British Pharmacopœia 1980

Volume II

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Notices

The General notices included in Volume I of British Pharmacopœia 1980 apply equally to all matter contained in this volume

Patents

In this Pharmacopœia certain drugs and preparations have been included notwithstanding the existence of actual or potential patent rights. In so far as such substances are protected by Letters Patent their inclusion in this Pharmacopœia neither conveys, nor implies, licence to manufacture.

Formulary

The following paragraphs, which are an extension of the General Notices, apply to the statements made in the Formulary section of the British Pharmacopœia.

General Monographs

At the beginning of many sections of the Formulary, a general monograph is included describing the dosage form concerned and in some cases including tests and requirements of general application. These tests and requirements apply to all of the monographs for that dosage form included in the Pharmacopœia, unless otherwise indicated in the individual monograph.

'Water'

The term 'Water' used without qualification in recipes means potable water freshly drawn direct from the public supply and suitable for drinking, or freshly boiled and cooled Purified Water. The latter should be used if the public supply is from a local storage tank and when the potable water is unsuitable for a particular preparation.

'Freshly' and 'Recently' Prepared

The direction that a preparation must be freshly prepared indicates that it must be made not more than twenty-four hours before it is issued for use. The direction that a preparation should be recently prepared indicates that deterioration is likely if the preparation is stored for longer than about four weeks at 15° to 25°. Provided that the preparation has been shown to be stable in other respects, deterioration due to microbial or fungal contamination may be discouraged by the incorporation of suitable antimicrobial preservatives during manufacture. In such circumstances the label on the container states appropriate storage conditions and the date after which the product should not be used.

Labelling

The label on the container states (1) the name given at the head of the monograph, or an approved synonym; (2) except in the case of a monograph in which a fixed recipe is given, the names and proportions of the medicaments; (3) the names and proportions of any added preservatives additional to or alternative to any included in the recipe. The label on the container and the label on the package state a reference, which consists either of figures, or letters, or a combination of figures and letters, by which the history of the preparation may be traced. Additional labelling requirements may be given in General Monographs or in individual monographs where appropriate.

General Processes

Where the process of Maceration or Percolation is specified in a monograph, carry out the following procedures, with any modification indicated in the monograph, if necessary.

Maceration Place the solid materials with the whole of the menstruum in a closed vessel and allow to stand for seven days, shaking occasionally. Strain, press the marc, and mix the liquids obtained. Clarify by subsidence or filtration.

Percolation Moisten the solid materials with a sufficient quantity of the menstruum, allow to stand for four hours in a well-closed vessel, pack in a percolator, and add sufficient of the menstruum to saturate the materials. When the liquid commences to drop from the percolator, close the outlet, add sufficient of the menstruum to leave a layer above the drug, and allow to macerate for twenty-four hours. Allow percolation to proceed slowly until the percolate measures about three-quarters of the required volume. Press the marc, mix the expressed liquid with the percolate, and add sufficient of the menstruum to produce the required volume. Clarify by subsidence or filtration.

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General Processes

Where the process of Maceration or Percolation is specified in a monograph, carry out the following procedures, with any modification indicated in the monograph, if necessary.

Maceration. Place the solid materials with the whole of the menstruum in a closed vessel and allow to stand for seven days, shaking occasionally. Strain, press the marc, and mix the liquids obtained. Clarify by subsidence or filtration.

Percolation. Moisten the solid materials with a sufficient quantity of the menstruum, allow to stand for four hours in a well-closed vessel, pack in a percolator, and add sufficient of the menstruum to saturate the materials. When the liquid commences to drop from the percolator, close the outlet, add sufficient of the menstruum to leave a layer above the drug, and allow to macerate for twenty-four hours. Allow percolation to proceed slowly until the percolate measures about three-quarters of the required volume. Press the marc, mix the expressed liquid with the percolate, and add sufficient of the menstruum to produce the required volume. Clarify by subsidence or filtration.

APPLICATIONS

Applications are liquid or semi-liquid preparations containing one or more medicaments intended for application to the skin. They may contain suitable antimicrobial preservatives.

Labelling Comply with the general requirements for Labelling; in addition the label on the container states that the preparation is intended for external use only.

Benzyl Benzoate Application

Benzyl Benzoate Application may be prepared in the following manner.

Benzyl Benzoate	250 g
Emulsifying Wax	20 g
Purified Water, freshly boiled and cooled	sufficient to produce 1000 ml

Melt the Emulsifying Wax, add the Benzyl Benzoate, and mix. Pour the mixture into sufficient warm Purified Water to produce 1000 ml and stir thoroughly until cold.

Content of benzyl benzoate, $C_{14}H_{12}O_2$ 22.5 to 27.5 per cent w/v.

Assay Carry out the method for *determination of esters*, Appendix VIII L, using 8 g dissolved in 10 ml of the neutralised ethanol and employing 40 ml of 0.5M *ethanolic potassium hydroxide VS*. Each ml of 0.5M *ethanolic potassium hydroxide VS* is equivalent to 0.1061 g of $C_{14}H_{12}O_2$. Calculate the percentage w/v of $C_{14}H_{12}O_2$, assuming the weight per ml of the sample to be 1.02 g.

Labelling The label on the containers states that the contents should be shaken before use.

Gamma Benzene Hexachloride Application

Gamma Benzene Hexachloride	1 g
	or a sufficient quantity
Emulsifying Wax	40 g
Lavender Oil	10 ml
Xylene, of commerce	150 ml
Purified Water, freshly boiled and cooled	sufficient to produce 1000 ml

Dissolve the Gamma Benzene Hexachloride and the Lavender Oil in the xylene, mix the solution with the Emulsifying Wax, previously melted at a low temperature; pour the warm mixture into 750 ml of the Purified Water, previously warmed to the same temperature, stir thoroughly, add sufficient Purified Water to produce 1000 ml, and mix.

Content of gamma benzene hexachloride, $C_6H_6Cl_6$ 90.0 to 110.0 per cent of the prescribed or stated amount.

Identification Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel G* as the coating substance and a mixture of 93 volumes of *hexane* and 7 volumes of *butan-2-one* as the mobile phase. Apply separately to the chromatoplate 5 µl of each of the following solutions. Solution (1) is prepared by shaking a quantity of the application equivalent to 10 mg of Gamma Benzene Hexachloride with 20 ml of *chloroform*, filtering, evaporating the filtrate just to dryness with the aid of gentle heat and dissolving the residue in 1 ml of *acetone*; solution (2) is a 1 per cent w/v solution of *gamma benzene hexachloride* in *acetone*. After removal of the chromatoplate allow it to dry in a current of air and spray with a 0.5 per cent w/v solution of *o-dianisidine* in *acetone*. Expose the chromatoplate to unfiltered ultra-violet light for ten minutes then examine in daylight. The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

Alpha isomer Carry out the procedure described in the Assay using as solution (1) a solution prepared by diluting 1 ml of a 0.00010 per cent w/v solution of *alpha benzene hexachloride* in *acetone* to 100 ml with *hexane*. In the chromatogram obtained with solution (2) the area of the peak due to alpha benzene hexachloride is not greater than the corresponding peak in the chromatogram obtained with solution (1).

Assay Carry out the method for *gas chromatography*, Appendix III B, using the following solutions. For solution (1) dilute 1 ml of a 0.01 per cent w/v solution of *gamma benzene hexachloride* in *acetone* to 100 ml with *hexane*. For solution (2) dissolve a quantity of the application equivalent to 10 mg of Gamma Benzene Hydrochloride in 100 ml of *acetone* and dilute 1 ml to 100 ml with *hexane*. The chromatographic procedure may be carried out using (a) a glass column 1.5 m long and 4 mm in internal diameter packed with 3 per cent w/w of cyanopropylmethyl phenylmethyl silicone fluid (OV 225 is suitable) on *acid-washed silanised, diatomaceous support* (80 to 100 mesh) and maintained at 200°, (b) nitrogen as the carrier gas and (c) an electron capture detector. Calculate the content of $C_6H_6Cl_6$, using the declared content of $C_6H_6Cl_6$ in *gamma benzene hexachloride*.

