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**WHO EXPERT COMMITTEE
ON SPECIFICATIONS FOR
PHARMACEUTICAL
PREPARATIONS**

Twenty-First Report

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WHO EXPERT COMMITTEE ON SPECIFICATIONS
FOR PHARMACEUTICAL PREPARATIONS

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WHO EXPERT COMMITTEE ON SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS

Twenty-First Report *

1. INTRODUCTION

The WHO Expert Committee on Specifications for Pharmaceutical Preparations met in Geneva from 3 to 9 November 1964. Dr P. Dorolle, Deputy Director-General, opened the meeting on behalf of the Director-General and welcomed the participants. He expressed the thanks of the Organization for the assistance given by a number of the participants and other specialists who were collaborating in the difficult task of preparing and proposing at the international level specifications for the quality control of pharmaceutical substances. This work had, in the last few years, included revision of the specifications of the monographs and appendices of the three volumes of the first edition of the International Pharmacopoeia, and the preparation of specifications for new pharmaceutical substances introduced on the market in different countries. This co-operation made it possible for the WHO Secretariat to prepare the specifications that are now being proposed for the second edition of the International Pharmacopoeia. Meetings of consultants had been convened to discuss a number of problems concerning some of the specifications.

A provisional text of the second edition of the International Pharmacopoeia was sent on 9 March 1964 to members of the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations and a number of other specialists interested in this work with a covering letter asking for comments, which were examined for possible integration in the provisional text. It was thus possible to prepare the revised and completed provisional text, which was recently forwarded, in English and French, to the 118 Member States and 6 Associate Members of the World Health Organization. A letter from the Director-General,

* Reports Nos. 1-7 were published under the name *Expert Committee on the Unification of Pharmacopoeias* and reports Nos. 8 and 9 under the name *Expert Committee on the International Pharmacopoeia*; reports Nos. 10-20 were issued in mimeographed form only.

dated 28 October 1964, informed Member States of the despatch—by air mail—and asked Governments to submit comments within three months of the date of mailing. In the 526 monographs and 72 appendices of this provisional text, specifications are proposed for the quality control of the more important part of all pharmaceutical substances used in the different countries in various pharmaceutical forms and mixtures. It should prove of considerable help to countries in the difficult task of checking the quality both of the pharmaceutical preparations that they manufacture locally and of those that they import.

The control of the quality of pharmaceutical preparations presents difficulties in many countries, especially with the increasing number of pharmaceutical substances and pharmaceutical specialities now in international commerce and of pharmaceutical products made locally in the different countries for the internal market. A resolution of the World Health Assembly, WHA17.41,¹ called attention to the need to subject all pharmaceutical preparations, whether produced within a country for home consumption or for export or whether imported, to an adequate control, and to ensure that pharmaceutical preparations that are exported from a country will “comply with the same drug control requirements as apply to drugs for its domestic use”. The Committee had before it a report expressing the general aspects of the problem, prepared by the WHO Secretariat, as well as the report of the WHO International Reference Centre for Chemical Reference Substances.

A volume containing proposed specifications for reagents mentioned in the International Pharmacopoeia had been published in 1963.² Specifications for other reagents used in connexion with tests and assay described in the second edition of the International Pharmacopoeia would be included in that publication.

It was hoped that, with the continued assistance of members of the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations and of other specialists, national laboratories for quality control, manufacturing firms, etc., it would be possible for the Secretariat to integrate comments received from Member States and other sources into the proposed text of the second edition of the International Pharmacopoeia and have the text ready for printing within the next few months. The publication will help all Member States and be in the interests of public health and international commerce.

¹ *Off. Rec. Wld Hlth Org.*, 1964, 135, 18.

² World Health Organization (1963) *Specifications for reagents mentioned in the International Pharmacopoeia*, Geneva.

2. REVISION OF DRAFT MONOGRAPHS AND APPENDICES FOR THE SECOND EDITION OF THE INTERNATIONAL PHARMACOPOEIA

A large part of the Committee's deliberations was devoted to a number of studies and comments obtained from working groups, specialists, manufacturing firms, etc., in different countries on the provisional text for the second edition of the International Pharmacopoeia.

The convening of the meetings of consultants had also made it possible to prepare some of the material for discussion by the Committee. The Committee noted with satisfaction that a meeting of consultants earlier in the year had examined many of the comments received and had proposed specifications that have been incorporated in the specifications in the provisional text sent to Member States on 28 October 1964, complementing the provisional text sent to members of the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations and other specialists, with the circular letter of 9 March 1964.

Another meeting of consultants on the specifications for the important new group of the semi-synthetic penicillins had made it possible to present the members of the Committee with a complete set of up-to-date specifications that would considerably help the setting-up of an official quality control of the preparations and their pharmaceutical forms in national laboratories for pharmaceutical quality control.

The principal subjects discussed in connexion with these specifications are given in the following paragraphs :

2.1 Order of the monographs; titles; chemical names; formulas

The Committee noted that there were practical advantages in arranging the monographs in the Pharmacopoeia in such a way that the monograph on the basic drug is followed immediately by the monograph or monographs on preparations of the drug, such as injections and tablets. This arrangement has already been adopted in some national pharmacopoeias. It was agreed that in the second edition of the International Pharmacopoeia the strictly alphabetical arrangement of the monographs used in the first edition should be abandoned, and that the monographs on preparations should follow immediately after the monograph on the basic drug.

The Committee examined a document setting out the titles, chemical names, formulas, molecular weights and equivalents recommended for adoption in the monographs. It was agreed to express molecular weights to five significant figures with, in most instances, two figures after the decimal point. It was also agreed to apply rounding-off rules for the last figure, in accordance with the recommendation of ISO, if these are available.

It was noted that the title "digitoxoside" had a generic implication, and it was agreed to replace it by the title "digitoxin", which already has wide usage. The title "digitoxoside" would appear in the monograph as a synonym.

Proposals for the style and system to be followed for graphic formulas were received and approved.

2.2 General methods

2.2.1 *Determination of melting-range, melting-temperature and congealing-temperature*

The Committee considered a revised text of Appendix 6, entitled "Determination of melting-range, melting-temperature and congealing-temperature", intended for the second edition of the International Pharmacopoeia.

As most commercially available apparatus for the determination of melting-points uses thermometers calibrated for partial immersion, both partial and total immersion types of thermometer were recommended for mention in the second edition of the International Pharmacopoeia. The emergent-stem correction should be also applied to the thermometers calibrated for partial immersion.

