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The Expert Committee on Specifications for Pharmaceutical Preparations met in Geneva from 5 to 9 December 1960.

Participants

Members

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Dr Z. Margasinski, Head of the Department of Chemistry, Institute of Drugs, Warsaw

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Dr L. C. Miller, Director of Revision, Pharmacopoeia of the United States of America, New York (Rapporteur)

Professor Noronha da Costa, Professor of Industrial Pharmaceutical Chemistry, Rio de Janeiro*

Secretariat

Mr A. Arzamastsev, Pharmaceuticals, WHO

Mr P. Blanc, Chief, Pharmaceuticals, WHO (Secretary)

Mr G. R. Brown, Department of Pharmaceutical Sciences, Pharmaceutical Society of Great Britain, London (Consultant)

Dr P. L. Senov, Director of the Division of Biology & Pharmacology, WHO

Mr O. Wallén, Pharmaceuticals, WHO

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1. Introduction

Dr Grashchenkov, Assistant Director-General, opened the session on behalf of the Director-General by welcoming the members, and expressing the thanks of WHO to members of the Expert Advisory Panel on Specifications for Pharmaceutical Preparations and others who have undertaken collaborative work on the examination of draft specifications. In particular he thanked those who have carried out practical work at the laboratory bench, which was considered to be an indispensable step in making available to the national health authorities specifications of known practical value which can be used as a basis for the establishment of national specifications for laboratory control of the quality of pharmaceutical preparations. He emphasized the importance of this task to those Member States that are faced with a large influx of pharmaceutical preparations and lack means for adequate control of quality. He noted that WHO had already proved of assistance in this field. The extension of the services provided by the Centre for Authentic Chemical Substances would be of further help to laboratories engaged in control of quality of pharmaceutical preparations, and arrangements were being made to add to the collection reference chemicals for melting-point determinations and spectrophotometric assays and tests.

2. Revision of the International Pharmacopoeia

In reviewing the arrangements made by WHO for preparing and revising specifications for the second edition of the International Pharmacopoeia, the Expert Committee emphasized that, owing to the difficulty in carrying out such detailed work on an international level, the success of any programme must depend largely on the goodwill and help of the various national authorities, who have contributed much to the success of the work in the past. The Expert Committee expressed the hope that this close co-operation with pharmacopoeia commissions and other national bodies dealing with specifications would continue. It was agreed that the preparation of specifications for a second edition of the International Pharmacopoeia would best be accomplished by submitting draft specifications received from various sources, for consideration and critical examination by the members of the Expert Advisory Panel on Specifications for Pharmaceutical Preparations, co-ordinating the views expressed, and then referring the proposed specifications for laboratory checking.

The Expert Committee then examined several groups of monographs revised in accordance with this procedure, taking into account comments resulting from practical application of the tests and assays in the laboratory. In most cases a final text was agreed,¹ but others were deferred for the completion of further investigations.

As much of the progress made in revising monographs was dependent upon laboratory work carried out on behalf of WHO by the Control Laboratory of the Swedish Pharmaceutical Society, the Expert Committee agreed that it might be advisable to extend the facilities for practical work on the specifications by making arrangements with specialists in other laboratories.

Discussion of important points of detail and general matters concerned with the revision of these monographs occupied the greater part of the time available to the Expert Committee at this session. The detailed changes were incorporated in the draft monographs, and the following are the main points of general interest arising during these discussions.

Content of active ingredient in tablets and other dosage forms

The Expert Committee agreed that a statement should be added to the general notices, to indicate that the limits for content of active ingredient included in dosage forms were intended to provide sufficient allowance for all possible sources of deviation from the theoretical content, due to slight variations in the purity of the active ingredient, variations in processing, limitations of the assay method, or other causes. It was agreed that for many tablets a deviation of ± 5 per cent. from the theoretical content would be sufficient to cover variations likely to be encountered, although it might be considered necessary to widen these limits in cases which present special difficulties.

Odour

The terms "odourless" and "almost odourless" are used in the description of a number of substances included in the International Pharmacopoeia. As an aid to the interpretation of these terms, it was agreed that a general statement should be added

¹ Annex 1

describing the conditions under which substances are to be examined, namely, that a specified quantity of the material is to be exposed in an open dish for 15 minutes and then examined for odour.