Labelling The label on the container states that the contents should be shaken before use.

Strength available An Application containing 0.1 per cent w/v of Gamma Benzene Hexachloride is usually available.

Selenium Sulphide Scalp Application

Selenium Sulphide Application

Selenium Sulphide Scalp Application is a suspension of Selenium Sulphide in a suitable liquid basis.

Content of selenium sulphide, SeS_2 90.0 to 110.0 per cent of the prescribed or stated amount.

Identification A. Digest a quantity equivalent to 50 mg of Selenium Sulphide with 5 ml of *nitric acid* for one hour, dilute to 50 ml with *water* and filter. To 5 ml of the filtrate

add 10 ml of *water* and 5 g of *urea*, boil, cool and add 2 ml of *potassium iodide solution*; a yellow to orange colour, which darkens rapidly on standing, is produced.
B. Allow the coloured solution obtained in test A to stand for ten minutes and filter through a bed of *kieselguhr*; the filtrate yields the *reactions* characteristic of sulphates, Appendix VI.

Acidity pH, 4.0 to 5.5, Appendix V L.

Assay To a quantity equivalent to 0.15 g of Selenium Sulphide add 25 ml of *fuming nitric acid*, digest on a water-bath for two hours, cool and dilute to 250 ml with *water*. To 25 ml of this solution add 10 g of *urea* and 25 ml of *water*, boil, cool, add 10 ml of *potassium iodide solution* and 10 ml of *chloroform* and titrate immediately with 0.05M *sodium thiosulphate VS*, using *starch mucilage*, added towards the end of the titration, as indicator. Shake vigorously as the end-point is approached. Each ml of 0.05M *sodium thiosulphate VS* is equivalent to 0.001789 g of SeS_2.

Labelling The label on the container states (1) that the contents should be shaken before use; (2) the directions for using the contents; (3) that the contents should not be used within two days of the application of hair tints or permanent waving; (4) that the contents should not be allowed to come into contact with metals; (5) that all silver jewellery, hairpins and other metal objects should be removed whilst using the contents; (6) that the hands should be carefully washed after using the contents.

Strength available A Scalp Application containing 2.5 per cent w/v of Selenium Sulphide is usually available.

CAPSULES

Capsules are preparations with hard or soft shells, of various shapes and capacities, usually containing a single dose of medicament. They are intended for oral administration.*
The capsule shells are composed of gelatin or other materials, the consistency of which may be adjusted by the addition of substances such as Glycerol and Sorbitol or a mixture of these. Excipients such as surface-active agents, opaque fillers, antimicrobial preservatives, sweetening agents, flavouring agents and authorised colouring agents may be added. Capsules may bear surface markings. The contents of capsules may be of solid, liquid or paste-like consistency. They consist of one or more medicaments, with or without excipients such as solvents, diluents, lubricants, or disintegrating agents. The contents do not cause deterioration of the shell.

Standard for Content of Active Ingredients in Capsules Determine the amount of active ingredient by the method in the Assay; calculate, if necessary, the amount of active ingredient in the capsules taken for the assay and divide by the number of capsules. The result lies within the range for the content of active ingredient stated in the monograph. These ranges are expressed in terms of the weight stated in or indicated by the prescription or order. They have been framed to allow for all permissible variations, including that of the active ingredient itself and that due to the process of manufacturing the capsules. When a biological assay is specified, the standards for the content of active ingredient are set out in the Assay. The ranges are based on the requirement that 20 capsules, or such other number as may be indicated in the monograph, are used in the Assay.
In the circumstances where 20 capsules cannot be obtained, a smaller number, which must not be less than 5, may be used, but to allow for sampling errors the tolerances are widened in accordance with Table I.
The requirements of Table I apply when the stated limits are between 90 and 110 per cent. For limits less than 90 or greater than 110 per cent, proportionately larger allowance should be made.

Storage Capsules should be kept in well-closed containers at temperatures not exceeding 30°.

Labelling Comply with the general requirements for Labelling.

TABLE I

Weight of medicament in each capsule	Subtract from the lower limit for samples of			Add to the upper limit for samples of		
	15	10	5	15	10	5
	—	—	—	—	—	—
0.12 g or less	0.2	0.7	1.6	0.3	0.8	1.8
More than 0.12 g and less than 0.3 g	0.2	0.5	1.2	0.3	0.6	1.5
0.3 g or more	0.1	0.2	0.8	0.2	0.4	1.0

* This dosage form may be used for products intended for routes of administration other than oral, for example rectal or vaginal capsules. Such products need not necessarily comply with the requirements of this monograph.
Cachets (starch capsules) are excluded from the scope of this monograph.

HARD CAPSULES

The shells of the hard capsules consist of two prefabricated cylindrical sections, one end of which is rounded and sealed, the other being open. The contents of the capsule (medicaments with or without excipients) are filled into one of the sections, usually in solid form (powder or granules), which is then closed by slipping the other section over it. The security of the closure may be strengthened by suitable means.

Uniformity of weight Weigh an intact capsule. Open the capsule without losing any part of the shell, and remove the contents as completely as possible. Weigh the shell. The weight of the contents is the difference between the weighings. Repeat the procedure with a further nineteen capsules selected at random. Determine the average weight. Not more than two of the individual weights deviate from the average weight by more than the percentage deviation shown in Table II, and none deviates by more than twice that percentage.

TABLE II

Average weight of capsule contents	Percentage deviation
Less than 300 mg	10
300 mg or more	7.5

Disintegration Comply with the *disintegration test for capsules*, Appendix XII C. In cases where a Dissolution test is applied, it is justifiable to omit the disintegration tests.

SOFT CAPSULES

The shells of soft capsules are thicker than those of hard capsules. They consist of a single part and may be of various shapes. The shells are usually formed, filled and sealed in a combined operation but, in some cases, shells for extemporaneous use may be preformed. The shell material may contain a medicament.

Liquids may be enclosed directly; solids are usually dissolved or dispersed in a suitable excipient to give a paste-like consistency.

Partial migration of the capsule contents and shell constituents may occur because of the nature of the materials and surfaces in contact.

Uniformity of weight Comply with the test for Uniformity of weight described under Hard Capsules. To remove the contents of the capsule, the shell may be washed with *ether* or other suitable solvent, and the shell allowed to stand until the odour of the solvent is no longer perceptible.

Disintegration Comply with the *disintegration test for capsules*, Appendix XII C. In cases where a Dissolution test is applied, it is justifiable to omit the disintegration test.

ENTERIC CAPSULES

Enteric Capsules are hard or soft capsules prepared in such a manner that the shell resists the action of the gastric fluid but is attacked by the intestinal fluid to release the contents.

Uniformity of weight Comply with the test for Uniformity of weight described under Hard Capsules; the contents of soft capsules may be removed as described under Soft Capsules.

Disintegration Use the apparatus described under *disintegration test for tablets*, Appendix XII A, using one capsule in each tube. Operate the apparatus for two hours (or such time as is authorised in the individual monograph, which must be not less than one hour) in 0.1M *hydrochloric acid*. No capsule shows signs of disintegration or of rupture permitting the escape of the contents. Replace the liquid in the beaker with *mixed phosphate buffer pH 6.8*, add the disc to each tube and operate the apparatus for a further sixty minutes. Remove the apparatus from the liquid and examine the capsules. They pass the test if no residue remains on the screen or on the underside of the discs or, if a residue remains, it consists of fragments of shell or of a soft mass with no palpable core.

MODIFIED-RELEASE CAPSULES

Modified-release Capsules are hard or soft capsules in which the contents (for example, where the contents are made gastro-resistant) or the shell, or both, contain added substances or are prepared by a special process designed to modify the rate or the place at which the medicaments are released. Certain preparations intended to prolong the action of the medicament are entitled 'Slow Capsules' in the individual monographs.

Uniformity of weight Comply with the test for Uniformity of weight described under Hard Capsules; the contents of soft capsules may be removed as described under Soft Capsules.