The revised text includes a definition of the term "melting-temperature about...", which means that the melting-temperature obtained by the method described should not differ by more than $\pm 2^{\circ}\text{C}$ from the stated temperature. This term will be used in the identification tests of the International Pharmacopoeia when the melting-temperature is to some extent affected by the state of purity of the derivative obtained in the test.

2.2.2 *Radioactive pharmaceuticals*

The text of a general chapter on radioactivity based upon the relevant chapter in the seventeenth edition of the US Pharmacopoeia was agreed upon for use as an appendix to the second edition of the International Pharmacopoeia.

The necessity for applying tests for sterility and freedom from pyrogens was examined, and the Committee agreed that, where indicated, these requirements should be added to the individual monographs for products intended for injection. With respect to the pyrogen test, the Committee noted that test animals are to be used only once for tests on radioactive substances.

2.2.3 *Determination of calcium*

The Committee agreed that hydroxynaphthol blue and calconcarbonic acid should be used instead of calcein-thymolphthalein and methylthymol blue.

2.2.4 *Determination of melting-range and identification by the Kofler method*

The Committee considered and approved the inclusion in the second edition of the International Pharmacopoeia of tables containing data for identification of the substances of the International Pharmacopoeia, submitted by Professor M. Kuhnert Brandstätter, and using the Kofler hot stage and the Kofler hot bar. These tables contain melting-points, eutectic temperatures and data for the identification of substances, using the hot stage and glass powders of defined refractive indices.

Since the melting-temperatures of the WHO melting-point reference substances as determined by the capillary method differ from those determined by the Kofler method, it was agreed that an additional statement should be added on the label of the WHO melting-point reference substances to indicate the melting-point according to the Kofler method.

2.2.5 *Steroid assay*

The Committee accepted a revised procedure for the determination of those pharmacopoeial steroids, including their pharmaceutical forms, that have reducing functional groups of the α -ketol type. A blue tetrazolium reagent will be used in the tests instead of triphenyltetrazolium chloride. The method requires the use of the specific chemical reference substance.

2.2.6 *Folic acid assay*

A modified procedure was accepted for the determination of folic acid. It involves the use of potassium permanganate as a cleaving agent and a folic acid chemical reference substance.

2.3 **Action and use**

The Committee received with appreciation and agreed to accept the list of proposed statements on Action and Use.

Special attention was drawn to the footnote to the list, which states :

“ The statements given under this heading in monographs are intended only as information on the principal pharmacological actions and uses of the materials in medicine or pharmacy. It should not be assumed that the substance has no other action or use. The statements are in no way intended to be binding on prescribers or to limit their discretion. ”

It was noted that the categories in the list are based on criteria of several kinds—chemical, pharmaceutical, pharmacological and therapeutic. However desirable it might be to adhere to any one system of classification, limitations of terminology make this impossible. Furthermore, any one group of criteria, e.g., pharmacological, is bound to cut across the lines of other groups, e.g., chemical or pharmaceutical.

2.4 Doses for adults and children

The Committee examined the proposed table of Usual and Maximal Doses for Adults and the related table of Usual Daily Doses for Children for use as appendices to the second edition of the International Pharmacopoeia, and expressed appreciation of the care with which the tables had been prepared.

2.5 Ergot alkaloids

Methods for the determination of ergometrine in Ergometrine Maleate Injection and Ergometrine Maleate Tablets were discussed.

A proposed procedure, based upon thin-layer chromatography, was provisionally adopted for inclusion in the second edition of the International Pharmacopoeia. The proposed limits for ergometrine, namely 5% of the ergometrine content for the tablets, and 10% of the ergometrine content for the injection, were provisionally accepted, but it was felt that further investigation was needed before the limits could be finally adopted.

2.6 Assay method for morphine in opium

It is proposed that the adoption of a new assay for the alkaloids in opium should be approached in two stages. In order to provide quickly an improved assay for the principal alkaloid, morphine, laboratories already engaged in opium assay will be asked to compare the method of the Austrian Pharmacopoeia IX with whatever method they now use routinely. The collaborating laboratories might be two or more of the firms producing morphine, the Food and Drug Directorate Laboratories in Ottawa, the laboratory of the British Pharmacopoeia Commission, the Institute for the Control of Drugs in Zagreb, and the laboratory of the Narcotics Division of the United Nations in Geneva. Suitable samples will be selected from authenticated stocks already available.

Comparative collaborative tests will be arranged as necessary, and the results will be incorporated in a report which will include proposals for suitable methods.

It was moreover considered desirable to initiate longer-term studies of available sensitive and selective methods for the assay of morphine in formulations, including official opium, and for the determination of the main subsidiary alkaloids in both raw opium and in official opium formulations. Requests will be made to the same collaborating laboratories to try one or more selected test methods, using the same opium samples provided for the above-mentioned trial of the modified Mannich method of the Austrian Pharmacopoeia IX.

2.7 Tuberculostatics

Specifications for a number of tuberculostatic preparations were examined and the following decisions were taken :

(a) *Sodium para-aminosalicylate*. The limit of 0.03% for 3-aminophenol was accepted, and a new revision of the monograph was also adopted.

(b) *Sodium para-aminosalicylate tablets*. The test for colour of solution should be deleted.

(c) *Sodium para-aminosalicylate and isoniazid tablets*. The proposed assay method for isoniazid was adopted. It has been reported to give low results, and it was therefore agreed to have the method further examined and to revise the monograph.

(d) *Calcii para-aminosalicylate*. It was decided to describe only the trihydrate form.

(e) *Isoniazid*. The proposed test for isonicotinic acid was adopted with 1% limit. A new test for the clarity and colour of the solution was accepted.

(f) *Isoniazid tablets. Cycloserinum*. The relevant monographs were adopted.

2.8 Specifications for semi-synthetic penicillins

Ampicillin	Methicillin Sodium
Ampicillin Trihydrate	Nafcillin Sodium
Ampicillin Capsules	Nafcillin Sodium Capsules
Ampicillin Sodium	Nafcillin Sodium Injection
Ampicillin Sodium Injection	Phenethicillin Potassium
Cloxacillin Sodium	Phenethicillin Potassium Capsules
Cloxacillin Sodium Capsules	Phenethicillin Potassium Tablets
Cloxacillin Sodium Injection	Propicillin Potassium
Oxacillin Sodium	Propicillin Potassium Capsules
Oxacillin Sodium Capsules	Propicillin Potassium Tablets
Oxacillin Sodium Injection	

As a general test for identification an infra-red method was accepted. The assay procedures accepted included a method based on the hydrolysis of the β -lactam ring of the penicillanic acid nucleus by sodium hydroxide under controlled conditions. Further, it was thought advisable to include an assay for the specific penicillin side-chain; for instance, a non-aqueous titration of the amino-group of the aminophenylacetic acid in ampicillin.

