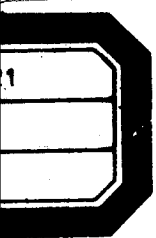


British Pharmacopœia 1973
Addendum 1975



British Pharmacopœia 1973 Addendum 1975

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WELSH OFFICE
MINISTRY OF HEALTH AND SOCIAL SERVICES FOR NORTHERN IRELAND

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Notices

The General Notices and Appendices included in the British Pharmacopœia 1973 apply to all matter contained in this Addendum unless the contrary is specifically stated.

The Addendum has the same authority as the British Pharmacopœia 1973. Monographs and Appendices of the British Pharmacopœia 1973 that are amended by this Addendum supersede, in their amended forms, the original monographs and appendices.

Patents

In this Addendum 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 Addendum neither conveys, nor implies, licence to manufacture.

Preface

On the completion of the British Pharmacopœia 1973, the British Pharmacopœia Commission which had been appointed by the Health Ministers under the Medicines Act 1968 to conclude this work demitted office.

Under Section 4 of the Medicines Act 1968, a new British Pharmacopœia Commission was appointed by the Health Ministers on the advice of the Medicines Commission and took office in June 1973. The membership of the new body is set out on page viii with an indication of the period of office of each member. Half the membership is due to retire at the end of 1975 but the members concerned are eligible for reappointment for periods of four years.

The new British Pharmacopœia Commission has been given a wider range of duties than its predecessors and is responsible for the preparation of all published standards for articles used in both human and veterinary medicine. Hitherto the British Pharmacopœia has not provided standards for articles used exclusively in veterinary practice and it is intended to implement this aspect of the work by the preparation of a separate volume.

This Addendum amends the British Pharmacopœia 1973 and is published by Her Majesty's Stationery Office for the Health Ministers on the recommendation of the Medicines Commission in accordance with Section 99 (6) of the Medicines Act.

The Medicines Commission records its appreciation of all who have contributed to the preparation of the Addendum.

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* Term of office ends 31 December 1975.

† Term of office ends 31 December 1977.

Introduction

This Addendum to the British Pharmacopœia 1973 has been prepared by the British Pharmacopœia Commission which took office in June 1973. The Addendum affords a means of adding to the main book a number of monographs on medicinal articles not previously included in the Pharmacopœia and of improving the requirements of substances and preparations already official.

The Commission appointed the following Committees and Panels to assist it in its task of keeping the Pharmacopœia up-to-date and is indebted to the members for their contribution to the preparation of the Addendum.

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Valuable advice was received on special topics from A. J. M. Bailey, D. Banes, L. F. Dodson, J. N. T. Gilbert, K. L. G. Goldsmith, H. H. Gunson, J. Powell, and A. G. Shaw and the help of members of the staffs of the following organisations is also gratefully acknowledged; the Association of the British Pharmaceutical Industry, Department of Pharmaceutical Sciences of the Pharmaceutical Society of Great Britain, National Institute for Biological Standards and Control, Laboratory of the Government Chemist of the Department of Industry, Chemical Society, National Biological Standards Laboratory (Australia), Food and Drug Directorate of the Department of National Health and Welfare (Canada), Committee of Revision of the United States Pharmacopœia, and American Pharmaceutical Association.

Members of the staff of the Commission who have taken part in the production of the Addendum are: Irene Ladden, B. PHARM., Sylvia Richens, F.P.S., G. P. R. Carr, B.SC., PH.D., GRAD.R.I.C., A. Islam, M.SC., PH.D., Cherry M. King, B.SC., R. B. Trigg, A.R.I.C., Christine M. Allen, D. C. Brougham, A.R.I.C., Patricia O. Creed, L.R.I.C., R. Middleton, L.R.I.C., Janet M. Batson, B.SC., and R. N. Slinn, L.R.I.C.

Monographs in the Addendum on substances described for the first time in the Pharmacopœia cover a wide range of medicinal agents, including the antibiotics, amoxycillin trihydrate and candidin (of the quality used topically), the anabolic steroids, ethylœstrenol and stanolone, the parasympatholytic, biperiden, the antihistamine, diphenylpyraline hydrochloride, the anti-depressants, dothiepin and doxepin, and the analgesics, flufenamic acid, ibuprofen and pentazocine. Other new medicinal chemicals are diazoxide, used in the treatment of hypertension and endogenous hyperinsulinism; the oral hypoglycæmic, glibenclamide; and methisazone, which is used for the prevention of smallpox. Oxprenolol hydrochloride is a further addition to the group of beta adrenergic blocking agents given official recognition; thymoxamine hydrochloride is an alpha adrenergic blocking agent. Substances of biological origin now described for the first time are the polypeptide, glucagon, obtained from mammalian pancreas and used to increase the blood glucose level, the fibrinolytic enzyme, streptokinase, and the hormone, calcitonin. Of the several possible types of calcitonin, the monograph deals with that obtained from pork thyroid and a test to ensure freedom from other than residual amounts of thyroxine and liothyronine is in process of development. New immunological preparations are the injections of anti-D (Rh_0), anti-tetanus and anti-vaccinia human immunoglobulins, adsorbed pertussis vaccine and adsorbed influenza vaccine.

