



EXPERT COMMITTEE ON SPECIFICATIONS
FOR PHARMACEUTICAL PREPARATIONS

Geneva, 25-29 November 1969

TWENTY-THIRD REPORT

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INTRODUCTION

The WHO Expert Committee on Specifications for Pharmaceutical Preparations met in Geneva from 25 to 29 November 1969. Dr L. Bernard, Assistant Director-General, opened the meeting on behalf of the Director-General.

1. SPECIFICATIONS FOR THE INTERNATIONAL PHARMACOPOEIA

1.1 Proposed specifications for antituberculosis drugs

The Committee continued work on specifications for some antituberculosis drugs that are not included in the second edition of the International Pharmacopoeia¹ but are widely used in UNICEF/WHO-assisted field projects.

Draft specifications for calcium benzamidosalicylate, ethionamide, pyrazinamide, thioacetazone, thioacetazone tablets and thioacetazone and isoniazid tablets had been accepted by the Committee at its twenty-second meeting subject to changes and additions being made.

Suitable tests were evolved as a result of collaboration among the laboratories of the British Pharmacopoeia Commission, London, the National Biological Standards Laboratory, Canberra, the WHO Centre for Chemical Reference Substances, Solná, the State Institute for the Control of Drugs, Prague, and manufacturers.

In addition, the same laboratories carried out work to establish specifications for calcium benzamidosalicylate tablets, ethionamide tablets, pyrazinamide tablets, compound tablets of calcium benzamidosalicylate and isoniazid and compound tablets of sodium para-aminosalicylate and isoniazid.

The Committee agreed to specifications for the following drugs after they had been reviewed, verified and commented upon:² calcium benzamidosalicylate, calcium benzamidosalicylate tablets, calcium benzamidosalicylate and isoniazid tablets, ethionamide, ethionamide tablets, pyrazinamide, pyrazinamide tablets, sodium para-aminosalicylate and isoniazid tablets, thioacetazone, thioacetazone tablets and thioacetazone and isoniazid tablets.

1.1.1 Future work

The Committee gave consideration to related subjects which should be explored for possible inclusion in future editions of the International Pharmacopoeia.

It was agreed that a spectrophotometric assay for calcium benzamidosalicylate in tablets should be verified by collaborative testing in a number of laboratories.

It was also considered that a more satisfactory test intended to demonstrate the absence of isoniazid in these tablets should be developed.

¹ World Health Organization (1967) Specifications for the quality control of pharmaceutical preparations - second edition of the International Pharmacopoeia, Geneva.

² These specifications are available in the unpublished document WHO/PHARM/70.457.

The desirability of improving the specification for thioacetazone by including either a melting-point range and/or a test for identification by infra-red spectroscopy should be investigated.

Work carried out on specifications for ethambutol was reviewed. It was agreed that further work was required before this monograph could be completed.

1.2 Specifications for radioactive pharmaceuticals

In the twenty-second report of the Committee¹ it was recommended that WHO expand its work on the preparation of specifications for radioactive pharmaceutical products. It was noted in the report that, although WHO was responsible for the preparation of such specifications, it collaborated on certain technical matters with the International Atomic Energy Agency.

1.2.1 Specifications

Proposed specifications for radioferric citrate (⁵⁹Fe) injection, sodium radio-iodide (¹²⁵I) solution, radiocyanocobalamin (⁵⁷Co), radiocyanocobalamin (⁵⁸Co), radio gold (¹⁹⁸Au) colloidal injection, radio-iodinated (¹³¹I) human serum albumin injection, radio-iodinated (¹²⁵I) human serum albumin injection, sodium radio-iodohippurate (¹³¹I) injection and radio-iodinated (¹³¹I) sodium rose bengal injection were examined and accepted with minor modifications.²

1.2.2 Appendix on Radioactivity

During preparation of the monographs detailed above it became apparent that Appendix 13 to the second edition of the International Pharmacopoeia, "Radioactivity", was in need of revision. Accordingly, a revised text was submitted to the Committee who accepted it with minor modifications.³

