



FIFTEENTH REPORT

The Expert Committee on the International Pharmacopoeia held its fifteenth session in Geneva from 2-8 October 1957.

Members

Professor H. Baggesgaard Rasmussen, Professor of Organic Chemistry, Royal Danish School of Pharmacy, Copenhagen; Member of the Danish Pharmacopoeia Commission and of the Scandinavian Pharmacopoeia Council (Vice-Chairman)

Dr T. Canbäck, Director of Chemical Research, Pharmaceutical Control Laboratory, Stockholm; Vice-Chairman of the Swedish Pharmacopoeia Commission; Member of the Scandinavian Pharmacopoeia Council (Chairman)

Mr T. C. Denston, Secretary, British Pharmacopoeia Commission, London (Rapporteur)

Professor H. Flück, Professor of Pharmacognosy at the Federal Institute of Technology, Zürich; Member of the Federal Pharmacopoeia Commission

* Professor R. Hazard, Professor of Pharmacology and Materia Medica, Faculty of Medicine of Paris University; Member of the Permanent French Pharmacopoeia Commission

Dr T. Itai, Chief of the Division of Non-Official Drugs, National Institute of Hygiene, Tokyo; Member of the Japanese Pharmacopoeia Commission

Mr F. A. Maurina, Director, Analytical Laboratories Messrs Parke, Davis & Co., Detroit; Member of the Committee of Revision of the Pharmacopoeia of the United States of America

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

Dr J. L. Powers, Chairman of the Committee on National Formulary, American Pharmaceutical Association, Washington, D. C.; Member of the Committee of Revision of the Pharmacopoeia of the United States of America

Consultants

Mr G. R. Brown, Scientific Publications Department, Pharmaceutical Society of Great Britain, London

Mr O. Wallén, Apotekens kontrollaboratorium, Stockholm

* Unable to attend

Secretariat

Dr W. Aeg. Timmerman, Assistant Director-General, Department of Central
Technical Services

Mr P. Blanc, Chief, Pharmaceutical Section, Division of Therapeutic Substances
(Secretary)

1. The Assistant Director-General opened the session by welcoming the members and thanking them for their work which, with the collaboration of the members of the Expert Advisory Panel and other specialists, had made it possible within the last few years to publish volumes I and II of the first edition of the International Pharmacopoeia, including altogether 409 monographs and 69 appendices, and to prepare since the last session a provisional text of a Supplement including 93 monographs and 14 appendices.

Appreciation was expressed for the considerable work on collaborative assays undertaken in connexion with the preparation of a second edition of the International Pharmacopoeia. Another problem to be dealt with concerned the reagents referred to in volumes I and II and the Supplement, and for which draft specifications had been prepared. In view of the large number of new medicinal substances introduced into materia medica every year a further problem was the proposal to obtain, examine, collate and distribute information on specifications for new pharmaceutical preparations within a reasonable time of their introduction.

2. Resolutions of the Executive Board

Attention was drawn to Resolution EB19.R6 according to which the Executive Board noted the fourteenth report of the Expert Committee on the International Pharmacopoeia which met in Geneva from 26 April to 3 May 1956, and thanked the members for their work, and to Resolution EB20.R16 noting the report of the Study Group on the Use of Specifications for Pharmaceutical Preparations held in Geneva from 4-8 December 1956.

3. Publication of the International Pharmacopoeia

The Committee noted with appreciation that during 1957 a Spanish edition of volume II had been published by WHO and also that Japanese and German translations of this volume had been published, at no expense to the Organization, under the supervision of members of the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations.

4. Supplement to volumes I and II of the first edition of the International Pharmacopoeia

The greater part of the session was devoted to review and revision of the text for the Supplement.

The Expert Committee noted that the draft monographs and appendices approved at the fourteenth session had been circulated to Member States, national pharmacopoeia commissions, the World Medical Association, the International Pharmaceutical Federation members of the Expert Advisory Panel and other specialists. As a result, a number of comments and suggestions for improvements of the text in points of detail had been received. The Expert Committee examined these comments and approved a number of changes in the text of the monographs.

4.1 General Changes

In those instances where melting-points are actually decomposition points, it was agreed that a statement will appear under the heading "Identification" with only an approximate indication of the melting-temperature.

For a number of derivatives of barbituric acid the colour reaction with cobaltous chloride and ammonia was introduced as a rapid general test for the barbituric acid group.