The presence of the desired optical isomers of those penicillins that contain an active carbon atom in the side-chain is ascertained by the specified optical rotation.

It was agreed to base the chemical name on the model "benzylpenicillin" and not on "6-(phenylacetamido)penicillanic acid".

The WHO International Reference Centre for Chemical Reference Substances was asked to supply chemical reference substances as requested in the different tests and assays in the monographs.

2.9 Other monographs

Revised monographs for castor oil, nicotinamide injection, primaquine diphosphate, ethyl oleate and lidocaine hydrochloride injection were considered and approved for inclusion in the second edition of the International Pharmacopoeia.

It was agreed that ethyl oleate may contain a suitable antioxidant, the nature of which should be stated on the label.

The content of lidocaine hydrochloride in a lidocaine hydrochloride injection will be calculated on the basis of the anhydrous substance.

2.10 Correlation of official specifications for pharmaceutical quality control

The Committee was informed of the work of a Commission for Specifications recently set up under the Council of Europe. It is the aim of this Commission to prepare specifications for official adoption in eight countries. The Committee expressed the view that such unification of specifications would benefit public health and international commerce and should be undertaken whenever possible, in the different countries, using as a foundation the proposed draft specifications of the second edition of the International Pharmacopoeia.

A similar opinion was expressed with regard to the work of the Nordic Pharmacopoeia Commission, which has been preparing specifications for five countries, and it is hoped that similar inter-country organizations will be set up in other regions of the world with a view to establishing common specifications for official pharmaceutical quality control.

3. WHO INTERNATIONAL REFERENCE CENTRE FOR CHEMICAL REFERENCE SUBSTANCES

The Committee received with appreciation the report on the work of the WHO International Reference Centre for Chemical Reference Substances for the year 1964.

In accordance with the directions of the Expert Committee meeting of 19-23 November 1962 the Centre has planned to prepare chemical reference substances to be used in conjunction with monographs in the second edition of the International Pharmacopoeia in the following cases :

- (a) when infra-red identification is required ;
- (b) when chromatographic tests and assays are given in the monographs ;

(c) when spectrophotometric or photometric methods are necessary for the determination of the substance.

So far, of the substances that have been studied, four are proposed as chemical reference substances. These are dexamethasone, hydrocortisone acetate, methyltestosterone, and testosterone propionate. Each of these samples has been submitted to the following tests :

- (1) Melting-temperature determination by the methods of (a) the International Pharmacopoeia, (b) Kofler hot stage, and (c) Kofler hot bar.
- (2) Specific rotation.
- (3) Infra-red absorption.
- (4) Ultra-violet absorption.
- (5) Loss on drying.
- (6) Residue on ignition.
- (7) Thin-layer chromatography.
- (8) Phase-solubility analysis.

As an example of the manner used in presenting these data, the report on dexamethasone is given in Annex 3.

The present Progesterone Chemical Reference Substance, which is identical with the former biological standard, has been found to contain about 3% of impurities. It was decided to replace this Chemical Reference Substance by a substance of higher purity which is now readily available. It was also decided to replace the present Digitoxin Chemical Reference Substance, which contains about 2% of gitoxin, by a substance practically free from impurities.

The Committee approved of the test methods being used by the Centre. It also recognizes that a flexibility of approach is required. For instance, in some cases the determination of specific rotation or loss on drying might be superfluous, and in other cases additional test methods might be advisable or necessary. Further, methods already in use might be put on a more solid basis, perhaps through the use of instrumentation. For example, in thin-layer chromatography, it would be desirable for the Centre to use a densitometer to measure more accurately the separated components in the chromatogram. The Committee also recommended that the Centre consider adoption of new test approaches, such as crystallographic examination and description, optical rotatory dispersion, spectrofluorimetry, or other methods, as they become available. This recommendation recognizes the need for more and better methods for the establishment of purity characteristics, as the practice of drug manufacture becomes more complicated.

The Committee considered it necessary to establish a working method by which the Centre could advance the status of a proposed chemical

reference substance to the status of a WHO International Chemical Reference Substance, between meetings of the Expert Committee. The following steps were recommended :

The Centre, having obtained a supply of reference standard substance from a suitable supplier, examines it according to the tests already outlined. In the event of the analytical examination showing the sample to be acceptable, the Centre will select one or more national drug control laboratories, and will ask these laboratories to examine the sample by the methods used at the Centre. The collaborating laboratories will be free to use additional or equivalent tests, at their discretion.

If the collaborating laboratories confirm the acceptability of the sample, their reports will be added to that of the Centre, and the latter will submit a full report, together with a recommendation to accept the material represented by the analysed samples as a WHO International Chemical Reference Substance.

This report and a recommendation will be forwarded to the Secretariat, which, after consultation with the Chairman of the last WHO Expert Committee on Specifications for Pharmaceutical Preparations, can authorize the Centre to proceed with the use of the material as a WHO International Chemical Reference Substance.

When the substance has been selected between meetings of the Expert Committee, a full report will be submitted to the Committee for approval of the WHO International Chemical Reference Substance.

The Committee approved a revision of the appendix "WHO International Chemical Reference Substances" proposed for the second edition of the International Pharmacopoeia.

4. STABILITY OF PHARMACEUTICAL PREPARATIONS

It is self-evident that although the initial quality of purchased drugs can be controlled, pharmaceutical preparations may have suffered deterioration by the time they are administered. The types of packaging used can have great effects upon the stability of a drug, especially in the tropics, and yet drugs are frequently purchased solely on cost and initial quality, without regard to their keeping properties. The problem of drug stability as a whole is vast. Concentration on certain facets is therefore essential, and the Committee expressed the opinion that information should be collected under WHO on the investigations of producing firms, scientific institutes and others on the stability of certain pharmaceutical preparations.

The Committee proposed that practical work could be carried out on a selected pharmaceutical preparation and that para-aminosalicylic acid should preferably be chosen; studies should be made both on the pure

compound and on its pharmaceutical forms and mixtures. A reason for this choice is that large doses are administered for prolonged periods and that some of the decomposition products may possibly be toxic; the eighth report of the WHO Expert Committee on Tuberculosis stated that "checking on the purity and keeping properties of anti-tuberculosis drugs is of great importance, as is ensuring that commercial combinations of anti-tuberculosis drugs contain those drugs in adequate proportion and quantities".¹

The study on para-aminosalicylic acid and its pharmaceutical forms and mixtures would be divided into short-term and long-term studies.