1.2.3 Sodium radiochromate (⁵¹Cr) injection - methods for the determination of radiochemical purity

The Committee noted that a laboratory comparison of a number of methods for determination of the radiochemical purity of sodium radiochromate (⁵¹Cr) injection had been carried out by Dr L. Oniciu and Dr I. Galatzeanu of the International Atomic Energy Agency, and that a similar study had been carried out in the State Institute for the Control of Drugs in Prague. On the basis of these reports, and advice from other experts, the following conclusions were drawn:

(1) The method prescribed in the second edition of the International Pharmacopoeia (English edition, p. 370), relying on the precipitation of lead chromate, seriously underestimates the proportion of any chromic ion present as an impurity and cannot be recommended.

(2) With suitable instructions as to flow rates, the British Pharmacopoeia method based on ion exchange is a reliable one. Nevertheless, it is a tedious method.

¹ Wld Hlth Org. techn. Rep. Ser., 1969, 418.

² These specifications are available in the unpublished document WHO/PHARM/70.457.

³ The text is available in the unpublished document WHO/PHARM/70.457.

(3) Although the reports drew attention to possible difficulties which might arise in the method employing paper chromatography with the solvent system ethanol/water/ammonia, the indications were that this method was satisfactory in practice. Reasonable agreement between this method and the British Pharmacopoeia method had been found, and further, the method had been employed successfully for many years in a laboratory concerned with the production of this material.

(4) The thin-layer chromatographic method suggested by the International Atomic Energy Agency might well prove satisfactory, but it had not yet been examined for a sufficiently long period, and in such detail, as the other methods.

It was therefore agreed that the paper chromatographic method should be considered as a corrigendum to the International Pharmacopoeia, provided that attention was drawn to the necessity of beginning development of the chromatogram immediately after application of the spot to the paper and without allowing it to dry.¹

1.2.4 Sodium radiophosphate (³²P) injection - corrigendum

In order to correlate the test for identification included in the International Pharmacopoeia with the appendix on Radioactivity it was noted that the calculation should be based on the beta-ray absorption coefficient. A suitable text was approved.¹

1.2.5 Human serum albumin

The Committee noted the need for a supply of human serum albumin for use in the test for radiochemical purity in the two monographs on radio-iodinated human serum albumin injection and requested the Secretariat to investigate the matter.

1.2.6 Appendix on radio-elements

A proposal was received that an appendix giving essential data on those radio-elements of interest in pharmaceutical work should be prepared for possible inclusion in the International Pharmacopoeia. This proposal was approved and the Secretariat was asked to obtain the necessary information.

1.2.7 Future work

It was noted that work was proceeding on the preparation of monographs for chlormerodrin (¹⁹⁷Hg) injection, xenon (¹³³Xe) injection, sodium pertechnetate (^{99m}Tc) injection, L-selenomethionine (⁷⁵Se) injection, sodium iodide (¹³¹I) diagnostic capsules, macroaggregates of iodinated (¹³¹I) human serum albumin, tritiated water injection and 3-bromomercuri-2-hydroxypropane (¹⁹⁷Hg) injection.

The Committee noted with satisfaction the considerable technical assistance that had been provided by the International Atomic Energy Agency and expressed the hope that further collaboration in the field of radiochemical and radionuclidic studies could be continued in the future.

1.3 General recommendations

Arising from the discussion on the monographs for antituberculosis drugs and radioactive pharmaceuticals, the following general recommendations were made:

¹ The text is available in the unpublished document WHO/PHARM/70.457.