In several instances it was agreed to investigate the applicability of the general assay method of non-aqueous titration using perchloric acid in acetic acid solutions as described in the draft appendix.

Acidum Salicylicum. A limit test for iron and colouring matter was added to the monograph.

Aethylis Bescoumacetas. A test for purity depending on the solubility in acetone was added to this monograph.

Aqua Demineralisata. It was agreed that a method for the determination of specific resistivity of demineralised water should be included in an appendix to the International Pharmacopoeia. It was also agreed to check whether a specific resistivity of 1 million ohms measured on the water flowing from demineralizing apparatus could be attained in practice. A test for albuminoid ammonia was added.

Compressi Isoprenalini Sulfatis. It was agreed to permit the addition of 1 per cent. of citric acid and 1 per cent. of sodium pyrosulfite for the purpose of minimizing discoloration of the tablets during storage, and also to indicate that they should be protected from light.

Compressi Obducti. The methods of analysis given in the draft monograph were considered inadequate and it was decided that they should be omitted.

Compressi Hyoscini Hydrobromidi. A working group of members of the Expert Committee investigated a suggested change in the assay method and it was agreed to replace the assay in the draft monograph by the method of the US National Formulary which is similar to that of the British Pharmacopoeia. This method, which requires a larger sample of material, is reported to be more precise and it was therefore agreed to increase the lower limit for hyoscyne hydrobromide from 80 per cent. to 90 per cent.

Hyaluronidasum pro Injectione. A working group of members of the Expert Committee agreed to report on a suggested change in the requirements for potency. These requirements should take into consideration the commercial practice of adding lactose or other inert material in order to give bulk to the highly refined product. A requirement for clarity and colour of a solution was added to this monograph and it was agreed also that the label should include a warning that the product must not be administered intravenously.

Lidocaini Hydrochloridum. It was agreed to add a test for copper.

Metamphetamini Hydrochloridum. The chemical name was changed to indicate that the monograph applies to the dextrorotatory isomer.

Nalorphini Hydrochloridum. It was agreed that an attempt should be made to supply a more specific identification test.

Natrii Tetraboras. The monograph was amended to allow for the loss of water of crystallization from the decahydrate.

Phthalylsulfathiazolum. It was agreed to insert the test for free sulfathiazole and the requirement for colour and clarity of a solution as for the analagous substance succinylsulfathiazolum described in volume I.

Injectio Testosteroni Propionatis. Arrangements were made to obtain details of a new assay method stated to be more convenient than the one provided in the draft monograph and to have it investigated promptly with a view to its inclusion in the monograph.

Preparation of isotonic solutions. It was pointed out that some solutions used for injections are hypertonic due to concentration of the drug. However, it was agreed that it is useful to have information such as that provided in the draft appendix for the convenience of hospital pharmacists and others preparing solutions for special purposes, and that the appendix should be included in the Supplement.

Determination of pH. A report was received of research into the standard Clarke and Lubs buffer solutions used for the determination of pH and appropriate changes in detail will be made in the draft appendix.

Chemical nomenclature and graphic formulae. A number of comments on chemical nomenclature were reviewed. Professor Baggesgaard Rasmussen agreed to provide a correct systematic chemical name and to submit graphic formulas where required for the monographs of the Supplement.

5. Reagents and test solutions for volumes I and II and the Supplement to the First Edition

The Expert Committee noted that following the examination of draft specifications for reagents at its fourteenth session, all the drafts at that time available had been revised and their number considerably extended by Dr Powers with the object of providing specifications for all the reagent chemicals required for the tests of the International Pharmacopoeia, volumes I, II and Supplement. A discussion of the specifications by a working group of the Expert Committee indicated that judgement of the adequacy of the specifications could not be exercised without having information on the purposes for which the reagents are required in the tests and assays. A member of the working group undertook to prepare a list of the respective uses of all but the most commonly used reagents. Arrangements would then be made to ensure that the specifications for reagent chemicals generally suitable for laboratory work would describe materials adequate for all the tests for which they are prescribed in the International Pharmacopoeia.

With respect to the form in which the reagent specifications will be published no decision was taken but it was possible that the specifications for reagents might be published initially as a Supplement to the International Pharmacopoeia. Alternatively they might be made available as a separate WHO publication with a suitable preface explaining that they were intended to apply to reagent chemicals required for tests in volumes I, II and the Supplement to the International Pharmacopoeia.