Disintegration Modified-release capsules do not necessarily comply with the disintegration test for capsules.

Alclofenac Capsules

Alclofenac Caps.

Alclofenac Capsules contain Alclofenac.

Content of alclofenac, $C_{11}H_{11}ClO_3$ 95.0 to 105.0 per cent of the prescribed or stated amount.

Identification Extract a quantity of the contents of the capsules equivalent to 100 mg of Alclofenac with 10 ml of *absolute ethanol*, filter and evaporate the filtrate to dryness. The residue, after drying at 60° at a pressure not exceeding 0.7 kPa (about 5 torr), complies with the following tests.

A. The *infra-red absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of alclofenac.

B. *Melting point*, about 91°, Appendix V A.

Phenolic compounds Comply with the test described under Alclofenac using a quantity of the contents of the capsules equivalent to 100 mg of Alclofenac.

Assay Dissolve a quantity of the mixed contents of 20 capsules equivalent to 0.5 g of Alclofenac in 100 ml of *ethanol (96 per cent)*, previously neutralised to *phenolphthalein solution* and titrate with 0.1M *sodium hydroxide VS* using *phenolphthalein solution* as indicator. Each ml of 0.1M *sodium hydroxide VS* is equivalent to 0.02267 g of $C_{11}H_{11}ClO_3$.

Usual Dose Range Alclofenac, 1.5 to 3 g daily, in divided doses.

Strengths available Capsules containing, in each, 500 mg are usually available.

Amoxycillin Capsules

Amoxycillin Caps.

Amoxycillin Capsules contain Amoxycillin Trihydrate.

Content of amoxycillin, $C_{16}H_{19}N_3O_5S$ 92.5 to 110.0 per cent of the prescribed or stated amount.

Identification Shake a quantity of the contents of the capsules equivalent to 0.5 g of amoxycillin with 5 ml of *water* for five minutes, filter, wash the residue first with *absolute ethanol* and then with *ether*, and dry under reduced pressure for one hour. The residue complies with the tests for Identification described under Amoxycillin Trihydrate.

Assay To a quantity of the mixed contents of 20 capsules equivalent to 0.15 g of amoxycillin, add sufficient *water* to produce 500 ml, shake for thirty minutes, filter, and complete the Assay described under Amoxycillin Trihydrate, beginning at the words 'Transfer 10 ml...'.

Labelling The quantity of the active ingredient is stated in terms of the equivalent amount of amoxycillin. The label on the container also states (1) the date after which the capsules are not intended to be used; (2) the conditions under which they should be stored.

Usual Dose Range The equivalent of 750 mg to 4500 mg of amoxycillin daily, in divided doses.

Strength available Capsules containing, in each, the equivalent of 250 mg of amoxycillin are usually available.

Ampicillin Capsules

Ampicillin Caps.

Ampicillin Capsules contain Ampicillin or Ampicillin Trihydrate.

Content of ampicillin, $C_{16}H_{19}N_3O_4S$ 92.5 to 107.5 per cent of the prescribed or stated amount.

Identification The contents of the capsules comply with the following tests.

A. Place 0.1 ml of a 0.1 per cent w/v solution of *ninhydrin* on a filter paper, dry at 105°, superimpose 0.1 ml of a 0.1 per cent w/v solution of the substance being examined, heat for five minutes at 105°, and allow to cool; a mauve colour is obtained.

B. Suspend 10 mg in 1 ml of *water* and add 2 ml of a mixture of 2 ml of *potassium cupri-tartrate solution* and 6 ml of *water*; a magenta-violet colour is immediately produced.

Assay To a quantity of the mixed contents of 20 capsules equivalent to 0.15 g of ampicillin, add sufficient *water* to produce 500 ml, shake for thirty minutes, filter, and complete the Assay described under Ampicillin, beginning at the words 'Transfer 10 ml...'.

Labelling When the active ingredient is Ampicillin Trihydrate, the quantity is stated in terms of the equivalent amount of ampicillin. The label on the container states (1) the date after which the capsules are not intended to be used; (2) the conditions under which they should be stored.

Usual Dose Range Ampicillin, 1 to 8 g daily, in divided doses.

Strengths available Capsules containing, in each, 250 mg and 500 mg of Ampicillin or an equivalent amount of Ampicillin Trihydrate are usually available.

Amylobarbitone Sodium Capsules

Amylobarb. Sod. Caps.; Amobarbital Sodium Capsules

Amylobarbitone Sodium Capsules contain Amylobarbitone Sodium.

Content of amylobarbitone sodium, $C_{11}H_{17}N_2NaO_3$ 92.5 to 107.5 per cent of the prescribed or stated amount.

Identification A. Dissolve 0.2 g of the residue obtained in the Assay in 25 ml of boiling *ethanol (25 per cent)*, filter, and allow the filtrate to cool. The crystals, after drying at 105°, have a *melting point* of about 156°, Appendix V A, and comply with the following tests:

The *infra-red absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of amylobarbitone.

Dissolve 50 mg in 2 ml of a 0.2 per cent w/v solution of *cobalt(II) acetate* in *methanol*, warm, add 50 mg of powdered *sodium tetraborate*, and heat to boiling; a bluish-violet colour is produced.

B. Shake a quantity of the contents of the capsules equivalent to 0.1 g of Amylobarbitone Sodium with 10 ml of *water* and filter. To the filtrate add 2 ml of 2M *hydrochloric acid*; a white precipitate is produced (distinction from amylobarbitone).

C. The contents of the capsules, when moistened with *hydrochloric acid* and introduced on a platinum wire into the flame of a Bunsen burner, give a yellow colour to the flame.

Assay Dissolve a quantity of the mixed contents of 20 capsules equivalent to 0.3 g of Amylobarbitone Sodium as completely as possible in 10 ml of a 2 per cent w/v solution of *sodium hydroxide*, saturate with *sodium chloride*, acidify with *hydrochloric acid*, and extract with successive quantities, each of 15 ml, of *ether* until complete extraction is effected. Wash the combined extracts with two quantities, each of 2 ml, of *water* and extract the combined washings with 10 ml of *ether*. Add the ether to the main ether layer, filter, and wash the filter with *ether*. Evaporate the solvent and dry the residue to constant weight at 105°. Each g of residue is equivalent to 1.097 g of $C_{11}H_{17}N_2NaO_3$.

Usual Dose Range Amylobarbitone Sodium. As a hypnotic, 100 to 200 mg; as a sedative, up to 600 mg daily, in divided doses.

Strengths available Capsules containing, in each, 60 mg and 200 mg are usually available.

Cephalexin Capsules

Cephalexin Caps.

Cephalexin Capsules contain Cephalexin.

Content of cephalexin, $C_{16}H_{17}N_3O_4S$ 92.5 to 110.0 per cent of the prescribed or stated amount.

Identification Shake a quantity of the contents of the capsules equivalent to 0.5 g of Cephalexin with 1 ml of

water and 1.4 ml of M *hydrochloric acid*, filter, and wash the filter with 1 ml of *water*. Add, slowly, to the filtrate a saturated solution of *sodium acetate* until precipitation occurs. Add 5 ml of *methanol*, filter, and wash the precipitate with two quantities, each of 1 ml, of *methanol*. The residue, after drying at a pressure not exceeding 0.7 kPa (about 5 torr), complies with the following tests.
A. The *infra-red absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of cephalexin.
B. Mix 20 mg with 0.25 ml of an 80 per cent v/v solution of *sulphuric acid* containing 1 per cent v/v of *nitric acid*; a yellow colour is produced.
C. Mix 20 mg with 0.25 ml of a 1 per cent v/v solution of *glacial acetic acid* and add 0.1 ml of a 1 per cent w/v solution of *copper(II) sulphate* and 0.1 ml of 2M *sodium hydroxide*; an olive green colour is produced.

Disintegration Maximum time, fifteen minutes, using a 0.6 per cent v/v solution of *hydrochloric acid* in place of *water*, Appendix XII C.