(i) that, in the International Pharmacopoeia, the description of identification tests based on spectrophotometry should include the following data:

- (a) the solvent and concentration used;
- (b) ranges within which the spectrum is to be registered;
- (c) wavelength(s) corresponding to characteristic peak(s) together with the thickness of the layer to be measured and the approximate absorbance found;
- (d) if characteristic for the identification, shoulders and minima without absorbance data may be indicated;

(ii) that early consideration should be given to the complete revision of Appendix 14 to the second edition of the International Pharmacopoeia - "Chromatography" - to meet increased needs brought about by the expanding use of such techniques;

(iii) that amendments to the General Notices of the second edition of the International Pharmacopoeia should be made as follows:

- (a) the present general notice on page xxxi, headed "Standards for drugs and preparations", should be amended as follows:

"Standards for Drugs and Preparations

"All statements of the monograph with the exceptions given below constitute standards for pharmacopoeial substances. The substance is not of pharmacopoeial quality unless it complies with all the requirements stated. The methods given for assays and tests are those on which the requirements have been based but the analyst is not precluded from employing alternative methods - provided he has satisfactorily demonstrated that such methods will give results of equivalent precision, accuracy and selectivity.

"The chemical formula and solubility statements are presented for informative purposes only and are not to be considered in the same category as the standards or tests for purity."

- (b) the following general notice should be added:

"Added Substances

"Any substances added in preparing dosage forms described in the pharmacopoeia shall be innocuous, shall have no adverse influence on the therapeutic efficacy of the active ingredients and should not interfere with the assays and tests, in the amounts present. Should interference with assays and tests occur, alternative methods of equivalent precision, accuracy and selectivity may be used to overcome the difficulty."

- (c) the following general notice should be added:

"Use of Trade Names

"Reference to a particular trade name in the description of certain materials used in assays and tests does not imply that other, equivalent, materials are not also suitable."

2. DETERMINATION OF MORPHINE IN OPIUM

The Committee reviewed the progress of work to date on this project, which had been proceeding for five years. Reports on the investigations and views of a number of experts had served to survey the problem, clarify ambiguities and reject unsatisfactory methods. Partly through WHO efforts and partly through the simultaneous efforts of outside experts, an improved assay method for morphine in opium appeared to be in sight.

Reference was made in the report of the twenty-second Expert Committee to the Schultz and Schneckenburger method¹ and a method described by Smith, Levine and Banes.²

Careful analytical research had not yet succeeded in correcting minor difficulties remaining in the Schultz and Schneckenburger method.

Collaborative studies on the Smith, Levine and Banes method, which had originally been used for the assay of paregoric, revealed deficiencies when this was adapted for the assay of opium. Further work by Smith and Levine³ appeared to have resolved these difficulties and the results of collaborative studies undertaken in one country with the method were very promising.

However, the particular importance of the assay of morphine in opium makes it most desirable to carry out corroborative studies in a number of countries on this new method in parallel with present methods. To be acceptable there should also be a satisfactory correlation between the yields of morphine in factories and the results of the Smith and Levine method.

The Committee agreed that there should be a tentative acceptance of the Smith and Levine method. Full acceptance of the method will await the results of the proposed corroborative studies. The Committee recommended that a report giving details of this project should be prepared and published.

3. INTERNATIONAL CHEMICAL REFERENCE SUBSTANCES

The twenty-second Expert Committee recommended that certain work be undertaken and that further consideration should be given to possible means of fostering closer international co-operation in the provision of reference substances. Reports on the work were considered by the Committee.

3.1 Prednisolone

It was noted that further efforts to obtain a purer substance than hitherto available had been made, but without success. Further analytical work had been carried out on the existing sample and the Committee considered that it was sufficiently pure for the purpose for which it was to be provided. Purification procedures on a small scale had been carried out at the WHO Centre and a small amount of purer material had been obtained, but it was decided not to attempt purification of the larger quantities that would be necessary for establishment of a reference substance.

¹ Arch. Pharm. (Weinheim), 1965, 298, 548.

² J. Ass. off. anal. Chem., 1968, 51, 180.

³ J. Ass. off. anal. Chem., (in press)

3.2 Nafcillin Sodium

During the establishment of this reference substance it had been noted that the Karl Fischer method of water determination appeared to give more reliable results than a loss on drying method. Results by the Karl Fischer method were, however, appreciably higher and it was therefore recommended that the limit for water content given in the International Pharmacopoeia should be increased to four per cent.