The Committee noted that the basis for the preparation of these specifications had been drawn from several sources including "Analar" Standards for Reagent Chemicals, the British Pharmacopoeia, the United States Pharmacopoeia, the American Chemical Society Specifications for Reagent Chemicals, and from "Reagent Chemicals" (Rosin). The opinion was expressed that a suitable acknowledgement should be included in the final publication.

It was considered essential to invite opinions from manufacturers and certain users of reagent chemicals by distributing the specifications through members of the Expert Advisory Panel serving in a liaison capacity in their respective countries. It was recommended that an announcement be prepared by the Secretariat for publication in chemical and pharmaceutical periodicals. This would announce the plan for publication of the reagent monographs and offer to supply draft copies of some or all of the draft monographs for comment and criticism.

The Expert Committee agreed that definitions and general directions should be given in a Preface, if the specifications for reagent chemicals are to be published other than as a Supplement to the International Pharmacopoeia.

It was decided that before publication, data on specific gravity would be converted into the corresponding density values by a member of the working group and another member agreed to tabulate the boiling-range and melting-point requirements. Dr Powers, with the advice of other members of the working group, would determine whether it might be possible to include reference to some of these characteristics in the description of the reagents involved. It was agreed that the most important immediate problem is to obtain comments and criticisms on the actual specifications and that the question of style might appropriately be postponed until comments and criticisms have been received and evaluated. The Committee recommended that a statement should be prepared to accompany the specifications to explain the proposed changes in the existing text in respect to the tests for specific gravity, boiling-range, melting-point and general style.

6. Future Activities and Programme of Work

The Committee surveyed the assignments undertaken since 1947. Volumes I and II had been published and the projects which now constitute its programme include:

- (1) Supplement to volumes I and II - completion of text
- (2) Reagents - correlation of tests and completion of text

- (3) New monographs - to deal with many important drugs not yet covered
- (4) Collaborative assays programme - to demonstrate applicability and appropriateness of the specifications of volumes I and II
- (5) Second edition - revision of volumes I and II in the light of the advice received from experts and specialists, the results of the collaborative assay programme, and new developments in analytical procedures.
- (6) International non-proprietary names - continuation of the selection and publication of proposed and recommended international non-proprietary names
- (7) Authentic Chemical Substances - the programme to provide pure specimens of selected chemicals which are of therapeutic interest or of importance in securing accuracy in analysis
- (8) Information Sheets - development of a programme to provide information on new drugs at an early stage and as a means of collecting data for possible development of specifications for the International Pharmacopoeia.

The Committee found that all of the above listed projects are of great importance and are considered necessary and hoped it would be possible to pursue them effectively.

Name of the Committee. The members discussed the name of the Committee and considered that the scope of its commitments would be more accurately expressed by a change to "Expert Committee on Specifications for Pharmaceutical Preparations".

6.1 Aims to be pursued

The Committee noted that the work undertaken by WHO had been fruitful in assisting the national authorities dealing with the establishment of specifications for pharmaceutical preparations and pharmacopoeia commissions, control laboratories, etc. Replies had been received to a circular letter sent to experts and pharmacopoeia commissions. They indicate that the specifications are being used to an increasing extent in the different countries. The specifications included in the International Pharmacopoeia were serving a practical need in the examination of the quality of pharmaceutical preparations and it was important that this work should be continued.

A common feature of the plans followed by the national pharmacopoeial authorities is the element of selectiveness and discrimination with a view to including only those well-established therapeutic agents and valuable adjuvants to medicine and pharmacy that reflect the needs of the practice of medicine within the area for which the particular pharmacopoeia is official. It was quite evident that despite agreement in purpose, great divergences exist among national pharmacopoeias because of individual differences in the interpretation and in carrying out the stated aims on scope. Furthermore, the fact that frequent and regular revision is the exception rather than the rule with national pharmacopoeias makes for even greater disparities among them.

The special needs which an international pharmacopoeia must fulfil within the framework of the WHO require that the Pharmacopoea Internationalis be drafted to serve a maximum degree of usefulness throughout the world. Cognizance must be taken of the existence of national practices generally and the fact that preferences vary as to the form used of any given drug. This speaks for providing a wider range of drugs than may be found in any national pharmacopoeia.