Completeness of solution

It was agreed that a test for clarity of solution could be deleted from the monographs for certain sulfonamides, particularly those intended for use by mouth; the test, however, should be retained for those sulfonamides used in the form of a solution, for example, in injections, where it is important that the substance shall go entirely into solution.

Chemical names and formulas

It was agreed that, where necessary, names and formulas should be amended to bring them into line with the latest recommendations of the International Union of Pure and Applied Chemistry. However, where the International Union of Pure and Applied Chemistry has not yet adopted definite rules applicable to pharmacopoeial compounds, it was agreed that the style adopted by other recognized authorities shall be consulted. Before publication the molecular and equivalent weights would be checked against the latest table of atomic weights issued by the International Union of Pure and Applied Chemistry.

Description

It was agreed that in the second edition the statements under this heading would include appearance, and in appropriate cases, odour and taste. Statements concerning the stability or deterioration of the compound would not be included under this heading, although in some cases they might be included in a separate note. For potent substances, the Expert Committee considered it appropriate to include the words "very poisonous", immediately after the description of the taste, as a warning to those who might have occasion to taste the compounds.

Infra-red spectrophotometry

The problems posed by generally specifying the use of infra-red spectrophotometry in the International Pharmacopoeia monographs were considered. It was agreed that this method should be specified only where other methods of identification are inadequate.

Tubocurarine chloride

The difficulties encountered in assaying and testing this alkaloid were discussed in detail, following an examination of a report on the collaborative testing of a batch of material intended for adoption as an Authentic Chemical Substance in the WHO Collection.¹ It was noted that the identification of tubocurarine chloride presents difficulties, and even ultra-violet spectrophotometry is not sufficiently reliable, as the test can be vitiated by the presence of small amounts of decomposition products and other impurities, and that infra-red spectroscopy should therefore be included as a means of identification. It was agreed to investigate a chemical assay procedure, and to include also a biological assay until sufficient data have been assembled to indicate whether the proposed chemical assay reflects the biological potency under all circumstances.

Alkaloids

The tests described for a number of alkaloids and their salts were revised. In many instances the identification tests given in the first edition were improved by the addition of directions for preparing derivatives having sharp melting-points to serve as a specific identification of the base. Methods based on non-aqueous titration having proved to be precise and simple to apply were adopted as assays of several of the alkaloids. It was arranged to re-examine the prescribed limits if the assay process is changed.

Calcium compounds

It was agreed that the determination of calcium by precipitation as the oxalate, described in the first edition, should be replaced by the more rapid and convenient method of titration with disodium edetate. An indirect method of determining calcium compounds was provided in the supplement to the first edition, and work had been continued towards developing a suitable direct titration, using an indicator specific for calcium. Provided that the suitability of the proposed indicator was confirmed, it was agreed to adopt such a method in the second edition.

¹ See item 7, unpublished working documents, No. 2

Bismuth compounds

It was agreed that the gravimetric methods described in the first edition should be replaced by the more convenient and more specific method of titration with disodium edetate. A new method in which the bismuth is held in solution as a complex with thiocarbamide or potassium iodide and titrated directly is reported to be an improvement on other methods and arrangements were made for this method to be included in the monographs.

Limit test for arsenic

In accordance with previous decisions of the Expert Committee, it was agreed to retain the Gutzeit-Flückiger technique for the second edition, and a modification was approved whereby cotton wool treated with lead acetate solution is used instead of rolled paper, to provide a more effective means for the removal of hydrogen sulfide evolved in the test reaction.

Determination of small quantities of adrenaline and levarterenol in solutions containing local anaesthetics

A report describing a method for the determination of adrenaline and levarterenol was examined. While not of immediate application in the preparation of monographs for the International Pharmacopoeia, it was agreed that the method would be of considerable interest to pharmaceutical analysts who frequently are called upon to make such determinations, and that it should form an annex to this report.¹

New monographs

The Committee considered the principles to be followed in selecting pharmaceutical substances or forms for the International Pharmacopoeia.

It agreed that monographs on such substances or forms which have appeared in at least two national pharmacopoeias issued during the ten years immediately preceding, or have been accepted for inclusion in the next edition of at least two national pharmacopoeias, should be considered. However, where it appears to be desirable for

¹ Annex 2. Determination of Small Amounts of Adrenaline and Levarterenol in Injections containing Local Anaesthetics.