Assay To a quantity of the powdered, mixed contents of 20 capsules equivalent to 0.25 g of Cephalexin add 100 ml of *water* and shake for thirty minutes. Add sufficient *water* to produce 250 ml and filter. Using the filtrate so obtained complete the Assay described under Cephalexin, beginning at the words 'Transfer 10 ml...'.

Labelling The label on the container states (1) the date after which the capsules are not intended to be used; (2) the conditions under which they should be stored.

Usual Dose Range Cephalexin, 1 to 4 g daily, in divided doses.

Strengths available Capsules containing, in each, 250 mg and 500 mg are usually available.

Cephradine Capsules

Cephradine Caps.

Cephradine Capsules contain Cephradine.

Content of cephradine, $C_{16}H_{19}N_3O_4S$ 90.0 to 110.0 per cent of the prescribed or stated amount.

Identification The contents of the capsules comply with tests for Identification A and B described under Cephradine.

Loss on drying When dried for three hours at 60° at a pressure not exceeding 0.7 kPa (about 5 torr) the contents of the capsules lose not more than 8.0 per cent of their weight.

Disintegration Maximum time, fifteen minutes, using a 0.6 per cent v/v solution of *hydrochloric acid* in place of *water*, Appendix XII C.

Related substances Carry out the test described under Cephradine on the contents of the capsules, applying separately to the chromatoplate, as streaks about 3 cm wide, 40 µl of each of three solutions freshly prepared as follows. For solution (1) shake, for forty-five minutes, an amount of the contents of the capsules equivalent to 100 mg of Cephradine with 25 ml of 0.01M *ammonia*. For solution (2) dilute 100 µl of solution (1) to 20 ml with 0.01M *ammonia*. Solution (3) is a solution in 0.1M *ammonia* containing 0.040 per cent w/v of *cephalexin BPCRS*, 0.0040 per cent w/v of *cyclohexa-1,4-dienylglycine BPCRS* and 0.0040 per cent w/v of *7-aminodesacetoxycephalosporanic acid BPCRS*. The bands in the chromatogram obtained with solution (3) are more intense than any corresponding bands in the chromatogram obtained with solution (1). Any other secondary bands in the chromatogram obtained with solution (1) are not more intense than the band in the chromatogram obtained with solution (2).

Assay Carry out the Assay described under Cephradine using a quantity of the powdered mixed contents of 20 capsules.

Labelling The label on the container states (1) the date after which the capsules are not intended to be used; (2) the conditions under which they should be stored.

Usual Dose Range Cephradine, 1 to 4 g daily, in divided doses.

Strengths available Capsules containing, in each, 250 mg and 500 mg are usually available.

Chloramphenicol Capsules

Chloramphen. Caps.

Chloramphenicol Capsules contain Chloramphenicol.

Content of chloramphenicol, $C_{11}H_{12}Cl_2N_2O_5$ 95.0 to 105.0 per cent of the prescribed or stated amount.

Identification Suspend a quantity of the contents of the capsules equivalent to 1.25 g of Chloramphenicol in 60 ml of *water* and extract with two quantities, each of 20 ml, of *petroleum spirit* (*boiling range, 120° to 160°*); wash the combined extracts with two quantities, each of 15 ml, of *water*, add the washings to the aqueous layer, extract with four quantities, each of 50 ml, of *ether* and remove the ether from the combined extracts. The residue complies with the following tests.
A. Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel GF254* as the coating substance and a mixture of 9 volumes of *chloroform*, 1 volume of *methanol*, and 0.1 volume of *water* as the mobile phase. Apply separately to the chromatoplate 1 µl of each of two solutions in *ethanol* (*96 per cent*) containing (1) 1 per cent w/v of the residue and (2) 1 per cent w/v of *chloramphenicol EPCRS*. After removal of the chromatoplate, allow it to dry in air and examine under an ultraviolet lamp having a maximum output at about 254 nm. The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).
B. Dissolve about 10 mg in 2 ml of *ethanol* (*50 per cent*), add 4.5 ml of M *sulphuric acid* and about 50 mg of *zinc powder*, and allow to stand for ten minutes. Decant the supernatant liquid or filter if necessary. Cool the resulting solution in ice and add 0.5 ml of *sodium nitrite solution* and after two minutes, 1 g of *urea*, followed by 1 ml of *2-naphthol solution* and 2 ml of 10M *sodium hydroxide*; a red colour develops. Repeat the test omitting the *zinc powder*; no red colour is produced.

2-Amino-1-(4-nitrophenyl)propane-1,3-diol Not more than 1.0 per cent of the content of chloramphenicol determined by the following method. To a quantity of the contents of the capsules equivalent to 0.75 g of Chloramphenicol add 10 ml of M *hydrochloric acid*. Extract with 30 ml of *ether*, previously shaken with M *hydrochloric acid*, followed by three quantities, each of 10 ml, of the *ether* and discard the extracts. Dilute the aqueous solution to 100 ml with M *hydrochloric acid*, filter and dilute 10 ml of the

filtrate to 100 ml with M *hydrochloric acid*. Measure the *absorbance* of the resulting solution at the maximum at about 272 nm, Appendix II B. Calculate the content of 2-amino-1-(4-nitrophenyl)propane-1,3-diol, taking 474 as the value of A(1 per cent, 1 cm) at the maximum at about 272 nm.

Assay Dissolve a quantity of the mixed contents of 20 capsules equivalent to 0.2 g of Chloramphenicol in 800 ml of *water*, warming if necessary to effect solution, and add sufficient *water* to produce 1000 ml. Dilute 10 ml of this solution to 100 ml with *water* and measure the *absorbance* of the resulting solution at the maximum at about 278 nm, Appendix II B. Calculate the content of $C_{11}H_{12}Cl_2N_2O_5$, taking 298 as the value of A(1 per cent, 1 cm) at the maximum at about 278 nm.

Labelling The label on the container states (1) the date after which the capsules are not intended to be used; (2) the conditions under which they should be stored.

Usual Dose Range Chloramphenicol, for an adult, 1.5 to 4 g daily, in divided doses; for a child, 25 to 50 mg per kg of body weight daily, in divided doses.

Strength available Capsules containing, in each, 250 mg are usually available.

Chlordiazepoxide Capsules

Chlordiazepoxide Caps.

Chlordiazepoxide Capsules contain Chlordiazepoxide Hydrochloride.

Content of chlordiazepoxide hydrochloride, $C_{16}H_{14}ClN_3O,HCl$ 92.5 to 107.5 per cent of the prescribed or stated amount.

Identification A. The light absorption, in the range 280 to 350 nm, of the solution obtained in the Assay exhibits a maximum only at 308 nm.

B. Dilute 1 volume of the solution obtained in the Assay to 3 volumes with 0.1M *hydrochloric acid*. The light absorption, in the range 230 to 280 nm, exhibits a maximum only at 246 nm; *absorbance* at 246 nm, about 1.0, Appendix II B.

C. Shake a quantity of the contents of the capsules with *water* and filter; the filtrate yields *reaction A* characteristic of chlorides, Appendix VI.

Related substances and decomposition products Carry out in subdued light the method for *thin-layer chromatography*, Appendix III A, using *silica gel HF254* as the coating substance and a mixture of 47.5 volumes of *ethyl acetate* and 2.5 volumes of *absolute ethanol* as the mobile phase, but allowing the solvent front to ascend 12 cm above the line of application. Prepare immediately before use the following three solutions in *acetone* containing 2 per cent v/v of 13.5M *ammonia* and 8 per cent v/v of *water*; for solution (1) shake a quantity of the contents of the capsules equivalent to 0.10 g of Chlordiazepoxide Hydrochloride with 10 ml of the solvent, allow to settle and decant the clear supernatant liquid; for solution (2) dilute 3 volumes of solution (1) to 100 volumes with the same solvent; (3) a 0.0010 per cent w/v solution of *2-amino-5-chlorobenzophenone*. Apply separately to the chromatoplate 2 µl and 20 µl of solution (1), 2 µl of solution (2) and 20 µl of solution (3). After removal of the chromatoplate allow the solvent to evaporate and examine under an ultra-violet lamp having a maximum output at about 254 nm. Any spot in the chromatogram obtained with 2 µl of solution (1), other than the principal spot, is not more intense than the spot in the chromatogram obtained with solution (2). Treat the chromatoplate by *Method I*, Appendix III A. The spot in the chromatogram obtained with solution (3) is more intense than any corresponding spot in the chromatogram obtained with 20 µl of solution (1).