The Committee took the view that pharmacopoeial standards require regular revision to be of the greatest value so that further work on the second edition was urgently required. Inasmuch as the same pharmaceutical preparation is likely to appear on the market and be brought to the attention of the medical profession in several countries simultaneously, the Committee felt that specifications for it should be made available promptly to control authorities and pharmacopoeial commissions.

6.2 Information Sheets

Considering that new medicinal chemical substances are being introduced every year in hundreds of different pharmaceutical forms for prescription or direct public sale in the different countries, the Committee thought it imperative that national health authorities should be supplied with the necessary data and suitable specifications to facilitate the examination of the substances and their various pharmaceutical forms.

The Committee examined the possibilities of providing such specifications within a reasonable time after the appearance of the new preparation. In this connexion the Expert Committee expressed its full agreement with the views set out in the report of a Study Group on the Use of Specifications for Pharmaceutical Preparations held in Geneva, 4-8 December 1956, and in particular with the suggestion that information sheets on new pharmaceutical preparations should be obtained by WHO, collated and distributed

to national health authorities, pharmacopoeia commissions, etc. at an early stage of the introduction of the preparation.¹ In the opinion of the Expert Committee this would afford the best possible means for dealing with the great influx of new preparations on the market. The Committee agreed that the active collaboration of the pharmaceutical industry is indispensable to the success of this project and noted with appreciation that the reports from members of the Expert Committee who had consulted national administrations and some sections of the pharmaceutical industry suggested that considerable support would be forthcoming.

It was agreed that full assurance should be given to those contributing information that careful consideration would be given to existing proprietary interests. Due regard should also be given to the existence of differences in regulations governing patents rights in various countries. For instance, in certain countries both the process and the product may be patented, whereas in others only the process may be covered by a patent.

Manufacturers asked to supply information would be informed that it would be distributed by WHO to those concerned with the establishment of the specifications for, and the testing of, pharmaceutical preparations. This information should be sought by members of the Expert Advisory Panel and other specialists. On the assumption that collaboration from the pharmaceutical industry would be forthcoming, the Expert Committee expressed the hope that contact could also be established through pharmacopoeia commissions, manufacturers' associations, national health authorities, etc., in order to facilitate the receipt of information by WHO and that should this approach need to be supplemented, WHO might seek the information directly from the manufacturing firms. It was recommended that a cautionary statement should appear on the sheets stating that the issue of this information did not carry any recommendation by WHO of use of the substance and that it should not be interpreted as an indication that the substance would necessarily be later included in the International Pharmacopoeia.

Information sheets would include the systematic chemical name, international or other non-proprietary names, trade names, known or contemplated in various countries, names of manufacturers, molecular formula, molecular weight, structural formula, literature references to syntheses of the final product, various physical data (melting, congealing, freezing or boiling-range, refractive index, optical rotation, density,

¹ See Annex I to this report: "Draft Information Sheet on Pharmaceutical Preparations".

visible, U.V. and I.R. absorption, crystallographic data, viscosity, pH of solutions), solubility, identification reactions, assay, assay of pharmaceutical forms, sterilization methods, purity tests and tolerances for trace impurities, pharmacology, toxicity, side effects, clinical applications, usual dose, range and route of administration, specific antidotes (if known) and general literature references.

Comments would be invited from those receiving the information sheets, and revised sheets would be used in the preparation of monographs where required for the International Pharmacopoeia. It should be emphasized that information sheets would not concern mixtures but only individual drugs available either in bulk or in dosage forms.

After a technical examination by WHO the information would be circulated to Member States as well as directly to national pharmacopoeia commissions and official laboratories of control and other persons interested in the use of these specifications for the examination of pharmaceutical preparations.

The Committee agreed that a draft information sheet¹ intended only to give the outline form should be annexed to this report in order to obtain comments at this stage which would be of use for the preparation of the information sheets.

The Committee felt that in the coming year the Secretariat should conduct a survey of all new medicinal substances recently introduced to provide a basis for estimating the amount of work involved in processing information sheets. This would also indicate the most fruitful sources of published information and announcements of the introduction of new drugs. It would be expected that the results of such a survey would prove helpful in completing plans for the entire programme.