WHO to provide specifications for other substances or forms, monographs for these may be prepared for subsequent approval by an Expert Committee although neither of the above conditions may have been met.

The Expert Committee examined a working document prepared by the Secretariat and agreed that (subject to the above considerations) it could be used as a basis of future work. The proposals of the Secretariat would be submitted to a number of experts who would help to prepare the drafts. It was agreed that, in order to avoid delay, these could then be submitted for practical checking in the laboratory, and examined by the Expert Committee in a fairly complete form, as a draft text for the second edition.

3. Authentic Chemical Substances

The Expert Committee received a report on work carried out at the WHO Centre for Authentic Chemical Substances.¹ Requests had continued to be received from various countries for samples from the collection, and arrangements have been made to replace some of the authentic chemicals as stocks become exhausted. It was proposed to add to the collection a set of thirteen substances intended for use as standards in melting-point determinations. Suitable materials had been obtained and were now under examination in a number of laboratories. The Expert Committee agreed that subject to a satisfactory completion of these tests the substances should be established as WHO Authentic Chemical Substances for melting-point determinations. It was agreed that it would be useful for WHO to issue a notice giving an indication of the materials available from this Centre when the collection had expanded in this way. As recorded in the report on the session of the Expert Committee held 9-14 November 1959² there is a need for a further series of authentic chemical substances required for checking the identity and quality of pharmaceutical preparations by spectrophotometry, and work on these is in hand. The Expert Committee expressed its thanks to the Apotekens Kontrollaboratorium, Stockholm, for the way in which it had carried out its function as WHO Centre for Authentic Chemical Substances in addition to undertaking laboratory work in connexion with the revision of specifications.

¹ See item 7, unpublished working documents, No. 2

² See item 7, unpublished working documents, No. 3

4. International Non-Proprietary Names

The Expert Committee noted that its Sub-Committee on Non-Proprietary Names had reconsidered the principles used in the creation of international non-proprietary names. It had considered especially the problems which arise in coining names for a large number of chemically related compounds, and suggested a number of measures for dealing satisfactorily with this problem.¹ In this connexion WHO was arranging to issue a number of reports in order to encourage the application of the proposals put forward in the reports in the selection of names of related pharmaceutical preparations. The Expert Committee agreed that this would be a useful step towards the establishment of an improved system of nomenclature, as it should be helpful in dealing with groups of drugs.

Further lists of proposed international non-proprietary names had been issued after examination by the Sub-Committee and correspondence with members of the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations. It was noted that a total of 872 names for medicinal substances had already been published in the WHO Chronicle and many of these names had also been published in lists of recommended international non-proprietary names in accordance with the procedure specified in the Executive Board Resolution EB15.R7. An increasing interest in the names has led to numerous requests for reprints of the ten lists of proposed international non-proprietary names. Therefore, a recapitulative list of all these names is in preparation.² The existence of this recapitulative list, together with the publication of lists on names from time to time in the WHO Chronicle, pharmaceutical journals and otherwise, should encourage the free use of the names in national pharmacopoeias, by national control authorities, manufacturers, and editors of medical and pharmaceutical journals, and so assist national health authorities and international commerce.

The Expert Committee expressed its gratitude to the Sub-Committee for the considerable effort of its members, in correspondence and at sessions, in selecting international non-proprietary names and studying the underlying problems.

¹ See item 7, unpublished working documents, No. 4

² See item 7, unpublished working documents, No. 5

5. Identification of Tablets

A suggestion was considered that all tablets should bear markings indicating the nature and quantity of the medicament in order to assist rapid identification in cases of poisoning and other emergencies, and possibly also in medical practice.¹ The suggestion was received that the markings should conform to a code available to hospital personnel, pharmacists and physicians. It was agreed that any such scheme would be very difficult to organize, because very many varieties of tablets are produced, and the number is continually increasing.