Many of the new monographs are accompanied by specifications for pharmaceutical forms such as tablets, injections and capsules. The practice customary in previous Pharmacopœias of stating the strength of these preparations to be supplied in the absence of directions has been continued in this Addendum but in a more restricted manner and it is the intention of the Commission to abandon this practice completely in future Pharmacopœias. This decision has been taken on the grounds that with many modern therapeutic agents it is essential for explicit instructions on dosage to be included in every prescription, in accordance with the needs of the particular patient.

A number of new monographs deal with pharmaceutical presentations of medicinal substances described in the main volume, among them being the injection of frusemide, methyl dopate hydrochloride, which provides an injectable form of the anti-hypertensive methyl dopa, the long-acting forms of fluphenazine used by depot injection in oily solution in the treatment of schizophrenia, and the cream and ointment of beclomethasone dipropionate. A test for freedom from pseudomonads was prepared for inclusion in the monograph on Beclomethasone Cream but has been withheld for the time being in order that similar tests may be developed and published simultaneously for other steroid creams and dilutions of the creams. The new monograph on Digoxin Pædiatric Injection describes the weaker solution used in both children and the elderly. Isoprenaline Injection is administered intravenously for stimulating the heart muscle. The new monograph on Kanamycin Acid Sulphate describes the more readily soluble form of Kanamycin and its addition to the Pharmacopœia has necessitated a change in the monograph on Kanamycin Injection to allow its use in this preparation.

Amendments are made to monographs in the main book. For Glyceryl Trinitrate Tablets, recent reports on stability have shown that severe losses of glyceryl trinitrate may be associated with the use of unsuitable containers and packing material. The amendments to the monograph draw attention to these aspects and recommend that when the tablets are dispensed or supplied for the patient, they should be in small containers holding at most a hundred tablets. When the monograph on gentamicin sulphate was added to the Pharmacopœia no satisfactory method of analysis was available for controlling the proportions of the three components known to be present. As the result of further work, a test involving nuclear magnetic resonance spectrometry has now been elaborated and

is added to the monographs on the substance and its preparation. The alterations to the monograph on Butylated Hydroxyanisole give official recognition to the grade of the material that is widely used in the food industry as an antioxidant and the monograph on Methotrexate Injection now recognises the stabilised injection instead of the preparation previously described, which had to be made immediately before use. The doses in the Pharmacopœia for the beta adrenergic blocking substances have been reviewed in light of the larger oral doses which are now given and changes have been made to the statements in the monographs on Alprenolol Hydrochloride, Practolol and Propranolol Hydrochloride. An addition to the labelling requirements in the monographs on the preparations of insulin specifies that the animal source or sources shall in future be declared on the label on the container or package; the terms beef insulin and pork insulin are recommended for this purpose.

The special requirements for injections supplied in plastic containers which were first included in the British Pharmacopœia 1973 were restricted in their application to containers of 500 millilitres and more but are now extended to include containers of not less than 50 millilitres. Changes affecting several monographs arise from the decision of the Commission to adopt wherever possible the Chemical Reference Substances issued by the European Pharmacopœia Commission. It is particularly desirable that these substances should be used for standardising pharmaceutical preparations containing those active ingredients which are the subjects of monographs in the European Pharmacopœia and it is the intention of the Commission to authorise such substitution immediately the appropriate European Pharmacopœia Chemical Reference Substances become available.

Amendments of the British Pharmacopœia 1973 published before this Addendum are reproduced in the immediately following pages. They include the monographs on Aspirin and Codeine Tablets, Soluble Aspirin and Codeine Tablets, and Aspirin and Caffeine Tablets which were introduced when the Medicines (Phenacetin Prohibition) Order 1974 restricted the supply of the corresponding official preparations which contain phenacetin as an additional ingredient. Also among the amendments is the test for solution rate added to the monograph on Digoxin Tablets as a further step in the process of securing more uniform release of digoxin from the tablets. In developing the test, a general procedure was devised for the determination of solution rate and this is also reproduced. In the interests of international uniformity of analytical methods, the procedure follows very closely the standard method for measuring the rate of solution from pharmaceutical forms adopted in the United States Pharmacopœia. The application of the method will be extended to tablets and capsules of other substances as the necessary investigations are completed.