6.3 The Expert Committee examined the remarks of the Study Group on the use of specifications for pharmaceutical preparations concerning the classification of poisonous pharmaceutical substances and expressed the opinion that at the present time the Expert Committee could not make a useful contribution to solving the many difficulties which arise on account of the different legislations and the large number of different hazards involved in the use of many new medicinal substances. It was pointed out that in recent years there have emerged several classes of compounds which, while not being poisons in the usual sense of the word, have special dangers consequent upon their use without proper medical supervision.

¹ Annex I to this report

7. Preparation of the Second Edition of the International Pharmacopoeia

The Expert Committee reviewed the progress which had been made in obtaining comment and criticism from laboratory workers and others using the specifications as a basis for revision of volumes I and II of the International Pharmacopoeia. A list of specialists who had agreed to collaborate with members of the Expert Advisory Panel was examined and members of the Expert Committee suggested several other workers who might be prepared to assist in the work of revision. It was noted that a large number of pharmaceutical preparations not included in volumes I, II or the draft Supplement are of sufficient importance to merit the preparation of monographs and a working group of members of the Expert Committee agreed to submit a list for consideration.

Preparations of human blood. A report was received from a working group which had under consideration the revision of a number of draft monographs and it was agreed to expand the working group and ask them to continue their work in order to provide suitable specifications.

Suture materials. It was agreed that a working group should continue the preparation of suitable draft monographs and appendices on materials used as surgical sutures.

Surgical dressings. Attention was drawn to the developments in the field of surgical dressings which have arisen from the use of so-called optical bleaching agents, and from the introduction of artificial fibres such as nylon and rayon. It was agreed that in view of the fact that rapid developments may be expected in this field a working group should report, with recommendations for future work, on the use of man-made fibres in surgical dressings and their treatment with optical bleaching materials with special reference to possible untoward effects.

Radioactive isotopes. It was agreed that a working group should continue preparation of proposed specifications for radioactive isotopes for use in clinical medicine together with recommendations on details of handling, storing, dispensing and administration of these substances.

Use of the term "teaspoonful". A number of reports have been received indicating considerable variation in the capacity of household teaspoons, dessertspoons, etc. such as are commonly used for measuring doses of medicine. It was agreed that the situation was far from satisfactory especially in relation to international implications. Further reports were awaited for examination at a later date.

Colouring of pharmaceutical preparations. Attention was drawn to the wide use of colouring agents in pharmaceutical preparation. It was agreed that when colours are permitted for the purpose they must be harmless to the user and not exert a deleterious effect on the active ingredients. Diversity of practice and legislation in various countries and lack of toxicity data in many cases, make it difficult or even impossible at present to draw up a list of suitable colours. It was agreed that a working group should keep the situation under review and report to future sessions of an expert committee. It was noted that another WHO section was considering the problem from the point of view of use of colouring material in foods and it was agreed to await developments.

Antioxidants. A report was received recommending the inclusion in the International Pharmacopoeia of a number of substances commonly used as antioxidants for the preservation of fats, essential oils and other pharmaceutical preparations. The Expert Committee noted that another unit of WHO would be considering the subject of specifications for these substances for use in foods, and evaluation of the safety of these products for that purpose. It was agreed that this work on antioxidants in food should be closely followed, and a working group agreed to report on antioxidants for pharmaceutical use.

8. International Non-Proprietary Names

The Expert Committee examined the report of its Sub-Committee on Non-Proprietary Names, WHO/Pharm/329, and noted that at the seventh session, 13-15 June 1957, agreement had been obtained on 150 proposed INN. Agreement on such a large number of names, especially in view of the difficulty of obtaining suitable names free from conflict with trademarks or other names, had been made possible by a considerable amount of correspondence between members of the Expert Advisory Panel prior to the session.

It was noted that the chemical names and graphic formulas were being checked by members of the Expert Advisory Panel in conjunction with the International Union of Pure and Applied Chemistry and the list (List No. 6) would be published in the near future. A special effort had been made by members of the Sub-Committee to obtain agreement on a series of names for narcotic drugs and list number 5 consisting of 26 names had been established by correspondence so as to obtain at an early stage INN suitable for use in the international control of narcotics. It was noted that certain authorities responsible for creating non-proprietary names on a national scale had agreed to give several weeks' notice to WHO before authorizing the issue of a name and it was noted that in this way the possibility of different names for the same substance becoming established would be considerably reduced. It was reported that INN appeared to be more widely acceptable; in the list of 150 proposed INN (List 4, published in 1956)¹ which had been available for comment or objection over a period of four months, few objections had been received and some of these had been withdrawn. The work on the preparation of graphic formulas which might later be included in the lists of names to be issued would be continued.