3.3 Warfarin

The twenty-second Expert Committee had noted that the monograph on Warfarin Sodium was urgently in need of revision, particularly in view of the fact that the International Chemical Reference Substance Warfarin Sodium had now been replaced by Warfarin itself. Revised monographs for Warfarin Sodium and for Warfarin Sodium Tablets were adopted by the Committee.¹

3.4 Gas-liquid chromatography

Since the newly established monograph for Warfarin Sodium requires the use of a gas-liquid chromatographic method, a suitable appendix for description of the technique was examined and adopted.²

3.5 Thin-layer chromatography of corticosteroid reference substances

It was noted that supplementary chromatographic work had been carried out in accordance with the requirements of the twenty-second Expert Committee. It was decided that this supplementary information be incorporated in the reports on the various corticosteroid reference substances.

3.6 Phase solubility analysis

In view of the importance of this technique in the evaluation of reference substances, it was decided that an appendix should be prepared for possible inclusion in the International Pharmacopoeia. A text was examined, modified and accepted by the Committee.²

3.7 Report of the WHO Centre for Chemical Reference Substances

A report was received from the WHO Centre for Chemical Reference Substances.

3.7.1 Phenoxymethylpenicillin

Work on this material was reported, but in view of certain variations between the sample examined and other, established, national reference substances, it was decided that further investigation should be carried out.

¹ These monographs for Warfarin Sodium and Warfarin Sodium Tablets are available in the unpublished document WHO/PHARM/70.457.

² The text is available in the unpublished document WHO/PHARM/70.457.

3.7.2 Tubocurarine Chloride

It was noted that a new stock of this material was required and that preliminary work had been carried out on a new batch. It was agreed by the Committee that the existing and proposed reference substances, together with other samples, should be compared in a number of laboratories by the biological method of the second edition of the International Pharmacopoeia, Appendix 58.

3.7.3 Prednisone Acetate

Material of suitable quality had now been obtained and was adopted as an International Chemical Reference Substance.

3.7.4 Fludrocortisone Acetate

It had not been possible to obtain this material in a suitable quality. In view of the apparently diminishing use of this substance for medicinal purposes it was agreed to delete the monograph from the International Pharmacopoeia.

3.7.5 New reference substances

It was noted that there would be a need to establish reference substances for o-iodohippuric acid, sodium rose bengal, p-acetamidobenzalazine, dicloxacillin and carbenicillin sodium.

3.8 Future work

The twenty-second Expert Committee had agreed that work should be initiated on the preparation of a number of reference substances. However, for adequate assessment of the work required to prepare any given reference substance it was considered essential to have full information on the use to which that substance was to be put, since this would determine the degree of purity that should be sought and the extent of testing that would be necessary. It is now required that, before any work be carried out on any substance, those who initiate the request for that substance should be invited to give full details of its intended use.

It was noted that a list of substances that might possibly figure in a revised collection of melting-point reference substances was now being considered by the Centre. It was suggested, however, that in view of the declining importance of precise melting-point determination as a means of assessing drug purity, a low priority should now be assigned to this work.

As regards the principles that should guide future policy on the establishment of reference substances, it was agreed that means of reserving as much freedom of action as possible should be adopted. It was therefore agreed that new substances should be prepared as required for the extension and possible revision of the International Pharmacopoeia and that such other substances should also be prepared as the Expert Committee may from time to time require.

The report of the twenty-second Expert Committee stated that a greater co-operative effort on the part of organizations that prepare reference standards would be desirable. Both internationally and scientifically this must certainly be the case, but it was recognized that factors existed that would make it difficult to achieve an integration of the various reference substance programmes, except as a long-term possibility. To initiate greater co-operation and a mutual exchange of knowledge and experience, it was agreed that informal contact among those responsible in the various organizations that are currently concerned in the assessment of reference substances should be encouraged to the utmost.

The Committee considered that a greater awareness of the problems associated with the preparation and provision of chemical reference substances should be encouraged. It would be advantageous if arrangements could be made to allow scientists involved in this field to work for some time at the WHO Centre in Solna.