It is proposed that one or two pharmaceutical institutes should be asked to undertake a study on the stability of para-aminosalicylic acid and to develop tests for the investigation of the decomposition products. Samples of the pharmaceutical chemical and its pharmaceutical forms would be obtained from producers and from the field, especially in countries where climatic conditions are likely to cause deterioration. The results of the tests could become part of the specifications for the quality control of the preparation. A longer-term study would deal with the isolation of the decomposition products of para-aminosalicylic acid, and chronic toxicity testing might also be undertaken.

A working group was asked to consider the general problem of the stability of pharmaceutical preparations in relation to pharmaceutical quality control, and to prepare a report for submission to members of the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations and other specialists.

The Committee noted with interest a report on the quality of the iodinated organic radio-opaques and recommended that it should be included as an annex to the report (see Annex 2).

5. INTERNATIONAL NON-PROPRIETARY NAMES

The thirteenth report of the Sub-Committee on Non-Proprietary Names was received and discussed. It was noted that more than 200 requests for non-proprietary names had been examined by members of the Sub-Committee during the preceding year and that as a result of the decisions taken a fourteenth list of Proposed International Non-Proprietary Names had been issued in accordance with the Procedure for the Selection of Recommended International Non-Proprietary Names for Pharmaceutical Preparations². Experience continued to show the advantages that accrued when

¹ *Wld Hlth Org. techn. Rep. Ser.*, 1964, 290, 17.

² Resolution EB15.R7 (*Off. Rec. Wld Hlth Org.*, 1955, 60, 3).

requests for international non-proprietary names were first scrutinized and then forwarded by a national authority rather than submitted direct by individual manufacturers or other persons. It had been agreed that when a name submitted direct to WHO by a manufacturer was not acceptable to the Sub-Committee, the manufacturer should be notified of the non-proprietary name that it was intended to adopt, and that publication should be deferred if objections were received.

It was noted that in the light of experience some amendments and additions had been made to the General Principles for Guidance in Devising International Non-Proprietary Names, and that a revised statement was annexed to the latest list of names.

During the discussion of the report, reference was made to the provision of an up-to-date Cumulative List and the possible extension of the information provided in the List. Members stressed the importance of providing revised editions of the Cumulative List at intervals in order to avoid the difficulties and inconvenience experienced when a number of supplementary lists had to be consulted.

Reference was also made to the value of an index of molecular formulas of the compounds as a means of rapid identification of the non-proprietary names, and it was suggested that this index would be a valuable addition as an annex to a cumulative list. The Sub-Committee was also asked to consider the inclusion of the graphic formula of the compound, where appropriate.

6. REFERENCE SAMPLES FOR VEGETABLE DRUGS

At the last meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, consideration was given to the establishment of reference samples of vegetable drugs. The Committee expressed the opinion that a study should be made of the possible needs for a Centre for such reference samples to be set up under WHO, on the lines of WHO Centres for Chemical Reference Substances in Stockholm and for Biological Standards in Copenhagen, Weybridge and London.

The Committee suggested that advice should be obtained from experts in this field to determine what vegetable drugs were of international interest in this respect. It was agreed that it would be advisable to collect information for the benefit of national pharmacopoeia commissions and other authorities dealing with pharmaceutical quality control on the arrangements for checking the quality of vegetable drugs. This information would also be useful in determining the possible needs for a Centre for reference samples.

7. PHARMACEUTICAL FORMULATIONS

Consideration was given to a proposal for the preparation of specifications for pharmaceutical forms and mixtures, in addition to the few tablets and injectable solutions of the International Pharmacopoeia. It was the opinion of the participants that this proposal should be discussed by correspondence and by a future Committee.

8. QUALITY CONTROL OF PHARMACEUTICAL PREPARATIONS

The Committee reviewed a document prepared by the WHO Secretariat on the quality control of pharmaceutical preparations. This resulted from a resolution of the World Health Assembly inviting each Member State to consider the feasibility of ensuring that "drugs which are exported from that State comply with the same drug control requirements as apply to drugs for its domestic use".¹ The Committee agreed with the general terms of the document and decided that it should be annexed to the present report (see Annex 1).

The Committee emphasized the importance of the subject and the necessity for action. It expressed the opinion that it would be advisable to hold meetings of persons directly responsible for pharmaceutical quality control in the various countries, preferably at the regional level. At these meetings, experts from other regions could be invited to attend and to contribute the results of their experience in this field.

It was agreed that the establishment of new facilities, or the extension of existing facilities, for the training at all levels of personnel in the analysis and quality control of pharmaceutical preparations was of primary importance in the interests of public health. In this connexion, reference was made to the chapters on the formation of personnel of a pharmaceutical control laboratory in the report of the WHO Study Group on the Use of Specifications for Pharmaceutical Preparations,² and on the organization of services for official pharmaceutical quality control in the report of the European Technical Meeting on the Quality Control of Pharmaceutical Preparations.³ Stress was also laid on the need to assist Member States, whenever requested, in the establishment of laboratories for pharmaceutical quality control, adequately staffed and equipped, with special reference to countries dependent largely on imported pharmaceutical preparations.

¹ Resolution WHA 17.41 (*Off. Rec. Wld Hlth Org.*, 1964, 135, 18).

² *Wld Hlth Org. techn. Rep. Ser.*, 1957, 138.

³ *Wld Hlth Org. techn. Rep. Ser.*, 1962, 249.

Annex 1**QUALITY CONTROL OF PHARMACEUTICAL PREPARATIONS****1. Introduction**

The following considerations are submitted for an examination of the general problem of the control of quality, purity, potency and sterility of pharmaceutical preparations.

For the purpose of this report, " pharmaceutical preparations " include pharmaceutical chemicals as raw material for the preparation of pharmaceutical forms, preparations in bulk to be packed in the importing country, and pharmaceutical specialities packed ready for use, including tablets, injectable solutions, dragees, ointments, suppositories, and ophthalmic preparations. These specialities may include preparations containing a single drug or a mixture of many active principles such as, for example, isoniazid with para-aminosalicylic acid, and mixtures of antibiotics, steroids, vitamins, analgesics, etc.