9. Centre for Authentic Chemical Substances

The Committee heard an oral report on the establishment and activities of the Centre for Authentic Chemical Substances. This Centre had been created in accordance with an agreement between the Apotekarsocieteten, Stockholm, and the World Health Organization, for the collection, storage and distribution of chemical reference preparations. A number of the substances had been received from the National Institute for Medical Research in London after they had been changed from their previous status as biological standards or biological reference preparations, these substances being now characterized entirely by physico-chemical methods. It also included other chemicals which were required as reference standards in the fields of medicine and pharmacy and it is intended to add to the present list of substances described in an annex to this report² on the advice of the Expert Committee

¹ Chron. Wld Hlth Org. (1956) 10, No. 1, 26-35

² Annex 2 to this report: Circular letter C.L.13.1957 and Annex

on the International Pharmacopoeia. The substances are at the disposal of government control laboratories and others. The list should be limited preferably to substances used in the laboratory control of medicine and for pure research.

The Committee was informed that during the first six months of operation there had been requests for the substances from 18 countries and that the demand was about equally distributed between all the substances available, although the greatest demand had been for vitamin A. The supply of D-tubocurarine chloride was nearing exhaustion and would be renewed.

The Expert Committee expressed its appreciation of the operation of the Centre and is of the opinion that it will prove of value for control purposes. It was suggested that a study should be made of the inclusion of authentic chemical substances for checking melting points and for checking the absorption reading of spectrophotometers operating in the ultra-violet and visible parts of the spectrum.

Note of Secretariat: This draft form is annexed to the report for consultation. Please address any comments to the Pharmaceutical Section, WHO, Geneva, Switzerland.

DRAFT

INFORMATION SHEET ON PHARMACEUTICAL PREPARATIONS

The issue of this information sheet does not imply any recommendation for the use of the substance in medicine or pharmacy.

This information has been submitted to WHO under the assumption that it will be circulated or published.

Submitted by:

Systematic chemical name:

2-Ethyl-crotonylurea

Proposed or recommended INN or other non-proprietary names:

ECTYLUREA (Prop. INN)

Trade names:
(and name of manufacturer)*

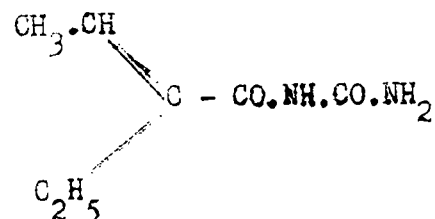
Nostyn (Ames)

Molecular formula and molecular weight:

$C_{12}H_{17}N_2O_2$

156.19

Structural formula:



* if available a copy of the label of a trade package would serve helpfully to identify the preparation

Annex I

Description:

Physical data:

The conditions used in the determinations should be specified or the pharmacopoeial or other method used should be mentioned. When no reference is given it will be assumed that the method in the International Pharmacopoeia has been followed.

- (a) Melting-range: 192° - 193° (2.)
- (b) Boiling-range:
- (c) Refractive index:
- (d) Optical rotation:
- (e) Density, expressed in grams per cubic centimetre at a temperature of 20° (if data not available specific gravity or weight per millilitre might be given).
- (f) Absorption curves in UV and IR etc.: Infra red spectrum, Nujol mull, see curve (2.) enclosed.
- (g) Crystallographic data:
- (h) Viscosity:

Solubility:

(At 20° or stated temperature. If exact data are lacking, general expressions such as "slightly soluble" etc. might be of value. If possible, solubilities should always be given for water, ethanol (95 per cent.), ether, chloroform and benzene.)

Water:	slightly soluble
Chloroform:	about 300 parts
Ether:	" 850 "
Benzene:	" 1600 "
Acetone:	" 150 "

pH of the solution:

Identification:

(Chemical reactions, spot tests, etc. also data on paper chromatography, melting-points of derivatives together with directions how to prepare the derivatives.)