It was also agreed that it would be helpful to include, in future reports of the WHO Centre, a list showing the countries to which chemical reference substances were distributed.

4. MICROBIAL CONTAMINATION OF NON-STERILE DRUGS

An unpublished WHO document on the microbial contamination of non-sterile drugs was considered by the Committee.¹

This document defines the scope of this very important matter and provides suggestions which could evolve into specifications for the control of microbial contamination. However, despite much valuable work it was considered that more information should be accumulated before precise specifications are published or made mandatory.

The comments upon this document received from many individuals and organizations raised a number of questions which will require further study.

Notwithstanding the unresolved problems, the Committee endorsed the general approach expressed in this document.

Arising from the discussion of the document it was suggested that all preparations designed for ophthalmic use, for introduction into normally sterile body cavities and for use in certain topical applications should be sterile.

One important aspect of this problem was recognized to be the control of contamination during manufacture. The Committee therefore recommended that, having regard to Resolution WHA22.50, additions to Good Practices in the Manufacture and Quality Control of Drugs² be made as soon as appropriate.

The discussions showed that although many standards for foods are applicable to drugs, this is not always the case. Accordingly, the Committee advised that the present general notice of the International Pharmacopoeia, "Microbiological Contamination", was no longer suitable. It was therefore recommended that a revision of this general notice be undertaken.

The Committee noted with satisfaction that a working group of the International Pharmaceutical Federation is studying this problem in depth. The recommendations of this group when they appear will be studied with interest. The Committee welcomed the co-operation already received and urged that it be encouraged and extended in the future.

It was apparent to the Committee that these developments brought a new dimension to the quality control of drugs. Manufacturers, henceforth, would be obliged to give consideration to microbial contamination as it affects raw materials, manufacturing processes, drugs now in use and those to be introduced.

¹ WHO/PHARM/69.453.

² Wld Hlth Org. techn. Rep. Ser., 1969, 418, p. 17.

5. PROPOSALS FOR FURTHER WORK ON DRUG SPECIFICATIONS

5.1 The International Pharmacopoeia

The Committee had discussed many subjects that could become new monographs of the International Pharmacopoeia. Some changes in the General Notices had also been recommended. This led to a consideration of the need for a general revision of the International Pharmacopoeia. The Committee recommended that such a revision be undertaken as soon as possible.

In the meantime, it was considered desirable that an addendum, including corrigenda, should be published in the near future so as to keep the International Pharmacopoeia abreast of recent developments. The various monographs and appendices accepted during the meeting of the twenty-third Expert Committee and collected in unpublished WHO document WHO/PHARM/70.457 would form the basis of such an addendum. Corrigenda, also adopted by the Committee, are included in this same document.

The Committee recommended that the requirements for "Good Practices in the Manufacture and Quality Control of Drugs", which were recommended by the Twenty-second World Health Assembly for adoption and application by the Member States (WHA22.50, 25 July 1969), should be included in the addendum as an appendix, since these requirements constituted an integral part of the WHO programme in the field of quality control of drugs.

A tentative list of proposed additions was considered and it was recommended that work should be undertaken to establish monographs for the substances listed in the Annex to this report. It was also agreed that steps should be taken to consider the problems involved in preparing effective specifications for synthetic polypeptides; it was recognized, however, that this would be a long-term project. It was further recommended that an appendix on Electrophoretic Methods should be prepared.

It was recommended that the Secretariat should reconsider the means by which drugs are selected for inclusion in the International Pharmacopoeia. Some drugs of special importance in certain regions are not specified in pharmacopoeias. If such drugs were to be considered for inclusion in the International Pharmacopoeia, means should be evolved to ensure that appropriate medical opinion is obtained regarding their suitability.

5.2 Early provision of drug specifications

The Committee noted that work on the early provision of specifications for drugs had been initiated in respect to Rifampicin. It recommended that the project on the early provision of drug specifications, which is a long-term one, should be continued and extended because of its importance for the programme of WHO on quality control of drugs.