Assay Protect the solutions from light throughout the assay. Shake a quantity of the mixed contents of 20 capsules equivalent to 20 mg of Chlordiazepoxide Hydrochloride with 150 ml of 0.1M *hydrochloric acid* for twenty minutes. Add sufficient 0.1M *hydrochloric acid* to produce 250 ml and filter. Dilute 10 ml of the filtrate to 50 ml with 0.1M *hydrochloric acid* and measure the *absorbance* of the resulting solution at the maximum at about 308 nm, Appendix II B. Calculate the content of $C_{16}H_{14}ClN_3O$, HCl taking 292 as the value of A(1 per cent, 1 cm) at the maximum at about 308 nm.

Storage Chlordiazepoxide Capsules should be protected from light.

Usual Dose Range Chlordiazepoxide Hydrochloride, 10 to 60 mg daily, in divided doses.

Strengths available Capsules containing, in each, 5 and 10 mg are usually available.

Chlorotrianisene Capsules

Chlorotrianisene Caps.

Chlorotrianisene Capsules contain a solution of Chlorotrianisene in Maize Oil.

Content of chlorotrianisene, $C_{23}H_{21}ClO_3$ 90.0 to 110.0 per cent of the prescribed or stated amount.

Identification Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel G* as the coating substance and a mixture of ninety-two volumes of *1,2-dichloroethane*, 8 volumes of *methanol*, and 0.5 volume of *water* as the mobile phase. Apply separately to the chromatoplate 1 µl of each of the following solutions. For solution (1) shake a quantity of the contents of the capsules equivalent to 24 mg of Chlorotrianisene with 5 ml of *ethanol (96 per cent)*, allow to separate, and use the upper layer. Solution (2) is a 0.1 per cent w/v solution of *chlorotrianisene BPCRS* in *ethanol (96 per cent)*. After removal of the chromatoplate, allow it to dry in air for a few minutes, heat at 110° for ten minutes, spray while still warm with a 10 per cent v/v solution of *sulphuric acid* in *absolute ethanol*, and heat at 110° for a further ten minutes. The chromatogram obtained with solution (1) shows a pink spot corresponding in position to the pink spot in the chromatogram obtained with solution (2).

Assay Weigh 10 capsules. Open the capsules carefully without loss of shell material, express as much of the contents as possible, and reserve the expressed material. Wash the shells with *ether*, add the washings to the expressed contents, allow the shells to stand at room temperature until the odour of ether is no longer perceptible, and weigh. The difference between the weights represents the weight of the total contents. Evaporate the ether from the combined contents and washings, removing the last traces with a current of warm air. Carry out the Assay described under Chlorotrianisene, using a quantity of the residue equivalent to 80 mg of Chlorotrianisene, 0.02M *ammonium thiocyanate VS*, and 0.02M *silver nitrate*

VS. Each ml of 0.02M *silver nitrate VS* is equivalent to 0.007618 g of $C_{23}H_{21}ClO_3$.

Usual Dose Range Chlorotrianisene. For the relief of menopausal symptoms, 12 to 48 mg daily, for thirty days. In the treatment of carcinoma of the prostate, 12 to 24 mg daily.

Strength available Capsules containing, in each, 12 mg are usually available.

Chlortetracycline Capsules

Chlortetracycline Caps.

Chlortetracycline Capsules contain Chlortetracycline Hydrochloride.

Identification A. The contents of the capsules comply with test for Identification A described under Doxycycline Hydrochloride, solution (1) being freshly prepared by extracting a quantity of the contents of the capsules equivalent to 10 mg of Chlortetracycline Hydrochloride with 20 ml of *methanol*, centrifuging, and using the supernatant liquid; solution (2) is a freshly prepared 0.05 per cent w/v solution of *chlortetracycline hydrochloride EPCRS* in *methanol*.

B. To a quantity of the contents of the capsules equivalent to 10 mg of Chlortetracycline Hydrochloride, add 20 ml of warm *ethanol (96 per cent)*, allow to stand for twenty minutes, filter, and evaporate to dryness on a water-bath. The residue complies with the following tests:

To 0.5 mg add 2 ml of *sulphuric acid*; a deep blue colour is produced, which becomes bluish-green. Add 1 ml of *water*; a brown colour is produced.

A 0.1 per cent w/v solution yields a precipitate with *iodine solution* and with *trinitrophenol solution*.

A 0.1 per cent w/v solution in *phosphate buffer pH 7.6*, heated at 100° for one minute, exhibits a strong blue fluorescence in ultra-violet light.

Dissolution Comply with the *dissolution test for tablets and capsules*, Appendix XII D, using as the medium 1000 ml of 0.1M *hydrochloric acid* and placing one capsule in the basket assembly for each test. Withdraw a sample of 10 ml of the medium. Measure the *absorbance* of the filtered sample, suitably diluted if necessary, at the maximum at about 266 nm, Appendix II B. Calculate the total content of chlortetracycline hydrochloride, $C_{22}H_{23}ClN_2O_8,HCl$, in the medium, taking 346 as the value of A(1 per cent, 1 cm) at the maximum at about 266 nm.

Loss on drying When dried at 60° at a pressure not exceeding 0.7 kPa (about 5 torr) for three hours, the contents of the capsules lose not more than 2.0 per cent of their weight.

Assay To a quantity of the mixed contents of 20 capsules equivalent to 0.25 g of Chlortetracycline Hydrochloride, add 500 ml of *water*, mix, and carry out the *biological assay of antibiotics*, Appendix XIV A. The precision of the assay is such that the fiducial limits of error are not less than 95 per cent and not more than 105 per cent of the estimated potency.

Calculate the content of chlortetracycline hydrochloride in the average weight of the contents of the capsules, taking each 1000 Units found to be equivalent to 1 mg of chlortetracycline hydrochloride. The upper fiducial limit of error is not less than 95.0 per cent, and the lower fiducial limit of error is not more than 110.0 per cent, of the prescribed or stated content.

Labelling The label on the container states (1) the date after which the capsules are not intended to be used; (2) the conditions under which they should be stored.

Usual Dose Range Chlortetracycline Hydrochloride, 1 to 3 g daily, in divided doses.

Strengths available Capsules containing, in each, 250 mg are usually available.

Clindamycin Capsules

Clindamycin Caps.

Clindamycin Capsules contain Clindamycin Hydrochloride.

Content of clindamycin, $C_{18}H_{33}ClN_2O_5S$ 90.0 to 110.0 per cent of the prescribed or stated amount.

Identification In the Assay the retention time of the principal peak due to clindamycin hydrochloride in the chromatogram obtained with solution (3) is the same as the retention time of the principal peak due to *clindamycin hydrochloride BPCRS* in the chromatogram obtained with solution (1).

Water The contents of the capsules contain not more than 7.0 per cent w/w of water, Appendix IX C; use 1 g.

Assay Carry out the Assay described under Clindamycin Hydrochloride, using in the preparation of solutions (2) and (3) a quantity of the mixed contents of 20 capsules, equivalent to 50 mg of clindamycin hydrochloride.

Labelling The quantity of the active ingredient is stated in terms of the equivalent amount of clindamycin.

The label on the container states (1) the date after which the capsules are not intended to be used; (2) the conditions under which they should be stored.

Usual Dose Range The equivalent of 600 mg to 1800 mg of clindamycin daily, in divided doses.

Strengths available Capsules containing, in each, the equivalent of 75 mg and 150 mg of clindamycin are usually available.

Clofibrate Capsules

Clofibrate Caps.

