change "between 4.0 and 5.0" to:

between 3.0 and 6.0

(Official Sept. 1, 1970)

Hydrocortisone Acetate Ophthalmic Ointment, page 310—Add the following:

Microbial limits, page 846 and page 33 of this Supplement—The total microbial count does not exceed 10 per g., and the tests for *Staphylococcus aureus* and *Pseudomonas aeruginosa* are negative.

Hydroxyprogesterone Caproate Injection, page 320—In the last sentence of the *Assay*, change "$2.5(C/V)(A_U/A_S)$" to:

$5(C/V)(A_U/A_S)$

(Official Jan. 1, 1971)

Idoxuridine Ophthalmic Ointment, page 322—Add the following:

Microbial limits, page 846 and page 33 of this Supplement—The total microbial count does not exceed 10 per g., and the tests for *Staphylococcus aureus* and *Pseudomonas aeruginosa* are negative.

Insulin Injection, page 329—In the section, *Zinc*, change "not less than 0.1 mg. and not more than 0.4 mg." to:

not less than 0.01 mg. and not more than 0.04 mg.

Globin Zinc Insulin Injection, page 330—In the section, *Biological reaction*, in the second sentence under *Solution 3*, change "sodium hydroxide T.S." to:

sodium hydroxide solution (1 in 250)

Isophane Insulin Suspension, page 332—In the section, *Zinc*, change "0.016 mg." to:

0.01 mg.

Insulin Zinc Suspension, page 333—In the fourth sentence of the section, *Insulin not extracted by buffered acetone solution,* change "diluted hydrochloric acid" to:

dilute hydrochloric acid (1 in 100)
(Official Jan. 1, 1971)

Extended Insulin Zinc Suspension, page 333—In the fourth sentence of the section, *Insulin not extracted by buffered acetone solution,* change "diluted hydrochloric acid" to:

dilute hydrochloric acid (1 in 100)
(Official Jan. 1, 1971)

Ipecac, page 343—Change the definition and the *Description* to read:

Ipecac consists of the dried rhizome and roots of *Cephaëlis acuminata* Karsten, known in commerce as Cartagena, Nicaragua, or Panama Ipecac (Fam. *Rubiaceæ*).

Ipecac yields not less than 2.0 percent of the total ether-soluble alkaloids of ipecac. Its content of emetine ($C_{29}H_{40}N_2O_4$) and cephaeline ($C_{28}H_{38}N_2O_4$) together is not less than 90.0 percent of the total amount of the ether-soluble alkaloids. The content of cephaeline varies from an amount equal to, to an amount not more than twice, the content of emetine.

Description: A mixture of segments of the roots and rhizomes. The root segments are mostly curved and flexuous, occasionally branched, up to 15 cm. in length and usually from 3 to 6.5 mm. in diameter, but may be up to 9 mm. in diameter, grayish, grayish brown, or reddish brown, the reddish brown type often having light-colored abrasions, transverse ridges about 0.5 to 1.0 mm. wide that extend about halfway around the circumference of the root and fade at their tapering extremities into the general surface, with from 1 to 6 of these ridges per cm., and annulations sometimes seen at irregular intervals. The rhizomes are cylindrical, about 2 mm. thick, finely longitudinally wrinkled, with a few elliptical scars. The odor is distinctive; the dust is sternutatory. The taste is bitter, nauseating, and acrid.

Histology—At the center of the root is a well-defined primary xylem but no pith. Surrounding this is a dense wood of secondary xylem crossed by medullary rays. These elements are all lignified. External to the wood is a narrow band of secondary phloem and a wide parenchymatous phelloderm surrounded by a narrow layer of cork a few cells thick. The secondary xylem consists of narrow, bordered-pitted tracheidal vessels and tracheids in combination with xylem parenchyma. The latter have simple pits and contain starch grains. Starch is present also in the medullary rays. The phloem occurs as small groups of sieve tissue embedded in parenchyma. The wide phelloderm consists of round-celled cellulose parenchyma filled with starch grains and a few idioblasts, each of which contains a bundle of acicular raphides of calcium oxalate crystals about 30 to 80 μ long. The starch grains are rarely single but usually occur as 2 to 4 and sometimes 8 in a clump. Individual grains measure up to 22 μ in diameter.

The rhizome differs from the root in having a ring of xylem around a large pith. The pericycle contains characteristic sclerenchymatous cells. Spiral vessels are found in the protoxylem. The pith is composed of pitted parenchyma, which is somewhat lignified.

Change the heading, **Assay,** to:

Assay for total ether-soluble alkaloids