In the course of discussion of this problem it became apparent that dispensing practice varies from country to country. In Sweden, original packages only must be dispensed, and the containers must be labelled not only with any directions provided by the physician, but also with the name of the drug or speciality, the name of the patient and the physician. In the USSR, Poland, and Germany, it is also usual to indicate the name of the material described, but in other countries such as Canada, Japan, United Kingdom and the United States of America, the name of the drug does not appear on the label of the package which the patient receives, unless specifically requested by the prescriber. The practice in Switzerland varies between these extremes, according to the canton and the nature of the medicine. It was realized that the problem of tablet identification assumes greater importance in those countries where the nature of prescribed medicine is not disclosed, but there are a number of objections to a system of marking tablets as it may lead to errors in prescribing and to patients being informed of the nature of their treatment to a degree not desired by their physician. It was agreed that the application of such a scheme would depend upon the co-operation of all manufacturers, and as it had not yet proved possible on the national level, co-ordinating activities on the part of WHO gave, as yet, little prospect of success. However, the Expert Committee expressed the hope that it would be possible to find alternative solutions to the problem of identifying tablets quickly in emergencies.

¹ See item 7, unpublished working documents, No. 6

6. Reagents

The Expert Committee noted that specifications for all the reagents required to carry out tests mentioned in Volume I, Volume II and the Supplement to the first edition of the International Pharmacopoeia had been prepared and revised with the aid of specialists on this subject. This work had been undertaken to complete the information given in the International Pharmacopoeia, and the reagents described were suitable for general laboratory use, while being of a sufficiently high degree of purity for all the tests for which they are needed in the pharmacopoeia. Following the recommendations included in the Seventeenth Report of the Expert Committee, some instrumental methods such as flame photometry had been included as alternatives to older methods, and the specifications were now being completed and would be published, subject to any further comments which might be received, in the form of a reagent volume supplementary to the first edition of the International Pharmacopoeia. An introduction for the reagent volume had been prepared, and the Committee made some suggestions for consideration in completing the text.

7. List of Unpublished Working Documents

1. Daily Records of the Session of the Expert Committee on Specifications for Pharmaceutical Preparations, Pharm S.203, 205, 206.
2. Centre for Authentic Chemical Substances: Report on the work in 1960: WHO/Pharm/385, and 387.
3. Seventeenth Report of the Expert Committee on Specifications for Pharmaceutical Preparations. WHO/Pharm/377.
4. Tenth Report of the Sub-Committee on Non-Proprietary Names of the Expert Committee on Specifications for Pharmaceutical Preparations. WHO/Pharm/383.
5. Proposed International Non-Proprietary Names for Pharmaceutical Preparations (prop.INN) Lists 1-9, WHO/Pharm/Nom/8.
6. A scheme for the identification of tablets: Pharm S.195, Pharm S.201, WHO/Pharm/Exa/15, p. 4-5.

EXAMPLES OF MONOGRAPHS REVISED BY THE EXPERT COMMITTEE

I. EPHEDRINI HYDROCHLORIDUM

Revised monograph (cf. I.Ph., first ed., Vol. I)

$C_{10}H_{15}NO, HCl$

Mol. Wt. 201.70.

Ephedrine Hydrochloride is the hydrochloride of (-)-1-hydroxy-2-methyl-amino-1-phenylpropane. It contains not less than 99.0 per cent. and not more than the equivalent of 101.0 per cent. of $C_{10}H_{15}NO, HCl$, calculated with reference to the substance dried to constant weight at 105° .

Description. White crystals or a fine, white powder; odourless; taste, bitter.

Solubility. Soluble in about 4 parts of water and in about 14 parts of ethanol (95 per cent.) R; practically insoluble in ether R.

Identification

A. Dissolve 0.01 g in 1 ml of water, and add 0.1 ml of a 10.0 per cent. w/v solution of copper sulfate R in water, followed by 1 ml of a 20.0 per cent. w/v solution of sodium hydroxide R in water; the liquid becomes violet in colour. Add 1 ml of ether R, and shake; the ethereal layer is purple and the aqueous layer is blue.

B. Dissolve 0.2 g in 5 ml of water, add 1 ml of a 20.0 per cent. w/v solution of sodium hydroxide R in water, shake with four successive quantities, each of 15 ml, of ether R, wash the mixed ethereal solutions with 5 ml of water and allow the ether to evaporate just to dryness on a warm water-bath. Dissolve the residue in 30 ml of chloroform R, cover the dish, and set aside for twelve hours; crystals separate from the liquid which, after drying, yield the reactions characteristic of chlorides.