2. Quality control of imported and exported products

The control of the identity, purity, potency, sterility, etc., of these preparations is covered by the expression " pharmaceutical quality control ". Pharmaceutical quality control does not cover the clinical and pharmacological evaluation of pharmaceutical preparations. It is therefore a pharmaceutical problem, concerned with the conformity of pharmaceutical preparations with their labelling (whereas the evaluation of pharmaceutical preparations is a medical problem concerned with the therapeutic action of the preparations, including any adverse reactions they may produce). It can be effected by :

(a) The manufacturer, during the making of the basic pharmaceutical chemical and during the processing of the chemical for use, when it is combined with one or more active principles, excipients, colouring material, buffering agents, stabilizers, preserving agents, etc. A difficulty arises from the fact that a pharmaceutical speciality made in an exporting country will often contain drugs produced in another country, and the manufacturer of the speciality may not know what quality tests have been carried out on these chemicals. The producing country may exercise no official quality control over pharmaceutical products. It should be remembered that all batches of manufactured pharmaceutical chemicals and preparations must be examined. Evidence establishing the safety and effectiveness of one or more batches of a drug is no guarantee of the safety and effectiveness of subsequent batches.

(b) The national control authority, which can inspect the work done by the manufacturers in the testing of the quality of their products and take samples for analysis in a national control laboratory. A number of countries make provision for national quality control in their legislation. However, in many cases preparations are checked in the national laboratories only at the time of their first appearance on the market, if at all, and some exporting countries, in practice, carry out little or no official quality control of the preparations sold in their own and in other countries. Other countries that are large exporters of drugs have no regulations at all regarding quality control by a national or provincial authority, even for the drugs and pharmaceutical specialities used within the country itself.

The problem of finding ways and means to ensure that exported drugs comply with the requirements of the exporting country is further complicated by the fact that manufacturers and agents may produce and export drugs that conform to the requirements of their country but that are used only to a very limited extent in their country, or not at all. In such a case, there may be no quality control of the preparations.

Quality control is growing more urgent year by year, as the number of manufacturers of pharmaceutical products and the number of countries exporting these products steadily increase.

Inspection of the plants of pharmaceutical manufacturers and examination of the qualifications of their staff and of their equipment for quality control could, to a certain extent, ensure the adequacy of the quality of the drugs produced in a country. For drugs imported into a country, however, the importing country would need to be satisfied that pharmaceutical quality control has been carried out adequately in the exporting country. Certain countries have now introduced legislation requiring inspectors to be sent to verify the adequacy of the quality control in the country from which they believe the drug originates. However, whether the exporting country or the manufacturers in that country would allow such inspection of factories is an open question.

3. Packaging

The quality of the packing material is a matter of some importance, since chemical changes will take place if proper packing and storage conditions are not observed. This is particularly relevant when products are sent to tropical countries, since the formation of decomposition products may increase the toxicity of the drug or decrease its strength, even to the point of complete inactivity. Packaging providing sufficient protection in one country may be wholly insufficient for export purposes to certain climates, especially in poor transport and storage conditions. In such cases, even expiry dates may not afford sufficient protection, and it may happen that

products (for instance, antibiotics) that are of the required quality at the time of export will lose much of their strength before they are used in the importing country. The instability of certain drugs makes retesting necessary at certain intervals.

4. Testing in an official laboratory

The most effective way of controlling the quality of imported drugs is to test representative samples in an official laboratory in the importing country. The quality control of pharmaceutical preparations requires a national laboratory with a well-trained staff and adequate equipment. Reference to the problems involved can be found in section 8 of the report of the WHO Study Group on the Use of Specifications for Pharmaceutical Preparations,¹ and in section 4 of the report of the European Technical Meeting on the Quality Control of Pharmaceutical Preparations.²

5. Certification of quality

Certificates issued by the pharmaceutical manufacturers, agents or government authorities in the exporting country would at first sight appear to give the importer a valid assurance that the pharmaceutical preparation concerned is of a sufficiently high quality. However, these certificates may afford only a temporary and inadequate solution to the problem, and the following considerations are submitted on this subject.

In certain countries, pharmaceutical quality control is left in the hands of the manufacturers, and there is no quality control by the national authority either of the drugs used in the country or of the drugs exported. In such circumstances, a certificate stating that the "drugs which are exported from that State comply with the same drug control requirements as apply to drugs for its domestic use"³ can hardly be satisfactory.

When drugs are imported from countries that do maintain official quality control, both of drugs used domestically and of drugs exported, it may nevertheless be insufficient merely to receive an assurance that the drugs are fit for therapeutic use.

A certificate issued by the exporter or the exporting country may be of practical help to a country that has not yet made arrangements for an adequate quality-control laboratory of its own, but only if the importer is satisfied that :

(a) pharmaceutical preparations for export have been submitted to the same quality-control regulations as those governing domestic use ;

¹ *Wld Hlth Org. techn. Rep. Ser.*, 1957, 138.

² *Wld Hlth Org. techn. Rep. Ser.*, 1962, 249.

³ Resolution WHA17.41 (*Off. Rec. Wld Hlth Org.*, 1964, 135, 18).

(b) an efficiently organized quality control exists within the pharmaceutical manufacturing industry, including control of every batch of raw material and of every batch of the pharmaceutical preparations produced in bulk or ready for use ;

(c) an efficient inspection is carried out by the national authority of all pharmaceutical manufacturing establishments, as well as of the staff and facilities for quality control ;

(d) all pharmaceutical preparations for local use or for export have been registered by competent staff, together with adequate physicochemical and biological quality-control specifications ;¹

(e) the packing of the pharmaceutical preparation is adequate for transportation and storage, especially in tropical countries, and the storage in the importing country is adequate to preserve the drug from loss of potency and from decomposition, which may lead to the production of undesirable or toxic side effects ;

(f) the certificate of quality concerns the specific batch of pharmaceutical preparation imported.

A country importing pharmaceutical preparations should first ascertain that the above requisites exist in the exporting country by studying both the regulations of that country and the standard of quality control in the industrial and official laboratories. There may be significant differences between regulations on pharmaceutical quality control and their application in the laboratory. When these requisites are met, two or more countries can make arrangements to accept each other's certificates.

6. Laboratory testing for quality

When the requisites listed in section 5 cannot be met, assurance that the quality of imported drugs is sufficient for therapeutic use can be obtained only by examination of samples of the imported drug in :

(a) a national laboratory for quality control in the importing country ;
or

(b) the laboratory of a pharmaceutical, chemical or medical institute in the country, or, if found satisfactory, a private laboratory ; or

(c) a laboratory accepted by the importing country in the exporting country or in a third country.

¹ In this connexion it would be useful to obtain a statement from the national authorities of the exporting country that the pharmaceutical preparation exported is still on its market. In this way, obsolete preparations that may still be registered can be eliminated.

Samples of the imported batches of the raw material or of the pharmaceutical forms (including pharmaceutical specialities in bulk or as the finished product ready for use) should be obtained and sent to the selected laboratory for quality control.