Additions

The following monographs are added to the British Pharmacopœia 1973

Adsorbed Influenza Vaccine	Diazoxide Tablets
Adsorbed Pertussis Vaccine	Diethyltoluamide
Aluminium Glycinate	Digoxin Pædiatric Injection
Amoxycillin Trihydrate	Dimethyl Sulphoxide
Amoxycillin Capsules	Diphenylpyraline Hydrochloride
Anti-D (Rh ₀) Immunoglobulin Injection	Dothiepin Capsules
Beclomethasone Cream	Dothiepin Hydrochloride
Beclomethasone Ointment	Doxepin Capsules
Biperiden	Doxepin Hydrochloride
Biperiden Lactate Injection	Ethylœstrenol
Calcitonin (Pork)	Ethylœstrenol Tablets
Candididin	Flufenamic Acid
Carbomer	Flufenamic Acid Capsules
Diazoxide	Fluphenazine Decanoate
Diazoxide Injection	Fluphenazine Decanoate Injection

Fluphenazine Enanthate
 Fluphenazine Enanthate Injection
 Frusemide Injection
 Glibenclamide
 Glibenclamide Tablets
 Glucagon
 Glucagon Injection
 Halquinol
 Human Antitetanus Immunoglobulin
 Injection
 Human Antivaccinia Immunoglobulin
 Injection
 Ibuprofen
 Ibuprofen Tablets
 Isoprenaline Hydrochloride
 Isoprenaline Hydrochloride Injection
 Kanamycin Acid Sulphate
 Methisazone

Methisazone Mixture
 Methyldopate Hydrochloride
 Methyldopate Injection
 Octaphonium Chloride
 Oxprenolol Hydrochloride
 Oxprenolol Tablets
 Pentazocine
 Pentazocine Hydrochloride
 Pentazocine Lactate Injection
 Pentazocine Tablets
 Pregelatinised Maize Starch
 Sesame Oil
 Stanolone
 Stanolone Tablets
 Streptokinase
 Streptokinase Injection
 Thymoxamine Hydrochloride
 Thymoxamine Tablets

Amendments

The following monographs of the British Pharmacopœia 1973 are amended by this Addendum

Alcohol (95 per cent)
 Alprenolol Hydrochloride
 Alprenolol Tablets
 Amphotericin
 Anaesthetic Ether
 Atropine Eye Ointment
 Atropine Sulphate Injection
 Bacitracin Zinc
 Benzalkonium Chloride Solution
 Benzylpenicillin Injection
 Benzylpenicillin Tablets
 Betamethasone Sodium Phosphate
 Betamethasone Tablets
 Betamethasone Valerate
 Biphasic Insulin Injection
 Butylated Hydroxyanisole
 Calcium Lactate
 Cascara Dry Extract
 Cetostearyl Alcohol
 Chlormerodrin (197Hg) Injection
 Chloroform Water
 Cinchocaine Hydrochloride
 Clomiphene Citrate
 Cloxacillin Capsules
 Cortisone Injection
 Cortisone Tablets
 Cyproheptadine Hydrochloride
 Demeclocycline Capsules
 Deoxycortone Acetate Implants
 Deoxycortone Acetate Injection
 Deslanoside
 Dextropropoxyphene Napsylate
 Digitoxin Tablets
 Digoxin Injection
 Digoxin Tablets
 Dimenhydrinate Injection
 Dried Magnesium Sulphate
 Ergometrine Injection
 Ergometrine Tablets
 Ergotamine Injection
 Ergotamine Tablets
 Ethinylœstradiol Tablets
 Fenfluramine Hydrochloride
 Fenfluramine Tablets
 Folic Acid Tablets
 Framycetin Sulphate
 Frusemide