Annex 1

C. To 1 ml of a 5.0 per cent. w/v solution in water made alkaline with sodium hydroxide TS, add a few drops of a 1.0 per cent. w/v solution of potassium permanganate R in water and heat; benzaldehyde and methylamine vapours are evolved, which are alkaline to litmus paper R.

D. Yields the reactions characteristic of chlorides.

Melting-range. 217° to 220°.

Reaction. Dissolve 0.20 g in 10 ml of freshly boiled and cooled water and titrate with 0.02 N sodium hydroxide or 0.02 N hydrochloric acid using methyl red TS as indicator; not more than 0.1 ml of 0.02 N sodium hydroxide or 0.02 N hydrochloric acid is required.

Specific rotation. Determined in a 5.0 per cent. w/v solution in water at 20°, -34° to -36°.

Sulfate. Dissolve 0.2 g in 5 ml of water, add 0.5 ml of dilute hydrochloric acid R, followed by 0.5 ml of a 10.0 per cent. w/v solution of barium chloride R in water; the liquid shows no opalescence within fifteen minutes.

Loss on drying. When dried to constant weight at 105°, loses not more than 0.5 per cent. of its weight.

Residue on ignition. Not more than 0.1 per cent.

Assay. Dissolve about 0.5 g, accurately weighed, in 25 ml of glacial acetic acid R, add 10 ml of acetous mercuric acetate TS, and titrate with 0.1 N acetous perchloric acid until the colour changes from blue to green-blue, using 0.2 ml of acetous crystal violet TS as indicator or determining the end-point potentiometrically. Each ml of 0.1 N acetous perchloric acid is equivalent to 0.02017 g of $C_{10}H_{15}NO$, HCl.

Remarks

Chemical name (-)-l-hydroxy . . . (First edition: L-l-hydroxy . . .).

Annex 1

The percentage calculated with reference to the substance dried to constant weight at 105°. Limits 99.0 to 101.0 per cent. of C₁₀H₁₅NO, HCl (First edition: 80.0 per cent. to 82.5 per cent. of C₁₀H₁₅ON).

Reaction. The test revised as in BP 58 (First edition: a 5.0 per cent. w/v solution in freshly boiled and cooled water is neutral to litmus TS).

Specific rotation. Limits -34° to -36° (First edition: -33° to -36°).

Assay. Non-aqueous titration.

II. COMPRESSI EPHEDRINI HYDROCHLORIDI

Revised monograph (cf. I.Ph., first ed., Vol. II)

Ephedrine Hydrochloride Tablets contain not less than 93.0 per cent., and not more than 107.0 per cent., of the prescribed, or stated, amount of Ephedrine Hydrochloride, C₁₀H₁₅NO, HCl.

Identification. Triturate a quantity of the powdered tablets, equivalent to about 0.2 g of Ephedrine Hydrochloride, with 15 ml of warm ethanol (95 per cent.) R for twenty minutes, filter, and evaporate the filtrate to dryness on a water-bath; the residue complies with the tests for identification A, C and D described under "Ephedrini Hydrochloridum".

Assay. Weigh and powder 20 tablets. To an accurately weighed quantity of the powder equivalent to about 0.30 g of Ephedrine Hydrochloride, add 30 ml of glacial acetic acid R, 10 ml of acetous mercuric acetate TS and 0.2 ml of acetous crystal violet TS. Warm gently to ensure complete solution of the ephedrine, cool, and titrate with 0.1 N acetous perchloric acid until the colour changes from blue to green-blue or determine the end-point potentiometrically. Each ml of 0.1 N acetous perchloric acid is equivalent to 0.02017 g of C₁₀H₁₅NO, HCl. Calculate the average weight of ephedrine hydrochloride, C₁₀H₁₅NO, HCl in the tablets.

Storage. Tablets of Ephedrine Hydrochloride should be kept in a well-closed container, protected from light.

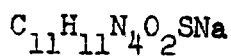
Remarks

First sentence changed. (First edition: "The average weight of ephedrine hydrochloride, $C_{10}H_{15}ON$, HCl, in the tablets is not less than 93.0 per cent., and not more than 107.0 per cent., of the prescribed, or stated, amount of Ephedrine Hydrochloride.")