Annex I

Assay of the substance:
(Chemical or biological)

Bromometric determination (3.)
Dissolve 0.1000 g, accurately weighed, in 15 ml of glacial acetic acid in a glass-stoppered flask, add 5 ml of sulfuric acid 2.5 M, then 25.00 ml of 0.1 N sodium bromate and 10 ml of sodium bromide solution 25 per cent. w/v, and immediately insert the stopper. Allow it to stand for 5 minutes, remove the stopper just sufficiently to introduce quickly 10 ml of a solution of potassium iodide (1 in 10). Titrate the liberated iodine with 0.1 N sodium thiosulfate, adding starch TS as the indicator. Each ml of 0.1 N sodium bromate is equivalent to 7.81 mg of $C_7H_{12}O_2N_2$.

Assay of the pharmaceutical forms:
(The methods should be described under the sub-titles, Tablets, Injections, etc. If necessary, the text should be divided into two parts, Principle and Method.)

Bromometric determination of tablets (3.)
Boil carefully finely powdered tablets equivalent to about 300 mg of ectylurea with 25 ml of glacial acetic acid for two minutes. Cool, filter, wash the flask and filter with glacial acetic acid until a final volume of 50 ml. Transfer exactly 15 ml of the solution to a glass-stoppered flask and proceed as directed in the Assay of the substance, beginning with "add 5 ml of sulfuric acid, 2.5 M".

Purity tests:

(Remarks on certain impurities which are likely to be found as a result of the synthesis. Laboratory findings. Suggestions for purity tests.)

Stability:

(Remarks on the stability of the substance and of preparations, e.g. with reference to heat, with reference to solutions of different pH, etc.)

Storage of the substance:
(Need for special precautions)