Frusemide Tablets
 Gentamicin Injection
 Gentamicin Sulphate
 Globin Zinc Insulin Injection
 Glyceryl Trinitrate Tablets
 Guanethidine Sulphate
 Guanethidine Tablets
 Halibut-liver Oil
 Halibut-liver Oil Capsules
 Hyaluronidase
 Hydrocortisone Acetate Injection
 Hydrocortisone Acetate Ointment
 Hydrocortisone Hydrogen Succinate
 Hydrocortisone Ointment
 Hydrocortisone Sodium Succinate
 Industrial Methylated Spirit
 Injections
 Insulin Injection
 Insulin Zinc Suspension
 Insulin Zinc Suspension (Amorphous)
 Insulin Zinc Suspension (Crystalline)
 Inulin
 Isophane Insulin Injection
 Kanamycin Injection
 Kanamycin Sulphate
 Lanatoside C
 Magnesium Chloride
 Meclozine Hydrochloride
 Mefenamic Acid
 Mefenamic Acid Capsules
 Menthol
 Mephentermine Injection
 Mercaptopurine
 Methotrexate
 Methotrexate Injection
 Methyldopa
 Methyldopa Tablets
 Methylergometrine Maleate
 Methyltestosterone Tablets
 Neostigmine Methylsulphate
 Neutral Insulin Injection
 Œstradiol Benzoate Injection
 Olive Oil
 Oxytetracycline Capsules
 Oxytetracycline Injection
 Oxytetracycline Tablets

Percutaneous Bacillus Calmette-Guérin Vaccine
 Phenoxymethylpenicillin Potassium
 Poliomyelitis Vaccine (Oral)
 Practolol
 Practolol Tablets
 Probenecid
 Prochlorperazine Tablets
 Progesterone Injection
 Propantheline Tablets
 Propranolol Hydrochloride
 Propranolol Tablets
 Protamine Zinc Insulin Injection

L-Selenomethionine (^{75}Se) Injection
 Senna Tablets
 Sodium Lactate Injection
 Testosterone
 Testosterone Propionate Injection
 Thiomersal
 Thioridazine Hydrochloride
 Tragacanth
 Tranlycypromine Sulphate
 Tropicamide
 White Soft Paraffin
 Xenon (^{133}Xe) Injection
 Xylose

Amendments of the British Pharmacopœia 1973

Effective date: 1 December 1973

Alcohol (95 per cent)

Page 16, left hand column

Line 11 from foot. For '0.3 to 0.4' read '3 to 4'.

Amphetamine Sulphate Tablets

Page 29, right hand column

Lines 37 to 39. Delete the statement on the strength to be dispensed or supplied.

Bethanidine Sulphate

Page 56, right hand column

Line 27 from foot. For '0.8' read '0.9'.

Line 26 from foot. For '0.6' read '0.7'.

Dried Human Albumin Fraction (Saline)

Page 64, left hand column

Line 22 from foot. For 'sodium' read 'potassium'.

Human Normal Immunoglobulin Injection

Page 67, left hand column

Lines 18 and 19 from foot. For 'Immunoglobulin Humanum Normale' read 'Immunoglobulinum Humanum Normale'.

Botulinum Antitoxin

Page 69, left hand column

Lines 13 and 16 from foot. For 'Antibotulinum' read 'Antibotulinicum'.

Calciferol

Page 73

Line 25 of left hand column. Add the subsidiary title 'Ergocalciferolum'.

Delete from line 21 from foot of left hand column to line 7 of right hand column inclusive and insert 'Calciferol complies with the requirements of the European Pharmacopœia for Ergocalciferolum'.

Line 14 of right hand column. For '20 mg' read '20 micrograms'.

Carbenicillin Sodium

Page 81, left hand column

Line 32 from foot. For '+175° to +185°' read '+182° to +196°'.

Cascara Tablets

Page 86, left hand column

Line 15 from foot. For '50' read '40'.

Cloxacillin Sodium

Page 117, left hand column

Line 25 from foot. For '+156° to +164°' read '+163° to +172°'.

Dexamphetamine Tablets

Page 147, left hand column

Lines 25 to 27. Delete the statement on the strength to be dispensed or supplied.

Dihydrocodeine Injection

Page 165, left hand column

Lines 35 to 37. Delete the statement on the strength to be dispensed.

Fenfluramine Hydrochloride

Page 200, right hand column

Line 1 from foot. For '80' read '120'.

Fenfluramine Tablets

Page 201, left hand column

Line 5 from foot. For '80' read '120'.

Heparin

Page 224, right hand column

Line 1 from foot. For '+35° to +55°' read 'not less than +35°'.

Heparin Injection

Page 225, right hand column

Line 3. Add the following statement 'When no bactericide is present, the label on the container states "Contains no bactericide; any portion of the contents not used at once should be discarded"'.

Indomethacin Suppositories

Page 240, right hand column

Line 23. Change the requirement for Disintegration to: **Disintegration** Maximum time, ninety minutes, page A132, using *solution of standard pH 6.8* instead of *water*.