Assay. Non-aqueous titration.

III. SULFAMERAZINUM NATRICUM

Revised monograph (cf. I.Ph., first ed., Vol. I.)



Mol. Wt. 286.30

Sulfamerazine Sodium is the sodium derivative of 2-sulfanilamido-4-methylpyrimidine. It contains not less than 99.0 per cent. and not more than the equivalent of 101.0 per cent. of $C_{11}H_{11}N_4O_2SNa$, calculated with reference to the substance dried to constant weight at 105° .

Description. White, or faintly yellowish-white, crystals or a crystalline powder; odourless or almost odourless; taste, bitter.

Solubility. Soluble in about 3 parts of water; slightly soluble in ethanol (90 per cent.) R; practically insoluble in ether R and in chloroform R. On exposure to humid air it absorbs carbon dioxide and becomes less soluble.

Identification

A. Dissolve about 1 g in 25 ml of water and add a slight excess of acetic acid R; a precipitate is formed which, after filtering, washing with water and drying at 105° , has a melting-temperature of about 237° , and complies with the tests for identification A and B described under "Sulfamerazinum".

Annex 1

B. Incinerate about 0.5 g; the residue yields the reactions characteristic of sodium.

Reaction. A solution in water is alkaline to phenolphthalein TS.

Completeness of solution. 1.0 g dissolves completely in 20 ml of water and the solution is not more than pale yellow.

Heavy metals. Not more than 20 parts per million.

Chloride. Dissolve 4.0 g in 45 ml of water. Add 5 ml of nitric acid R and filter; 25 ml of the filtrate complies with the limit test for chlorides.

Sulfate. Dissolve 3.0 g in 45 ml of water. Add 5 ml of hydrochloric acid R and filter; 25 ml of the filtrate complies with the limit test for sulfates.

Loss on drying. When dried to constant weight at 105°, loses not more than 2.5 per cent. of its weight.

Assay. Carry out the assay described under "Sulfanilamidum". Each ml of 0.1 M sodium nitrite is equivalent to 0.02863 g of $C_{11}H_{11}N_4O_2SNa$.

Storage. Sulfamerazine Sodium should be kept in a tightly-closed container, protected from light. Slowly darkens on exposure to light.

Remarks

Percentage calculated with reference to the substance dried to constant weight at 105° (First edition: four hours).

Upper limit of 101.0 per cent. (First edition: only lower limit).

Description. The following words transferred to Storage: "Slowly darkens on exposure to light".

Identification

A. Melting-temperature about 237° (First edition: melting-range 234° to 238°).

Completeness of solution. New test.

Arsenic. Test deleted (First edition: 2 p.p.m.)

Lead. Test deleted (First edition: 10 p.p.m.)

Chloride. New test. Limit 175 p.p.m.

Sulfate. New test. Limit 400 p.p.m.

IV. INJECTIO SULFAMERAZINI NATRICI

Revised monograph (cf. I.Ph., first ed., Vol. II.)

Sulfamerazine Sodium Injection is a sterile solution of Sulfamerazine Sodium in carbon-dioxide-free water for Injection. The content of Sulfamerazine Sodium, $C_{11}H_{11}N_4O_2SNa$, is not less than 95.0 per cent., and not more than 105.0 per cent., of the content of Sulfamerazine Sodium stated on the label. The solution is sterilized by method 1 (heating in an autoclave) described under "Injectiones".

Identification

A. To a volume equivalent to about 1 g of Sulfamerazine Sodium add a slight excess of acetic acid R; a precipitate is formed which, after filtering, washing with water and drying at 105° , has a melting-temperature of about 237° , and complies with the tests for identification A and B described under "Sulfamerazinum".

B. The filtrate from the identification test A yields the reactions characteristic of sodium.

Reaction. pH 8.5 to 10.5.

Other requirements. Complies with the requirements stated under "Injectiones".

Assay. Transfer an accurately measured volume, equivalent to about 0.5 g of Sulfamerazine Sodium, to a beaker or dish, add 75 ml of water and 10 ml of hydrochloric

Annex 1

acid R, and continue the assay as directed under "Sulfanilamidum", commencing with the words: "Cool the solution and titrate slowly with 0.1 M sodium nitrite ...". Each ml of 0.1 sodium nitrite is equivalent to 0.02863 g of $C_{11}H_{11}N_4O_2SNa$.