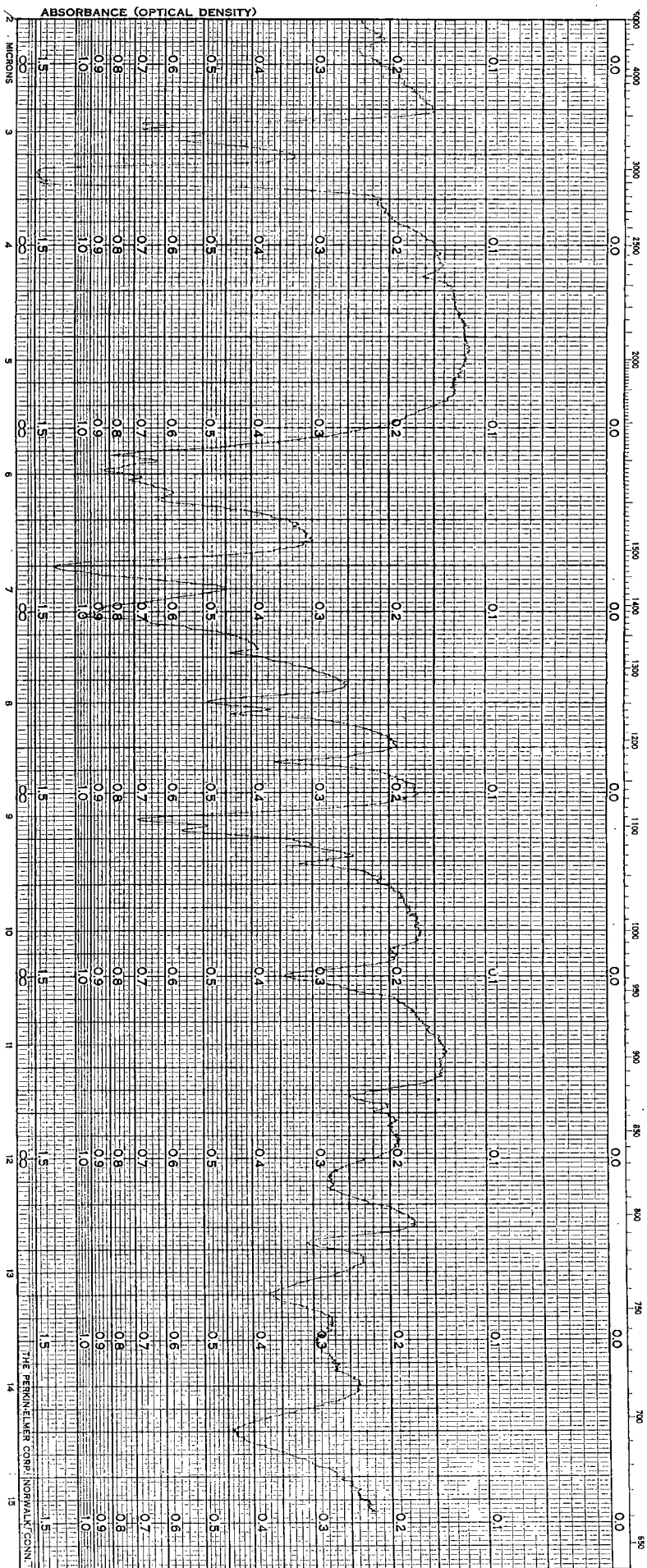
Storage of the pharmaceutical forms

Pharmacology:
(An indication of the pharmacological category and preferably with a citation of references to papers dealing with the pharmacology of the substance.)

Literature references:

1. DBP 948153
2. C.-G. Lindblad, Apotekens Kontrollaboratorium, Stockholm, unpublished
3. P. Lundgren, Apotekens Kontrollaboratorium, Stockholm, to be published.

SAMPLE



SPECTRUM NO. _____
 SAMPLE _____
of Hydroxybenzoinamide
 ORIGIN _____
 PURITY 99.5%
 PHASE *liquid mold*
 THICKNESS _____
 DATE _____
 OPERATOR *dl*
 REMARKS _____
 PRISM *NaCl*
 RESOLUTION 9.73
 RESPONSE 1
 GAIN *6.5*
 SPEED 5
 SUPPRESSION 2
 SCALE *1/4 = 5 cm*

C.L.13.1957

23 May 1957

Sir,

I have the honour to inform you that a Centre for authentic chemical substances has now been established in Stockholm in accordance with an agreement between the Apotekarsocieteten, Stockholm, and the World Health Organization, for the collection, storage and distribution of chemical reference preparations.

These arrangements are the outcome of the recommendations of the Expert Committee on Biological Standardization in its sixth report¹ to the Expert Committee on the International Pharmacopoeia and of the latter Committee in its twelfth report.²

The collection is to include mainly substances for which international biological standards have been provided in the past and which can now be characterized entirely by physico-chemical methods, and other chemicals required as reference standards in the fields of medicine and pharmacy, on the advice of the Expert Committee on the International Pharmacopoeia. A list of eight substances at present available at the Centre is enclosed, with their unit sizes and particulars concerning their shipment, and I propose to issue from time to time information on other substances which may be added to the collection.

It is not intended to make any charge for the substances or for the shipping charges by surface mail on requests received by the Centre from national administrations or from laboratories and institutes working on a non-profit basis. On requests received from commercial firms a charge of US\$ 4.00, or the equivalent amount in other currencies, will be made by the Centre in order to help to cover the cost of the preparation and to include the shipping expenses by surface mail. A charge will be made for the despatch whenever airmail is requested.

Any comments and suggestions you may wish to make in connexion with this Centre will be gratefully received and carefully considered.

I have the honour to be,

Sir,

Your obedient Servant

M. G. Candau, M.D.
Director-General

¹ Wld Hlth Org. techn. Rep. Ser. 1953, 68, Annex 3

² Document WHO/Pharm/266, paragraph 8

WORLD HEALTH ORGANIZATION
CENTRE FOR AUTHENTIC CHEMICAL SUBSTANCES

The authentic chemical substances now available at the Centre are listed below together with the unit and size. Most packages contain sufficient material for about 20 assays. All shipments are made by surface mail except when airmail is requested.

	<u>Size</u>
Chloramphenicol	300 milligrams
Digitoxoside	5 capsules of 10 milligrams
Ergometrine maleate	2 capsules of 10 milligrams
Melarsen	1 gram
Oestrone	30 milligrams
Progesterone	65 milligrams
Tubocurarine	30 milligrams
Vitamin A Acetate (this is an oily solution of Vitamin A Acetate)	5 capsules of approximately 8.6 milligrams (0.344 micrograms of Vitamin A Acetate is equivalent to 1 International Unit - <u>Wld Hlth Org. techn. Rep. Ser. 1950, 3, 34</u>)

Each package costs US\$ 4.00 or the equivalent amount in other currencies. The shipment by surface mail will be made free. A charge will be made for the despatch whenever airmail is requested.

Please send your orders and make cheques payable* to:

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