Insulin Injection

Page 143, right hand column
Line 15 from foot. For '200 ml' read '20 ml'.

Lymecycline and Procaine Injection

Page 272, left hand column
Line 12 from foot. For '0.25' read '0.135'.

Meglumine Diatrizoate Injection

Page 283, left hand column
Line 17. For 'megumine' read 'meglumine'.

Mephentermine Injection

Page 287, right hand column
Lines 14 to 17. Delete the statement on the strength to be dispensed.

Methicillin Sodium

Page 297, left hand column
Line 19 from foot. For '+225° to +233°' read '+235° to +245°'.

Methylamphetamine Injection

Page 302, right hand column
Lines 1 to 3 from foot. Delete the statement on the strength to be dispensed.

Methylamphetamine Tablets

Page 303, left hand column
Lines 25 to 27. Delete the statement on the strength to be dispensed or supplied.

Pancreatin

Page 340, left hand column
Line 20 from foot. For '2 mg' read '2 g'.

Phenethicillin Potassium

Page 353, right hand column
Line 7 from foot. For '+215° to +240°' read '+217° to +244°'.

Phenmetrazine Tablets

Page 358, left hand column
Lines 26 to 28. Delete the statement on the strength to be dispensed or supplied.

Propicillin Potassium

Page 397, left hand column
Line 1 from foot. For '+214° to +225°' read '+215° to +228°'.

Propylene Glycol

Page 399, right hand column
Lines 17 and 18. For 'odourless' read 'odourless or almost odourless'.

Rubella Vaccine (Live Attenuated)

Page 413, right hand column
Line 10. For 'Water for Injections' read 'a suitable sterile liquid'.
Page 414, left hand column
Lines 9 and 10. Change requirement (2) to read '(2) the nature and volume of the liquid to be used for reconstitution'.

Compound Sodium Lactate Injection

Page 436, left hand column
Line 2 from foot. For '4' read '2'.

Sucrose

Page 445, right hand column
Line 9. Add the subsidiary title 'Saccharum'.
Line 11. For 'Sucrosum' read 'Saccharum'.

Tetracosactrin Acetate

Page 466, left hand column
Lines 15 and 16 from foot. Delete 'calculated with reference to the peptide content'.

Tetracycline Hydrochloride

Page 468
After line 17, left hand column, add the subsidiary title 'Tetracyclini Hydrochloridum'.
Delete from line 28 from foot of left hand column to line 21 from foot of right hand column inclusive and insert 'Tetracycline Hydrochloride complies with the requirements of the European Pharmacopœia for Tetracyclini Hydrochloridum'.

Tetracycline Capsules

Page 469, left hand column
Line 18. For 'test' read 'tests'.
Line 19. For 'Hydrochloride' read 'Injection'.

Tetracycline Injection

Page 469, right hand column

Identification Delete test B and insert:

'B. To 0.5 mg add 2 ml of *sulphuric acid*; a purplish-red colour is produced. Add 1 ml of *water*; the colour changes to deep yellow.

C. Yields the *reactions* characteristic of chlorides, page A71'.

Tetracycline Tablets

Page 470, left hand column

Line 18. For 'Hydrochloride' read 'Injection'.

Urea

Page 492, left hand column

Line 24 from foot. For '0.5' read '5.0'.

Water for Injections

Page 500, right hand column

Line 8 from foot. Add the subsidiary title 'Aqua ad Iniectionabilia'.

Delete from page 500, right hand column, line 7 from foot to page 501, left hand column, line 14 from foot inclusive and insert 'Water for Injections complies with the requirements of the European Pharmacopœia for Aqua ad Iniectionabilia'.

Effective date: 1 September 1974

Add the following monographs.

Aspirin and Codeine Tablets

Aspirin and Codeine Tab.; Acetylsalicylic Acid and Codeine Tablets

For each tablet, take

Aspirin

400 mg

Codeine Phosphate

8 mg

Content of aspirin, $C_9H_8O_4$ 380 to 420 mg.

Content of codeine phosphate, $C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot \frac{1}{2}H_2O$. 7.2 to 8.8 mg.

Identification Comply with tests for Identification A and C described under Aspirin, Phenacetin, and Codeine Tablets, British Pharmacopœia 1973, page 38.