Clofibrate Capsules contain Clofibrate. The contents of the capsules comply with the requirements for Identification, Light absorption, Refractive index, Weight per ml, and Volatile related substances described under Clofibrate, and with the following requirements.

Free acidity Add 10.0 ml of the contents of the capsules to 100 ml of *ethanol (96 per cent)* previously neutralised to *phenolphthalein solution* with 0.1M *sodium hydroxide VS* and titrate with 0.1M *sodium hydroxide VS*; not more than 2.5 ml is required.

Free phenolic bodies Comply with the test described

under Clofibrate using a quantity of the contents of the capsules equivalent to 10.0 g of Clofibrate in the preparation of solution (2).

Uniformity of weight Carry out the test for Uniformity of weight for Soft Capsules, described under Capsules. The average weight of the contents of the twenty capsules is not less than 92.5 per cent and not more than 107.5 per cent of the prescribed or stated weight.

Usual Dose Range Clofibrate, up to 2 g daily, in divided doses, in accordance with the response of the patient.

Strength available Capsules containing, in each, 500 mg are usually available.

Cloxacillin Capsules

Cloxacillin Caps.

Cloxacillin Capsules contain Cloxacillin Sodium.

Content of cloxacillin, $C_{19}H_{18}ClN_3O_5S$ 92.5 to 107.5 per cent of the prescribed or stated amount.

Identification A. The *infra-red absorption spectrum*, Appendix II A, of the contents of the capsules is concordant with the *reference spectrum* of cloxacillin sodium.
B. The contents of the capsules yield the *reactions* characteristic of sodium salts, Appendix VI.

Assay To a quantity of the mixed contents of 20 capsules equivalent to 250 mg of cloxacillin, add 70 ml of *water*, shake for fifteen minutes, and add sufficient *water* to produce 500 ml. Filter and dilute 10 ml of the filtrate to 100 ml with *water*. Complete the Assay described under Cloxacillin Sodium, beginning at the words 'Pipette two 2-ml aliquots...', but calculating the content of $C_{19}H_{18}ClN_3O_5S$ using the declared content of $C_{19}H_{18}ClN_3O_5S$ in the *cloxacillin sodium BPCRS*.

Labelling The quantity of the active ingredient is stated in terms of the equivalent amount of cloxacillin. The label on the container also states (1) the date after which the capsules are not intended to be used; (2) the conditions under which they should be stored.

Usual Dose Range The equivalent of 1.5 to 3 g of cloxacillin daily, in divided doses.

Strengths available Capsules containing, in each, the equivalent of 250 mg and 500 mg of cloxacillin are usually available.

Cycloserine Capsules

Cycloserine Caps.

Cycloserine Capsules contain Cycloserine.

Content of cycloserine, $C_3H_6N_2O_2$ 90.0 to 110.0 per cent of the prescribed or stated amount.

Identification Shake a quantity of the contents of the capsules equivalent to 10 mg of Cycloserine with 100 ml of 0.1M *sodium hydroxide* and filter. To 1 ml of the filtrate add 3 ml of M *acetic acid* and 1 ml of a freshly prepared mixture of equal parts of a 4 per cent w/v solution of *sodium nitroprusside* and 5M *sodium hydroxide*; a blue colour gradually develops.

Light absorption Shake a quantity of the contents of the capsules equivalent to 0.25 g of Cycloserine with 80 ml of 0.1M *sodium hydroxide* for ten minutes, add sufficient 0.1M *sodium hydroxide* to produce 100 ml, mix, and filter. Dilute 5 ml of the filtrate to 1000 ml with 0.1M *hydrochloric acid*. *Absorbance* of the resulting solution at the maximum at about 219 nm, measured within fifteen minutes of making the dilution with acid, 0.39 to 0.48, Appendix II B.

Loss on drying When dried at 60° at a pressure not exceeding 0.7 kPa (about 5 torr) for three hours, the contents of the capsules lose not more than 2.0 per cent of their weight.

Assay Shake a quantity of the mixed contents of 20 capsules equivalent to 0.1 g of Cycloserine with 150 ml of *water* for thirty minutes, add sufficient *water* to produce 200 ml, and filter. To 10 ml of the filtrate add 10 ml of *water* and 25 ml of 0.2M *sodium hydroxide*, dilute to 50 ml with *water*, and mix. To 4 ml of the mixture add 10 ml of M *acetic acid* and 4 ml of *sodium nitroprusside solution*, dilute to 20 ml with M *acetic acid*, mix, and allow to stand for fifteen minutes. Measure the *absorbance* of the resulting solution at the maximum at about 625 nm, Appendix II B, using as the blank a solution prepared by treating 4 ml of 0.1M *sodium hydroxide* in the same manner, beginning at the words 'add 10 ml...'. Calculate the content of cycloserine, $C_3H_6N_2O_2$, from the *absorbance* obtained by repeating the operation using *cycloserine BPCRS* instead of the contents of the capsules.

Labelling The label on the container states (1) the date after which the capsules are not intended to be used; (2) the conditions under which they should be stored.

Usual Dose Range Cycloserine, 250 to 750 mg daily, in divided doses.

Strengths available Capsules containing, in each, 125 mg and 250 mg are usually available.

Demeclocycline Capsules

Demeclocycline Caps.

Demeclocycline Capsules contain Demeclocycline Hydrochloride.

Identification A. The contents of the capsules comply with test for Identification A described under Doxycycline Hydrochloride, solution (1) being freshly prepared by extracting a quantity of the contents of the capsules equivalent to 10 mg of Demeclocycline Hydrochloride with 20 ml of *methanol*, centrifuging, and using the supernatant liquid; solution (2) is a freshly prepared 0.05 per cent w/v solution of *demeclocycline hydrochloride EPCRS* in *methanol*.

B. To a quantity of the contents of the capsules equivalent to 10 mg of Demeclocycline Hydrochloride, add 20 ml of warm *methanol*, allow to stand for twenty minutes, filter, and evaporate the filtrate to dryness on a water-bath. The residue complies with the following tests:

To 0.5 mg add 2 ml of *sulphuric acid*; a purple colour is produced. Add 1 ml of *water*; the colour changes to yellow.

To 1 mg add 7 ml of *water* and 7 ml of 2M *hydrochloric acid* and heat gently for thirty seconds; no colour is produced immediately.

Loss on drying When dried at 60° at a pressure not

exceeding 0.7 kPa (about 5 torr) for three hours, the contents of the capsules lose not more than 5.0 per cent of their weight.

Assay To a quantity of the mixed contents of twenty capsules equivalent to 0.25 g of Demeclocycline Hydrochloride, add 500 ml of *water*, mix, and carry out the *biological assay of antibiotics*, Appendix XIV A. The precision of the assay is such that the fiducial limits of error are not less than 95 per cent and not more than 105 per cent of the estimated potency.

Calculate the content of demeclocycline hydrochloride in the average weight of the contents of the capsules, taking each 1000 Units found to be equivalent to 1 mg of demeclocycline hydrochloride. The upper fiducial limit of error is not less than 95.0 per cent, and the lower fiducial limit of error is not more than 110.0 per cent, of the prescribed or stated content.

Labelling The label on the container states (1) the date after which the capsules are not intended to be used; (2) the conditions under which they should be stored.

Usual Dose Range Demeclocycline Hydrochloride, 300 to 900 mg daily, in divided doses.

Strengths available Capsules containing, in each, 150 mg and 300 mg are usually available.

Dextropropoxyphene Capsules

Dextropropoxyphene Caps.; Propoxyphene Capsules

Dextropropoxyphene Capsules contain Dextropropoxyphene Napsylate.

Content of dextropropoxyphene, $C_{22}H_{29}NO_2$ 92.5 to 107.5 per cent of the prescribed or stated amount.

Identification Shake a quantity of the contents of the capsules equivalent to 150 mg of dextropropoxyphene with 5 ml of *chloroform* and filter. The filtrate complies with the following tests.

A. The *infra-red absorption spectrum*, Appendix II A, is concordant with the appropriate *reference spectrum* of dextropropoxyphene napsylate.