It is important to note that production of pharmaceutical preparations is increasing very rapidly in developing countries. Indigenous pharmaceutical factories are being established by governments in some of these countries. Satisfactory quality control of these preparations by inspection at the production level and in a national laboratory independent of the producer is a necessity for these developing countries.

A satisfactory quality of all drugs, whether produced within a country for home consumption or for export or imported, is indispensable for the protection of health. The establishment of good quality control will make it possible to ensure a comparative level of quality and potency for all drugs in the different Member States of WHO.

WHO gives on request lists of laboratories in a number of countries where samples of a drug can be sent by an importer or an importing country for analytical quality control.

The difficulties and expense of installing and staffing an adequate national laboratory for pharmaceutical quality control will be amply compensated by the assurance it can give that imported drugs are of the right quality and by enabling a good choice to be made when pharmaceutical preparations are offered at varying prices by exporters in different countries. A national laboratory will make it possible for national administrations, hospitals, etc., to purchase their pharmaceutical chemicals used as raw material for domestic pharmaceutical manufacturing and their bulk pharmaceutical preparations, including specialities, from manufacturers and agents in different countries and be confident that they are buying drugs of the right quality and at the best possible price.

7. Aids to quality control

WHO provides assistance for the establishment of national laboratories for physicochemical and biological control of the quality of pharmaceutical preparations, particularly by assisting, within its fellowship programme, in the training of pharmaceutical analysts and biologists. Postgraduate courses in pharmaceutical quality control have now been established in different pharmaceutical institutes, with the co-operation of WHO. The Organization also sends consultants to requesting countries to help health administrations to plan for proper quality control of their pharmaceutical preparations, either imported or locally produced. In addition, WHO supplies lists of the laboratory equipment necessary for pharmaceutical quality control.

Two or more countries can agree to help each other in establishing common laboratories for pharmaceutical quality control. On the other hand, effective quality control can often be provided in a country by the staff of the pharmaceutical, medical and other faculties of universities and institutes, using their facilities and equipment.

Quality control should also be instituted regularly in the pharmacies of larger hospitals, which dispense most of the drugs consumed in many of the developing countries, and these establishments may help their national authorities by effecting quality control on their behalf.

Great assistance is provided by WHO in issuing proposed specifications for the quality control of the more important pharmaceuticals, as published in the *International Pharmacopoeia*,¹ and requirements for a number of biological substances, as published in the *WHO Technical Report Series*. Moreover, the international non-proprietary names proposed by WHO for pharmaceutical substances² are of help to national administrations for the labelling of drugs and for regulatory purposes. International biological standards, as well as international chemical reference substances,³ are also supplied through WHO for pharmaceutical quality control.

Annex 2

QUALITY OF THE IODINATED RADIO-OPAQUES

The iodinated organic radio-opaques are unique objects in the pharmacopoeial armamentarium. Probably no other foreign organic substances are deliberately introduced parenterally into the human body in such large doses, all at one time. It has been recorded, for instance, that in the practice of angiocardiology (the visualization of the chambers and great vessels

¹ World Health Organization, *Pharmacopoea Internationalis*, 1st ed., Vol. I (1951), 1st ed., Vol. II (1955), 1st ed., Supplement (1959), Geneva; World Health Organization (1963) *Specifications for reagents mentioned in the International Pharmacopoeia*, Geneva.

The text of the second edition of the *International Pharmacopoeia*, including specifications for many additional pharmaceutical substances, was sent in October 1964 to Member States.

² World Health Organization (1962) *International Non-proprietary Names, Cumulative List*, Geneva; *Chron. Wld Hlth Org.*, 1962, 16, 385; *Chron. Wld Hlth Org.*, 1963, 17, 389; *Chron. Wld Hlth Org.*, 1964, 18, 433.

³ These standards are supplied by the International Laboratory for Biological Standards, Statens Seruminstitut, Copenhagen, the International Laboratory for Biological Standards, National Institute for Medical Research, London, the International Reference Centre for Chemical Reference Substances, Apotekens Kontrollaboratorium, Stockholm, and the International Laboratory for Biological Standards, Central Veterinary Laboratory, Weybridge.

of the heart) as much as two grams per kilogram of body weight have been administered, all in the space of a few seconds. Thus, for a man of 65 kg, as much as 130 g of foreign organic material might suddenly be injected into the heart. The contemplation of such an extraordinary blow to the physiological balance of the human organism leads one to realize the grave responsibility of the designers of pharmacopeial test monographs.

The problems of the purity, stability, and safety of drugs and paramedical substances are inextricably bound together. In the case of the iodinated radio-opaques, it is especially useful to keep in mind the possible differences between total toxicity and intrinsic toxicity. The toxicity of perfectly pure, typical radio-opaques (i.e., the intrinsic toxicity) is amazingly low. However, the presence of even small percentages of concomitant substances, whether deliberate or accidental, may raise the total toxicity of the dose to dangerous levels. This follows from the unusual size of the dose actually given. For example, in the case of urographic agents, an average dose is about 200 mg/kg body weight — that is, the ordinary range might be 10 to 18 g per dose. If an impurity were present to the extent of 0.1 %, as much as 10 to 18 mg might unintentionally be administered. The toxicity of many substances is sufficiently great to make such an additional burden on the patient a very serious matter. The potential danger is greatly increased in the case of radiology of the heart, already mentioned, or in pulmonary arteriography.

It is therefore prudent to require extraordinary standards of purity and stability for radio-opaque substances. In addition to fixing very stringent limits for known possible impurities, it would be wise to prescribe the use of general safety tests, intended to detect totally unexpected or unknown impurities. These remarks refer especially to radio-opaques administered by injection, but the same problems, to a lesser degree, exist in the case of oral dose forms, such as those intended for the visualization of the gall bladder.

Before considering the kinds of test that might be advisable to assure the quality and safety of the iodinated radio-opaques, it may be useful to classify the radiographic compounds according to intended use, route of administration, and size of dose.

CLASSES OF RADIOGRAPHIC COMPOUNDS

Class 1A — oral cholecystographic

This class is exemplified by Iopanoic Acid U.S.P. (Billijodin, Cistobil, Telepaque), a water-insoluble compound. The usual dose is about 50 mg/kg body weight, administered in the form of tablets. Problems of stability and toxicity are minor. Purity tests have generally been restricted to

proof of absence of inorganic iodine and iodide ion. These may be sufficient, but more extensive purity testing would be desirable. A more important practical problem with this class of contrast medium is the availability of the drug for assimilation and transport to the gall bladder and bile ducts, for which no official pharmacopeial tests exist.