Salicylic acid To a quantity of the powdered tablets equivalent to 0.50 g of Aspirin, add 50 ml of *chloroform* and 10 ml of *water*, shake well, and allow to separate. Filter the chloroform layer through a dry filter paper and without delay evaporate 10 ml of the solution as rapidly as possible to dryness by exposing a large surface to a current of dry air at room temperature. To the residue add 4 ml of *alcohol* (95 per cent), stir well, dilute to 100 ml with *water*, filter immediately and rapidly, transfer 50 ml to a Nessler cylinder, add 1 ml of *acid ferric ammonium sulphate solution*, mix, and allow to stand for one minute. The violet colour produced is not deeper than that produced by adding 1 ml of *acid ferric ammonium sulphate solution* to a mixture of 3 ml of a freshly prepared 0.01 per cent

Yellow Fever Vaccine

Page 504, left hand column

Line 20 from foot. For 'isotonic with blood' read 'so that the reconstituted vaccine is isotonic with blood'.

Lines 9 to 13 from foot. For 'The suspension . . . the glass' read 'The suspension so obtained is clarified by centrifuging or other suitable means. A suitable stabiliser may be added to the clarified vaccine, which is then distributed in sterile glass containers and dried from the frozen state before the containers are sealed.'

Appendix XVIII

Plastic Containers

Page A130, left hand column

Line 21 from foot. After 'mercury,' insert 'Infusion of the solution being examined should begin two minutes after recording the second carotid reflex.'

Appendix XIX

E. Uniformity of Diameter of Tablets

Page A135, right hand column

Under the entry for Tolbutamide Tablets change the diameter from 12.0 mm to 13.0 mm.

w/v solution of *salicylic acid*, 2 ml of *alcohol* (95 per cent), and sufficient *water* to produce 50 ml contained in a second Nessler cylinder.

Assay Weigh and powder 20 tablets.

For aspirin. To a quantity of the powder equivalent to 0.8 g of Aspirin add 20 ml of *water* and 2 g of *sodium citrate* and heat under a reflux condenser for thirty minutes. Cool, wash the condenser with 30 ml of warm *water*, and titrate with 0.5N *sodium hydroxide*, using *phenolphthalein solution* as indicator. Each ml of 0.5N *sodium hydroxide* is equivalent to 0.04504 g of $C_9H_8O_4$.

For codeine phosphate. To a quantity of the powder equivalent to 24 mg of Codeine Phosphate add 5 ml of *sodium hydroxide solution* and 15 ml of *water*, shake for two minutes, and extract with three quantities, each of 50 ml, of *chloroform*. Wash each extract with the same 10 ml of *water*, filter through a plug of cotton wool previously moistened with *chloroform*, and evaporate the combined extracts to about 60 ml on a water-bath in a current of air. Cool, add 25 ml of *water*, 5 ml of *acetate buffer solution*, pH 2.8 and 5 ml of *dimethyl yellow-solvent blue 19 solution*, and titrate with *dioctyl sodium sulphosuccinate solution* with vigorous swirling until near the end-point, then add the titrant dropwise and, after each addition, swirl vigorously, allow to separate and gently swirl for five seconds; the end-point is indicated by the appearance of a permanent pinkish-grey colour in the chloroform layer. Repeat the operation without the powdered tablets; the difference between the titrations represents the amount of *dioctyl sodium sulphosuccinate solution* required.

Calculate the content of $C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot \frac{1}{2}H_2O$, from the result obtained by dissolving 40 mg of *codeine*

phosphate in 25 ml of water and 5 ml of acetate buffer solution, pH 2.8, adding 60 ml of chloroform and 5 ml of dimethyl yellow-solvent blue 19 solution, shaking well to dissolve the codeine phosphate, and completing the method described above beginning at the words 'and titrate...'.
Storage Aspirin and Codeine Tablets should be protected from light.

Labelling The label on the container states that the tablets contain 'Aspirin', unless this word appears in the name of the tablets. This requirement does not apply in countries where exclusive proprietary rights in the name Aspirin are claimed.

DOSE 1 or 2 tablets.

Soluble Aspirin and Codeine Tablets

Sol. Aspirin and Codeine Tab.; Soluble Acetylsalicylic Acid and Codeine Tablets

For each tablet, take

Aspirin, in <i>fine powder</i>	400 mg
Codeine Phosphate	8 mg
Calcium Carbonate	130 mg
Anhydrous Citric Acid	40 mg
Saccharin Sodium	4 mg

Content of aspirin, $C_9H_8O_4$ 380 to 420 mg.

Content of codeine phosphate, $C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot \frac{1}{2}H_2O$ 7.2 to 8.8 mg.

Identification A. Effervesce on the addition of water.

B. Comply with tests for Identification A and C described under Aspirin, Phenacetin, and Codeine Tablets, British Pharmacopoeia 1973, page 38.