B. Evaporate 0.05 ml in a porcelain dish and streak the spot with *sulphuric acid* containing 0.05 ml of *formaldehyde solution* per ml; a purple colour is produced.

C. Evaporate 0.4 ml on a piece of filter paper and burn the residue by the method for *oxygen flask combustion*, Appendix VIII C, using 5 ml of 1.25M *sodium hydroxide* as the absorbing liquid. When the process is complete, dilute the liquid to 25 ml with *water*. To 5 ml of the solution so obtained add 1 ml of *hydrogen peroxide solution* (*100 vol*) and 1 ml of M *hydrochloric acid*, mix, and add 0.05 ml of *barium chloride solution*; a turbidity is produced.

Assay Stir a quantity of the mixed contents of 20 capsules equivalent to 0.5 g of dextropropoxyphene with 25 ml of *chloroform* and filter through a plug of cotton wool, washing the flask and filter with small quantities of *chloroform*. Add to the combined filtrates a mixture of 50 ml of *water* and 5 ml of 5M *sodium hydroxide*, shake, allow the layers to separate and wash the chloroform extract with 25 ml of *water*. Extract the aqueous layer with five further quantities, each of 25 ml, of *chloroform*, washing each extract with the 25 ml of *water* and adding it to the original extract. Dry the combined extracts with *anhydrous sodium sulphate*, evaporate to about 3 ml on a water-bath in a current of air, remove from the water-bath, and allow to evaporate to dryness at room temperature. Carry out Method I for *non-aqueous titration*, Appendix VIII A, on the residue, using *crystal violet solution* as indicator. Each ml of 0.1M *perchloric acid VS* is equivalent to 0.03395 g of $C_{22}H_{29}NO_2$.

Labelling The quantity of the active ingredient is stated in terms of the equivalent amount of dextropropoxyphene.

Usual Dose Range Up to the equivalent of 240 mg of dextropropoxyphene daily, in divided doses.

Strength available Capsules containing, in each, the equivalent of 60 mg of dextropropoxyphene are usually available.

Diazepam Capsules

Diazepam Caps.

Diazepam Capsules contain Diazepam.

Content of diazepam, $C_{16}H_{13}ClN_2O$ 92.5 to 107.5 per cent of the prescribed or stated amount.

Identification A. The light absorption, in the range 230 to 350 nm, of the solution obtained in the Assay, exhibits two maxima, at 242 nm and 284 nm.

B. Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel G* as the coating substance and a mixture of 10 volumes of *chloroform* and 1 volume of *methanol* as the mobile phase. Apply separately to the chromatoplate, 2 µl of each of two solutions in *methanol*. For solution (1) shake a quantity of the contents of the capsules with sufficient *methanol* to produce a solution containing the equivalent of 5 mg of Diazepam per ml, allow to settle, and decant the supernatant liquid. Solution (2) is a 0.5 per cent w/v solution of *diazepam BPCRS*. After removal of the chromatoplate, spray it with a 10 per cent v/v solution of *sulphuric acid* in *absolute ethanol*, heat at 105° for ten minutes, and examine under an ultra-violet lamp having a maximum output at about 366 nm. The principal spot in the chromatogram obtained with solution (1) corresponds to that in the chromatogram obtained with solution (2).

Related substances and decomposition products Carry out in subdued light the method for *thin-layer chromatography*, Appendix III A, using *silica gel GF254* as the coating substance and a mixture of 50 volumes of *ethyl acetate* and 50 volumes of *hexane* as the mobile phase, but allowing the solvent front to ascend 12 cm above the line of application. Apply separately to the chromatoplate the following two freshly-prepared solutions. (1) 20 µl of a solution prepared by shaking a quantity of the contents of the capsules equivalent to 50 mg of Diazepam with 5 ml of *ethanol* (*96 per cent*) and filtering; (2) 5 µl of a solution prepared by diluting 1 volume of solution (1) to 50 volumes with *ethanol* (*96 per cent*). After removal of the chromatoplate, allow the solvent to evaporate and examine under an ultra-violet lamp having a maximum output at about 254 nm. Any spot in the chromatogram obtained with solution (1), other than the principal spot, is not more intense than the spot in the chromatogram obtained with solution (2).

Assay To a quantity of the mixed contents of 20 capsules equivalent to 10 mg of Diazepam add 5 ml of *water*, mix, and allow to stand for fifteen minutes. Add 90 ml of a 0.5 per cent w/v solution of *sulphuric acid* in *methanol*, shake for fifteen minutes, add sufficient of the sulphuric acid solution to produce 100 ml and filter. Dilute 10 ml of the filtrate to 100 ml with the same solution and measure the

absorbance of the resulting solution at the maximum at about 284 nm, Appendix II B. Calculate the content of $C_{16}H_{13}ClN_2O$, taking 446 as the value of A(1 per cent, 1 cm) at the maximum at about 284 nm.

Storage Diazepam Capsules should be protected from light.

Usual Dose Range Diazepam. As a sedative, 5 to 30 mg daily, in divided doses.

Strengths available Capsules containing, in each, 2 mg and 5 mg are usually available.

Diphenhydramine Capsules

Diphenhydramine Caps.

Diphenhydramine Capsules contain Diphenhydramine Hydrochloride.

Content of diphenhydramine hydrochloride, $C_{17}H_{21}NO,HCl$ 92.5 to 107.5 per cent of the prescribed or stated amount.

Identification A. To a quantity of the contents of the capsules equivalent to 0.1 g of Diphenhydramine Hydrochloride add 1 ml of M *sulphuric acid* and shake with three quantities, each of 20 ml, of *ether*. Discard the ether layer, make the aqueous solution alkaline by the addition of 5M *sodium hydroxide* and extract with two quantities, each of 50 ml, of n-*heptane*. Wash the combined heptane extracts with 10 ml of *water*, filter through a layer of *anhydrous sodium sulphate* and evaporate the filtrate to dryness. The *infra-red absorption spectrum*, Appendix II A, of the residue is concordant with the *reference spectrum* of diphenhydramine.
B. Extract a quantity of the contents of the capsules equivalent to 0.1 g of Diphenhydramine Hydrochloride with two quantities, each of 15 ml, of *chloroform*. Evaporate the combined extracts to dryness on a water-bath and dry the residue at 80° for one hour; the residue has a *melting point* of about 168°, Appendix V A, and yields the *reactions* characteristic of chlorides, Appendix V I.

Related substances Comply with the test described under Diphenhydramine Hydrochloride, applying to the chromatoplate 5 µl of each of the following solutions. For solution (1) shake a quantity of the contents of the capsules equivalent to 50 mg of Diphenhydramine Hydrochloride with three quantities, each of 10 ml, of *chloroform*, filter, and evaporate the combined filtrates almost to dryness; dissolve the residue in 5 ml of *chloroform*. For solution (2) dilute 1 volume of solution (1) to 100 volumes with *chloroform*.

Assay Shake the mixed contents of 20 capsules with sufficient *water* to produce 100 ml and filter. To a volume of the filtrate equivalent to 0.3 g of Diphenhydramine Hydrochloride add 5 g of *sodium chloride* and 5 ml of 5M *sodium hydroxide* and extract with successive quantities, each of 20 ml, of *ether* until complete extraction is effected. Wash the combined extracts with two quantities, each of 5 ml, of *water*, extract the combined washings with two quantities, each of 10 ml, of *ether*, add the ether to the combined ether extracts, and evaporate to about 10 ml. Add 15 ml of 0.1M *hydrochloric acid VS*, warm gently to complete the removal of the ether, cool, and titrate the excess of acid with 0.1M *sodium hydroxide VS*, using *methyl red solution* as indicator. Each ml of 0.1M *hydrochloric acid VS* is equivalent to 0.02918 g of $C_{17}H_{21}NO,HCl$.

Usual Dose Range Diphenhydramine Hydrochloride, 50 to 200 mg daily, in divided doses.

Strength available Capsules containing, in each, 25 mg are usually available.