Class 1B — intravenous cholecystographic

Exemplified (perhaps uniquely) by Sodium Iodipamide U.S.P., and Iodipamide Methylglucamine U.S.P., B.P., these are water-soluble compounds. The usual dose is about 50 mg/kg body weight. Being in solution form, the problems of stability and purity, and consequently of unexpected toxicity, are significant. The British Pharmacopoeia prescribes tests for pH range, inorganic iodine and iodide, and free aryl amine. No test is suggested for homogeneity of the radio-opaque or for its resistance to pH change.

Class 2A — Retrograde urographic

Exemplified by the water-soluble Methiodal Sodium, N.F. (USA) (Abrodil, Skiodan). The usual dose is about 300 mg/kg body weight. The National Formulary prescribes tests for halide ions, sulfate, arsenic, and heavy metals.

Class 2B — intravenous urographic

Exemplified by the water-soluble sodium and/or N-methylglucamine salts of Diatrizoic Acid, U.S.P., B.P. (Urografin, Renografin, Hypaque). Usual dose about 200 mg/kg body weight. The British Pharmacopoeia prescribes tests for pH range, inorganic iodine and iodide. Since the dose is large, the comments made in regard to Class 1B are even more to the point here.

Class 3A — peripheral angiography

Dose range 50 to 300 mg/kg.

Class 3B — angiocardigraphy; pulmonary arteriography

Dose range 500 to 1000 mg/kg. For the purpose of this classification, classes 3A and 3B may be considered together, since the chief difference is in the dose size. The substances used are exemplified by highly concentrated (70%-90%) solutions of the sodium and/or N-methylglucamine salts of Diatrizoic Acid. The enormous doses and mode of administration used for these forms of radiography unequivocally demand the most exhaustive tests to assure the protection of the patient.

Class 4 — miscellaneous radiography (bronchography, myelography, hysterosalpingography, sialography, etc.)

These divisions of radiography are by no means unimportant, but perhaps not as widely practised as those already mentioned. In varying degrees, they are hazardous to the patient and call for correspondingly careful examination to assure effectiveness and safety.

VARIETIES OF TESTS FOR QUALITY AND SAFETY

The tests listed below are probably among those already used internally by reputable manufacturers, but not all of them are included in published test monographs. Certain of them, such as tests for pyrogens and sterility, are common requirements for all injections. Others (e.g., absence of heavy metals) are common to published monographs for most substances. Comments are offered for less frequently prescribed tests.

1. pH range

Although the normal pH of blood is in the vicinity of 7.3 or 7.4, its buffering capacity is sufficient to permit the intravenous administration of solutions outside this range, as long as the total amount of acid or alkali administered is small. In the case of radio-opaque solutions, where the amount injected may be very large, there is a danger of overwhelming the blood-buffering capacity if the pH of the injection differs much from that of the blood. A safe range would probably be pH 7.0 to 7.6. In those cases where official monographs permit a wider range, it would be in order to reconsider whether an unnecessary hazard is involved.

2. Resistance to change of pH, because of thermal or chemical effect

Even though the pH of an injection formulation is in a desirable range (7.0 to 7.6), it cannot be taken for granted that the pH will remain constant after long standing or after exposure to high temperature. A suitable test for resistance to pH change consists of autoclaving sealed ampoules of the formulation at 120°C for at least one hour, and requiring that the change in pH be small—for example, ± 0.3 . This apparently minor test is actually an important and significant measure of the potential stability of the solution.

3. Spectral absorption (visible light)

Well prepared aqueous injections are intrinsically crystal clear and colourless. To the extent that any discoloration occurs, the inescapable inference is that contaminants are present. Therefore, in line with the

thesis that only the highest purity can be acceptable, it is reasonable to require that the visible light absorption of radio-opaque solutions should be very small, as measured exactly with a spectrophotometer. Not only should the initial "colour" be at a very low level, but (like the pH) this colour should change very little after autoclaving. The lack of increase of visible light absorption after autoclaving is an important indication of the stability of the radio-opaque molecule, and a monograph requirement based upon such a test is definitely recommended.

4. Absence of "free" (non-acylated) aromatic amine

It is well known that the acetylation of aromatic amines is one of the common detoxifying mechanisms of the body. Making use of this information, the originators of several important radio-opaques were able to reduce very significantly the toxicity of their basic compounds. For example, Hoppe, Larsen & Coulston¹ found that introduction of the two acetyl groups in sodium diatrizoate changed the LD₅₀ in the mouse from 1310 mg/kg for the free diamino compound to 13 400 mg/kg for the diacetamino compound. It follows that purity tests for the various iodinated acylamino-phenyl radio-opaques should include a limit test for non-acylated amines. For different radio-opaque molecules, the permitted level of "free" amine might well vary, depending upon stability and toxicology. In any case, the permitted amount of non-acylated amino compound should be very low, probably under 0.1%.

5. Absence of inorganic iodine, and of iodide ion

6. Absence of heavy metals

7. Pyrogenicity

8. Sterility

9. Homogeneity, by thin-layer chromatography

The iodinated radio-opaques lend themselves very well to separation on paper, and perhaps even better to separation on silica-gel plates as in thin-layer chromatography. Such a purity test could be very important in detecting accidental or unexpected impurities not covered by conventional control tests. It should place limits on the number or size of spots or bands representing materials different from the desired substance.

¹ Hoppe, J. O., Larsen, A. A. & Coulston, F. (1956) *J. Pharmacol. exp. Ther.*, **116**, 394.

10. Preservatives and stabilizing agents

In some cases, antibacterial or antifungal or metal-chelating substances may be added to radio-opaque solutions. Methods and tests for the quantitative and qualitative examination of such substances should be available.

11. Estimation of acute toxicity as average LD₅₀

The final and most important purity test is an estimation in an animal of the toxicity of the solution as used. For the iodinated radio-opaques, a test involving intravenous injection in mice is useful. If every lot of radio-opaque intended for angiocardiology were held to a stringent level for LD₅₀, the patient would be afforded an important degree of protection.

Annex 3**REPORT ON DEXAMETHASONE :
PROPOSED WHO CHEMICAL REFERENCE SUBSTANCE****Description**

White, odourless crystalline powder.