ACKNOWLEDGEMENTS

The Committee extends its thanks to the following for the valuable assistance they have given: Mr W. H. Briner, Radiopharmaceutical Service, National Institutes of Health, Bethesda, Md., United States of America; Mr J. Buriánek, State Institute for the Control of Drugs, Prague, Czechoslovakia; Dr J. C. Charlton, The Radiochemical Centre, Amersham, England; Dr M. Gay, F. Hoffmann-La Roche & Co. AG, Basle, Switzerland; Professor L. O. Kallings, National Bacteriological Laboratory, Stockholm, Sweden; Mr W. J. Mader, Drugs Standards Laboratory, Washington, D.C., United States of America; Mr B. W. Mitchell, Smith & Nephew Research Ltd., Harlow, England; and Dr G. Urakubo, Department of Radiochemistry, National Institute of Hygienic Sciences, Toko, Japan.

ANNEX

LIST OF DRUGS SUGGESTED FOR INCLUSION
IN THE INTERNATIONAL PHARMACOPOEIA

Note: International nonproprietary names proposed by WHO are used whenever available. In the case of salts and esters the names are devised, in accordance with usual practice, from the INN applying to the free acid, base or alcohol. Names applying to substances for which no international nonproprietary names have yet been selected are designated with an asterisk.

aceclidine	cycloserine tartrate
aethoxyde*	desipramine hydrochloride
allopurinol	dexamethasone sodium phosphate
aminocaproic acid	dextromoramide tartrate
amitriptyline hydrochloride	dextropropoxyphene napsilate
anethole trithione*	diazepam
azethioprine	dicloxacillin
beclometasone dipropionate	dicolin*
bendazol hydrochloride	dihydrocodeine tartrate
benzatropine mesilate	dihydrotachysterol
benzonal*	dimetindene maleate
betanidine sulfate	disodium edetate
bupivacaine hydrochloride	doxycycline
capreomycin	ecothiopate iodide
carbenicillin sodium	etacrynic acid
cefaloridine	ethchlorvynol*
cefalotin sodium	ethosuximide
chinocide hydrochloride*	ethoxzolamide*
chloracyzine hydrochloride	etynodiol diacetate
chlordiazepoxide hydrochloride	fluorouracil
chlormadinone acetate	fluoxymesterone
chlorotrianisene	fluphenazine hydrochloride
chlorphenamine maleate	furosemide
chlorprothixene	galantamine hydrobromide
chlortalidone	ganglefene hydrochloride
clefamide	gentamicin sulfate
clioquinol	halazone*
clofibrate	haloperidol
cyclopenthiiazide	hydroxyprogesterone caproate
cyclopentolate hydrochloride*	idoxuridine
cyclophosphamide	imipramine hydrochloride

Annex

indometacin	phenelzine sulfate
kanamycin	phenformin hydrochloride
levodopa	phytomenadione
lincomycin hydrochloride	pipazetate hydrochloride
lithium carbonate*	propranolol hydrochloride
lynestrenol	protionamide
magnesium chloride*	quinethazone
mefenamic acid	securinine nitrate*
megestrol acetate	sodium acetate*
melphalan	sodium bicarbonate*
mestranol	sodium dioctyl sulfosuccinate
metacycline hydrochloride	sulfinpyrazone
metaraminol bitartrate	sulfomyxin sodium
metformin hydrochloride	sultiame
methacine*	thioridazine hydrochloride
methaqualone	thiotepa
methazide*	tiabendazole
methoserpidine	tiotixene
methotrexate	tolazamide
methoxyflurane	tolnaftate
methyl dopa	triamcinolone
methyl dopate hydrochloride*	triamcinolone hexacetonide
methylphenidate hydrochloride	triamterene
metronidazole	trimeperidine hydrochloride
metyrapone	tropicamide
mitomycin-C*	vinblastine sulfate
niclosamide	vincristine sulfate
norethisterone	xantinol nicotinate
norethisterone acetate	
noretynodrel	
orciprenaline sulfate	
oxazepam	
oxylidine*	
oxyphenbutazone	
panthenol	
phenazocine hydrobromide	