Disopyramide Capsules

Disopyramide Caps.

Disopyramide Capsules contain Disopyramide.

Content of disopyramide, $C_{21}H_{29}N_3O$ 92.5 to 107.5 per cent of the prescribed or stated amount.

Identification A. Shake a quantity of the contents of the capsules equivalent to 0.2 g of Disopyramide with 50 ml of *chloroform* for fifteen minutes, filter, evaporate the filtrate to dryness using a rotary evaporator and dissolve the residue in 2 ml of *chloroform*. The *infra-red absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of disopyramide.
B. The light absorption, in the range of 230 to 350 nm, of the solution obtained in the Assay exhibits a maximum only at 269 nm.

Related substances Carry out the method for *thin-layer chromatography*, Appendix III A, using *silica gel G* as the coating substance and a mixture of 80 volumes of *butan-1-ol* 15 volumes of *water* and 5 volumes of 13.5M *ammonia* as the mobile phase; if the mixture separates out, use the upper layer. Apply separately to the chromatoplate 20 µl of each of the following two solutions: for solution (1) shake a quantity of the contents of the capsules equivalent to 0.10 g of Disopyramide with 20 ml of *methanol* for thirty minutes and filter; for solution (2) dilute 1 volume of solution (1) to 400 volumes with *methanol*. After removal of the chromatoplate, allow it to dry in air and spray with *dilute potassium iodobismuthate solution*. Any spot in the chromatogram obtained with solution (1), other than the principal spot, is not more intense than the spot in the chromatogram obtained with solution (2).

Assay To a quantity of the mixed contents of 20 capsules equivalent to 40 mg of Disopyramide, add 40 ml of 0.05M *methanolic sulphuric acid*, shake for fifteen minutes, dilute to 100 ml with the same solvent and filter. Dilute 5 ml of the filtrate to 100 ml with 0.05M *methanolic sulphuric acid* and measure the *absorbance* of the resulting solution at the maximum at about 269 nm, Appendix II B. Calculate the content of $C_{21}H_{29}N_3O$ taking 198.5 as the value of A(1 per cent, 1 cm) at the maximum at about 269 nm.

Usual Dose Range Disopyramide, 300 to 800 mg daily, in divided doses.

Strength available Capsules containing, in each, 100 mg are usually available.

Disopyramide Phosphate Capsules

Disopyramide Phosphate Caps.

Disopyramide Phosphate Capsules contain Disopyramide Phosphate.

Content of disopyramide, $C_{21}H_{29}N_3O$ 92.5 to 107.5 per cent of the prescribed or stated amount.

Identification A. Suspend a quantity of the contents of the capsules equivalent to 200 mg of disopyramide in 50 ml of *chloroform*, add 2 ml of 13.5M *ammonia*, shake and filter through *anhydrous sodium sulphate*. Evaporate the filtrate to dryness using a rotary evaporator and dissolve the residue in 2 ml of *chloroform*. The *infra-red absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of disopyramide.
B. The light absorption, in the range 230 to 350 nm, of the solution obtained in the Assay exhibits a maximum only at 269 nm.
C. Shake a quantity of the contents of the capsules equivalent to 400 mg of disopyramide with 20 ml of *water* and filter; the filtrate yields the *reactions* characteristic of phosphates, Appendix VI.

Related substances Comply with the test described under Disopyramide Capsules but preparing solution (2) by diluting 1 volume of solution (1) to 200 volumes with *methanol*.

Assay Carry out the Assay described under Disopyramide Capsules.

Usual Dose Range The equivalent of 300 to 800 mg of disopyramide daily, in divided doses.

Strengths available Capsules containing, in each, the equivalent of 100 mg and 150 mg of disopyramide are usually available.

Dothiepin Capsules

Dothiepin Caps.

Dothiepin Capsules contain Dothiepin Hydrochloride.

Content of dothiepin hydrochloride, $C_{19}H_{21}NS,HCl$ 92.5 to 107.5 per cent of the prescribed or stated amount.

Identification Extract a quantity of the contents of the capsules equivalent to 0.1 g of Dothiepin Hydrochloride with 20 ml of *absolute ethanol*, filter, and remove the ethanol from the filtrate. The residue complies with tests for Identification A, B, C, and E described under Dothiepin Hydrochloride.

Related compounds Comply with the test described under Dothiepin Hydrochloride, but applying to the chromatoplate 10 µl of each of solutions (1) and (2) which are prepared in the following manner. Extract a quantity of the contents of the capsules equivalent to 0.25 g of Dothiepin Hydrochloride by shaking for two minutes with 5 ml of *chloroform*, centrifuge, and use the supernatant liquid as solution (1). Dilute 2 ml of the supernatant liquid to 5 ml with *chloroform* and use this as solution (2).

Cis-isomer Comply with the test described under Dothiepin Hydrochloride using as solution (2) the supernatant liquid obtained by extracting a quantity of the mixed contents of 20 capsules equivalent to 25 mg of Dothiepin Hydrochloride with 5 ml of *methanol* and centrifuging.

Assay Extract a quantity of the mixed contents of 20 capsules equivalent to 0.5 g of Dothiepin Hydrochloride with 20 ml and four quantities, each of 10 ml, of *chloroform*, filtering each extract through the same filter. Evaporate the solvent from the combined extracts, dissolve the residue in 100 ml of *acetone*, add 15 ml of *mercury(II) acetate solution*, and carry out Method I for *non-aqueous titration*, Appendix VIII A, using 3 ml of a saturated solution of *methyl orange* in *acetone* as indicator. Each ml of 0.1M *perchloric acid VS* is equivalent to 0.03319 g of $C_{19}H_{21}NS,HCl$.

Usual Dose Range Dothiepin Hydrochloride, 75 to 150 mg daily.

Strength available Capsules containing, in each, 25 mg are usually available.

Doxepin Capsules

Doxepin Caps.

Doxepin Capsules contain Doxepin Hydrochloride.

Content of doxepin, $C_{19}H_{21}NO$ 90.0 to 110.0 per cent of the prescribed or stated amount.

Identification Wash a quantity of the contents of the capsules equivalent to 0.1 g of doxepin with three quantities each of 5 ml, of *petroleum spirit* (*boiling range, 40° to 60°*). Extract the air-dried residue with three quantities, each of 10 ml, of *chloroform*, evaporate the combined extracts to dryness, and dry the residue at 105°. The residue complies with the following tests.
A. The *infra-red absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of doxepin hydrochloride.
B. The light absorption, in the range 230 to 350 nm, of a 2-cm layer of a 0.004 per cent w/v solution in 0.01M *methanolic hydrochloric acid* exhibits a maximum only at 297 nm; *absorbance* at 297 nm, about 1.05, Appendix II B.
C. Dissolve 5 mg in 2 ml of *nitric acid*; a red colour is produced.
D. Yields *reaction A* characteristic of chlorides, Appendix VI.

Cis-isomer Comply with the test described under Doxepin Hydrochloride, using for solution (2) the supernatant liquid obtained by extracting a quantity of the mixed contents of 20 capsules equivalent to 25 mg of doxepin with 5 ml of *methanol* and centrifuging.

Assay To a quantity of the mixed contents of 20 capsules equivalent to 30 mg of doxepin add 50 ml of 0.01M *methanolic hydrochloric acid*, shake for thirty minutes and add sufficient 0.01M *methanolic hydrochloric acid* to produce 100 ml. Centrifuge 40 ml and dilute 10 ml of the clear solution with sufficient 0.01M *methanolic hydrochloric acid* to produce a solution containing 30 µg of doxepin per ml. Measure the *absorbance* of the resulting solution at the maximum at about 297 nm, Appendix II B. Calculate the content of doxepin, $C_{19}H_{21}NO$, taking 150 as the value of A (1 per cent, 1 cm) at the maximum at about 297 nm.

Usual Dose Range The equivalent of 75 to 150 mg of doxepin daily.

Strengths available Capsules containing, in each, the equivalent of 10 mg, 25 mg and 50 mg of doxepin are usually available.