Melting-temperature

Method of the

International Pharmacopoeia : 257°-259°C

Kofler hot stage method : about 253°C (decomposition, droplets from 238°C)

Kofler hot bar method : decomposition, after 60 seconds about 265°C

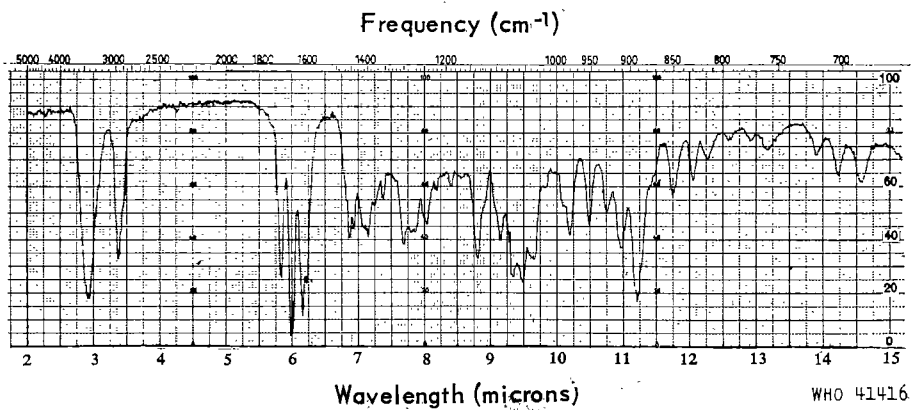
Specific rotation

In a 1.0% w/v solution in dioxan : +79.1 (+78.98, +79.20)

Loss on drying (105°C to constant weight) 0.1%

Residue on ignition : 0.0%

FIG. 1
 INFRA-RED ABSORPTION OF DEXAMETHASONE



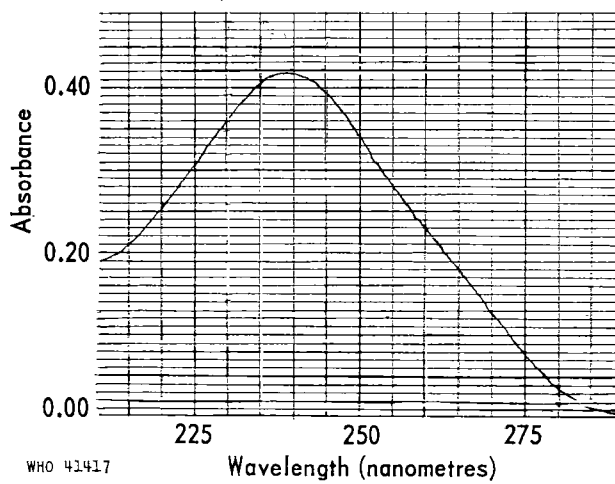
Infra-red absorption (See Fig. 1).

Potassium bromide disc, 1.8 mg in 200 mg KBr
 Instrument : Perkin-Elmer Model 21

Ultra-violet absorption (See Fig. 2).

10.6 µg per ml in absolute ethanol (curve with methanol practically identical)
 Maximum at 239 nanometres
 Absorptivity : 39.5
 Instrument : Beckman DK-2

FIG. 2
 ULTRA-VIOLET ABSORPTION OF DEXAMETHASONE



Thin-layer chromatography (See Fig. 3).

Two contaminants noted.

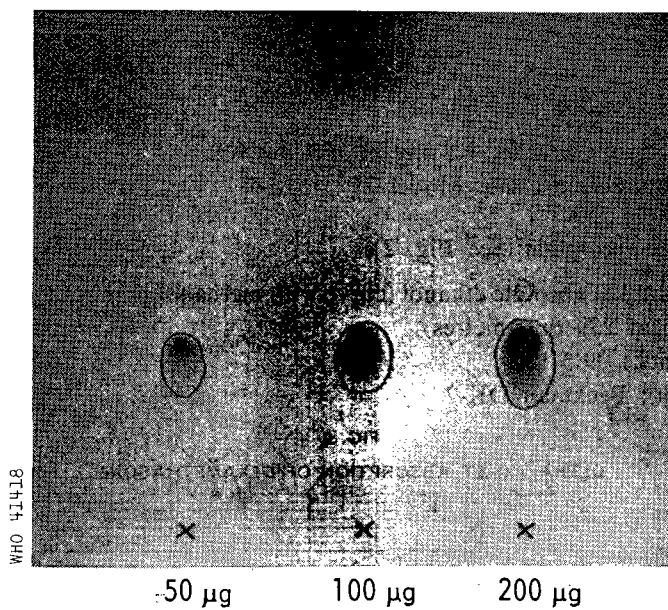
Adsorbent : Silica gel G

Solvent system : 15 parts of benzene to 10 parts of acetone

Reagent : 2% perchloric acid in methanol, plate heated for 5-10 minutes at 120°C.

FIG. 3

THIN-LAYER CHROMATOGRAPHY OF DEXAMETHASONE

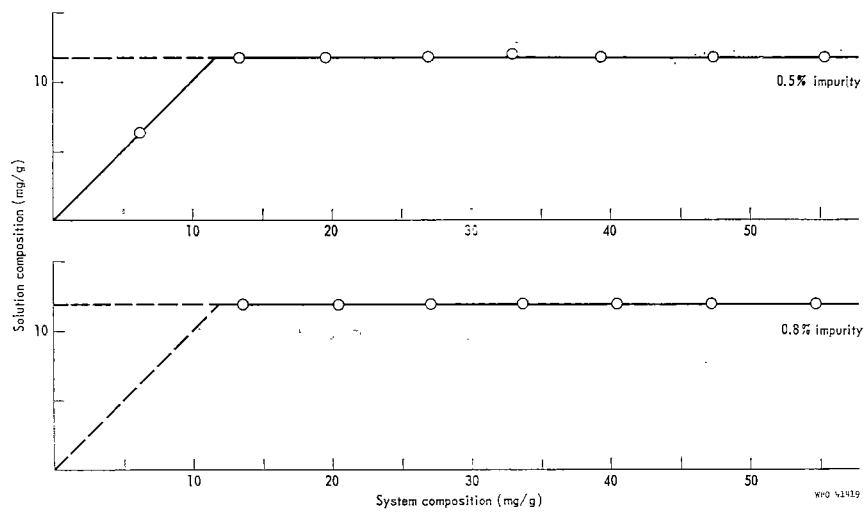
**Phase-solubility analysis (See Fig. 4)**

0.7% impurity (0.5, 0.8)

Method : As described in the US Pharmacopoeia XVI, p. 393, for mecamlamine hydrochloride, but solubility equilibrium was attained by use of a vibro-mixer for 20 or more hours.

Solvent : 70% methanol.

FIG. 4
PHASE-SOLUBILITY ANALYSIS OF DEXAMETHASONE



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