Storage. Sulfamerazine Sodium Injection should be kept in single-dose, hermetically-closed containers, under nitrogen, protected from light.

Remarks

English name Sulfamerazine Sodium Injection. (First edition: Injection of Sulfamerazine Sodium)

Identification

A. First edition: melting-range 233° to 238° .

Storage. The words, "under nitrogen", added.

DETERMINATION OF SMALL AMOUNTS OF ADRENALINE AND LEVARTERENOL
IN INJECTIONS CONTAINING LOCAL ANAESTHETICS

Reagents

Iodine solution. Dissolve 12 g of iodine R and 20 g of potassium iodide R in sufficient water to produce 1000 ml.

Arsenous acid solution. Dissolve 2 g of arsenic trioxide R in sufficient water to produce 1000 ml.

Phosphate buffer pH 7.0. See Supplement, p. 128.

Manganese dioxide acid-washed. Treat with shaking 250 g of manganese dioxide R with 1000 ml of 12 per cent. v/v solution of glacial acetic acid in water for 30 minutes. Decant the acid and repeat the treatment once more for 30 minutes. Again decant the acid and let the manganese dioxide R stand with the same volume of acid overnight. The acid is removed by decantation, and the manganese dioxide is washed with water until the washings have pH above 4. The manganese dioxide is air-dried, reduced to powder and finally heated, with intermittent stirring, at about 800° for 2 to 3 hours.

Ascorbic acid solution 0.1 per cent. Freshly prepared in boiled and cooled water.

Sodium hydroxide 1.1 M. Dissolve 44 g of sodium hydroxide R in sufficient ethanol (50 per cent.) R to produce 1000 ml.

Fluorescence standard. A solution of quinidine sulfate R in 0.005 M sulfuric acid is suitable. The strength of the solution depends on the fluorimeter used. A sensitive fluorimeter with primary filter with maximum transmission at 365 m μ and a secondary filter transmitting maximally over 505 m μ is suitable. It is preferable to use an instrument equipped with a photomultiplier as detector.

Method. Transfer an accurately measured volume containing about 25 to 50 μ g of levarterenol or adrenaline into a 15 ml volumetric flask. Add 2 ml of 0.1 N

Annex 2

hydrochloric acid, 2 drops of starch TS and iodine solution dropwise with shaking until a blue colour develops, then add 0.5 ml of arsenous acid solution and dilute the mixture with water to the mark. After mixing, transfer 5.0 ml to 5.0 ml of phosphate buffer pH 7.0 in a centrifuge tube. When mixing, the blue colour should disappear completely but the pH of the resulting solution should not be less than 6.5 to 6.7. Add about 0.10 g of acid-washed manganese dioxide to the tube and close with a rubber stopper and shake for about 90 seconds. Centrifuge the mixture 1 to 2 minutes at 3000 r.p.m.

Transfer 5.0ml of ascorbic acid solution 0.1 per cent. into a 25 ml volumetric flask, add 5.0 ml of the clear solution from the centrifuge tube and dilute immediately (with mixing) to the mark with sodium hydroxide 1.1 M. The time elapsing between the addition of the acid-washed manganese dioxide and the sodium hydroxide 1.1 M should not exceed 5 minutes. Transfer the solution into the fluorescence measuring cell and measure the fluorescence continuously. A slightly pronounced fluorescence maximum appears about 5 minutes after the addition of the sodium hydroxide 1.1 M and the maximum reading is recorded.

To determine the background fluorescence repeat the procedure beginning with "Transfer an accurately measured volume ...", but substitute the following for the paragraph beginning with "Transfer 5.0 ml of ascorbic acid solution 0.1 per cent ...": Transfer 5.0 ml of the clear solution from the centrifuge tube into a 25 ml volumetric flask. To this solution add 20 ml of sodium hydroxide 1.1 M and mix immediately. After 15 minutes dilute to the mark with ascorbic acid solution 0.1 per cent. and determine the fluorescence after 5 minutes. The background fluorescence can usually be neglected.

A reference curve is prepared from standard adrenaline or levarterenol solutions, also containing the other ingredients of the solution to be analysed.