Disintegration Maximum time, three minutes, British Pharmacopoeia 1973, page A131.

Salicylic acid To a quantity of the powdered tablets equivalent to 0.50 g of Aspirin, add 50 ml of chloroform and a mixture of 2 ml of *N* hydrochloric acid and 8 ml of water, and complete the test for Salicylic acid described under Aspirin and Codeine Tablets beginning at the words 'shake well...'.
Assay Weigh and powder 20 tablets.

For aspirin. To a quantity of the powder equivalent to 0.8 g of Aspirin add 15 ml of water and swirl until effervescence ceases. Add 5 ml of *N* sulphuric acid and extract with 50 ml of solvent ether followed by three quantities, each of 30 ml, of solvent ether. Wash the combined extracts with 10 ml of water, filter through a plug of cotton wool previously moistened with solvent ether, washing the separator and filter with solvent ether. Evaporate the ether in a water-bath at 30° in a current of air. Dissolve the residue in 5 ml of acetone and evaporate in a water-bath at 30°; again dissolve the residue in 5 ml of acetone and evaporate in a water-bath at 30°. Dissolve the residue in 25 ml of alcohol (95 per cent), previously neutralised to phenol red and titrate with 0.1N sodium hydroxide, using phenol red solution as indicator. Each ml of 0.1N sodium hydroxide is equivalent to 0.01802 g of $C_9H_8O_4$.

For codeine phosphate. To a quantity of the powder equivalent to 16 mg of Codeine Phosphate add 20 ml of water and 1 g of disodium edetate, swirl gently until effervescence ceases then shake to dissolve and carry out the Assay for codeine phosphate described under Aspirin and Codeine Tablets beginning at the words 'add 5 ml of sodium hydroxide solution...'.
Storage Soluble Aspirin and Codeine Tablets should be protected from light.

Labelling The label on the container states that the tablets contain 'Aspirin' unless this word appears in the name of the tablet. This requirement does not apply in countries where exclusive proprietary rights in the name Aspirin are claimed.

DOSE 1 or 2 tablets.

Aspirin and Caffeine Tablets

Aspirin and Caffeine Tab.; Acetylsalicylic Acid and Caffeine Tablets

For each tablet, take

Aspirin	350 mg
Caffeine	30 mg

Content of aspirin, $C_9H_8O_4$ 330 to 370 mg.

Content of caffeine, $C_8H_{10}N_4O_2$ 27.5 to 32.5 mg.

Identification A. Boil 1 g of the powdered tablets with 10 ml of *N* sodium hydroxide, cool, and filter. Acidify the filtrate with dilute sulphuric acid; a white precipitate is produced. To a solution of the precipitate, add ferric chloride test-solution; a deep violet colour is produced.

B. Shake 0.5 g of the powdered tablets with 10 ml of water for five minutes, filter and add 10 ml of *N* sodium hydroxide. Extract with three quantities, each of 30 ml, of chloroform, washing each extract with the same 10 ml of water. Filter the combined extracts through cotton wool and evaporate the filtrate to dryness. The residue complies with the following tests:

Dissolve 10 mg in 1 ml of hydrochloric acid; add 0.1 g of potassium chlorate, and evaporate to dryness in a porcelain dish; a reddish residue remains, which becomes purple on exposure to the vapour of dilute ammonia solution.

The light absorption, in the range 240 to 350 nm, of a 1-cm layer of a 0.001 per cent w/v solution exhibits a maximum at 273 nm.

Salicylic acid Comply with the test described under Aspirin and Codeine Tablets.

Assay Weigh and powder 20 tablets.

For aspirin. Carry out the Assay for aspirin described under Aspirin and Codeine Tablets using a quantity of the powder equivalent to 0.7 g of Aspirin.

For caffeine. To a quantity of the powder equivalent to 30 mg of Caffeine add 200 ml of water and shake for thirty minutes. Add sufficient water to produce 250 ml and filter. To 10 ml of the filtrate add 10 ml of *N* sodium hydroxide and extract immediately with five quantities, each of 30 ml, of chloroform, washing each extract with the same 10 ml of water. Filter the combined chloroform extracts, if necessary, through a plug of cotton wool previously moistened with chloroform. Evaporate the solution to dryness and dissolve the residue as completely as possible in water, warming gently if necessary. Cool, add sufficient water to produce 100 ml, mix, and filter if necessary. Measure the extinction of a 1-cm layer of the resulting solution at the maximum at about 273 nm. Calculate the content of $C_8H_{10}N_4O_2$, taking 504 as the value of $E(1 \text{ per cent}, 1 \text{ cm})$ at the maximum at about 273 nm.

Labelling The label on the container states that the tablets contain 'Aspirin', unless this word appears in the

name of the tablets. This requirement does not apply in countries where exclusive proprietary rights in the name Aspirin are claimed.

DOSE 1 or 2 tablets.

Appendix I

A. Reagents

Add the following:

Acetate buffer solution, pH 2.8 Dissolve 4 g of *anhydrous sodium acetate* in about 840 ml of *water*, add sufficient *glacial acetic acid* to adjust the pH to 2.8 (about 155 ml) and sufficient *water* to produce 1000 ml.

Change the entry for Codeine Phosphate to:

Codeine Phosphate Of the European Pharmacopœia (hemihydrate.)

Effective Date: 1 October 1975

Digoxin Tablets

Add the following requirement:

Solution rate Carry out the method for the *determination of solution rate* (see next column), using six tablets, 600 ml of *water* freshly prepared by distillation as the medium, and rotating the basket at 120 revolutions per minute for one hour. At the end of this time, withdraw 5 ml of the solution from a point approximately half way between the basket wall and the wall of the vessel, level with the mid-point of the side of the basket, filter through a membrane filter disc having an average pore diameter not greater than 0.8 μm , rejecting the first 1 ml of the filtrate, and transfer 1.0 ml to a 10-ml graduated flask. Add 3 ml of a 0.1 per cent w/v solution of *ascorbic acid* in *methyl alcohol* and 0.2 ml of a 0.009 M solution of hydrogen peroxide (prepared by accurately diluting *strong hydrogen peroxide solution* that has been standardised by titration with 0.1N *potassium permanganate*), mix, and dilute to volume with *hydrochloric acid*. After exactly two hours measure the fluorescence of the solution using an excitation wavelength of about 360 nm and an emission wavelength of about 490 nm and setting the spectrophotofluorimeter to zero with *water* and to 100 with a solution prepared at the same time as the test solution as follows. Dilute 2.5 ml of 0.100 per cent w/v solution of *digoxin B.C.R.S.* in *alcohol* (80 per cent v/v) to 100 ml with *water*, dilute the resulting solution further with *water* to produce a solution containing in 1 ml an amount of digoxin equal to one-hundredth of the strength of the tablets being examined, transfer 1.0 ml of the solution to a 10-ml graduated flask and carry out the operation described above, beginning at the words 'Add 3 ml . . .'. The amount of digoxin per tablet in solution is not less than 75 per cent of the prescribed or stated amount.

Appendix XIX

E. Uniformity of Diameter of Tablets

Add the following:

Tablet	Diameter in mm
Aspirin and Caffeine	10.5
Aspirin and Codeine	11.0
Soluble Aspirin and Codeine	12.5

Appendix XIX

Add the following:

F. Determination of Solution Rate

Apparatus

- A cylindrical, 1000-ml flat bottomed glass vessel, with a flanged upper rim (Quickfit No. FV1L is suitable) on to which fits a lid with a number of openings one of which is central (a suitable lid is Quickfit No. MAF 2/52).
- A variable speed motor which causes a basket to rotate in the vessel. The speed of the motor is capable of being varied between 25 and 150 revolutions per minute and maintained within 5 per cent of the required speed. The motor drives the basket by means of a shaft which is 6 mm in diameter and about 30 cm long, in such a way that the basket revolves smoothly without perceptible wobble. The shaft passes through the central opening in the lid of the vessel and carries at its lower end a solid stainless steel flanged disc of 2.5 cm diameter in which there is a 2-mm vent.
- A stainless steel cylindrical basket of No. 425 mesh woven wire cloth, 3.66 cm high and 2.5 cm in diameter, joined down the side with a welded seam and with a flanged rim at each end. The top is attached to the disc on the driving shaft by three steel clips.

Method

Place the specified number of tablets in the basket and assemble the apparatus. Adjust the distance between the bottom of the basket and the bottom of the vessel to between 1.8 and 2.2 cm. Start the motor, adjust the speed to approximately that stated in the monograph, and introduce into the 1000-ml vessel 900 ml (unless otherwise directed) of the specified medium, previously warmed to between 36.5° and 37.5°; maintain this temperature throughout the test. If necessary re-adjust the speed of the motor as quickly as possible until the basket is rotating within 5 revolutions per minute of the speed specified in the monograph and maintain at this speed for the time stated in the monograph. At the end of the specified time assay the solution in the vessel by the method described in the monograph.