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**WORLD HEALTH ORGANIZATION**

**TECHNICAL REPORT SERIES**

No. 127

**EXPERT COMMITTEE ON  
BIOLOGICAL STANDARDIZATION**

**Tenth Report**

**WORLD HEALTH ORGANIZATION**

**PALAIS DES NATIONS**

**GENEVA**

1957

EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION

Tenth Session \*

Geneva, 8-13 October 1956

*Members :*

- Lieutenant-Colonel M. L. Ahuja, Medical Adviser to the High Commissioner for India, London, England
- Dr A. do Amaral, Director, Instituto Butantan, São Paulo, Brazil (*Vice-Chairman*)
- Dr E. Grasset, Professor of Hygiene ; Director, Institute of Hygiene, University of Geneva, Switzerland
- Dr J. H. Humphrey, Department of Biological Standards, National Institute for Medical Research, Mill Hill, London, England (*Rapporteur*)
- Dr M. Kitaoka, Director, Department of Viral and Rickettsial Diseases, National Institute of Health, Tokyo, Japan
- Dr O. Maaløe, Chief, Department of Biological Standardization, Statens Seruminstitut, Copenhagen, Denmark (*Chairman*)
- Dr A. A. Miles, Director, Lister Institute of Preventive Medicine, London, England
- Dr G. Penso, Chief, Laboratory of Microbiology, Istituto Superiore di Sanità, Rome, Italy

*Temporary adviser :*

- Dr R. Murray, Director, Division of Biological Standards, National Institutes of Health (Public Health Service), Bethesda, Md., USA

*Representatives of the Food and Agriculture Organization of the United Nations :*

- Sir Thomas Dalling, Chief Veterinary Consultant, Animal Production Branch, Agriculture Division, FAO
- Dr A. W. Stableforth, Director, Central Veterinary Laboratory, Ministry of Agriculture, Fisheries and Food, Weybridge, Surrey, England

*Secretariat :*

- Dr W. Aeg. Timmerman, Director, Division of Therapeutic Substances, WHO
- Dr N. K. Jerne, Acting Chief, Biological Standardization Section, WHO (*Secretary*)

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\* Invited but unable to attend :

- Dr E. Dussert, Jefe del Departamento de Control y Laboratorios, Instituto Bacteriológico de Chile, Santiago, Chile
- Dr P. Lépine, Chef du Service des Virus, Institut Pasteur, Paris, France
- Dr E. A. North, Deputy Director (Research), Department of Health, Commonwealth Serum Laboratories, Parkville, Victoria, Australia
- Dr R. Prigge, Director, Paul-Ehrlich-Institut, Staatliche Anstalt für Experimentelle Therapie, Frankfurt-on-Main, Germany
- Dr H. Welch, Director, Division of Antibiotics, Food and Drug Administration, Department of Health, Education, and Welfare, Washington, D.C., USA

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# EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION

## Tenth report \*

The tenth session of the Expert Committee on Biological standardization was held in Geneva from 8 to 13 October 1956.

The Deputy Director-General, on behalf of the Director-General of the World Health Organization, welcomed the members of the Committee, the temporary adviser and the representatives of the Food and Agriculture Organization of the United Nations.

## IMMUNOLOGICAL

### ANTIGENS

#### 1. Pertussis Vaccine

The Committee noted that, as a result of field trials, there is now evidence that the protective value of pertussis vaccines in man is indicated by their potencies as determined in mice by the intracerebral challenge method.<sup>1</sup> The proposed international standard preparation has been extensively compared in the laboratory<sup>2</sup> (a) with the British Reference Vaccine which has been proved to be effective in man, and (b) with the

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\* The Executive Board, at its nineteenth session, adopted the following resolution:  
The Executive Board

1. NOTES the tenth report of the Expert Committee on Biological Standardization;
2. THANKS the members of the Committee for their work; and
3. AUTHORIZES publication of the report.

(Resolution EB19.R5, *Off. Rec. Wld Hlth Org.*, 1957, 76, 3)

<sup>1</sup> See *Brit. med. J.*, 1956, 2, 454 (Report to the Whooping-Cough Immunization Committee of the Medical Research Council).

<sup>2</sup> Participants: Institut Pasteur, Paris, France; Rijks Instituut voor de Volksgezondheid, Netherlands; Michigan Department of Health, USA; Biological Standards Control Laboratory, England; Department of National Health and Welfare, Canada; Statens Seruminstitut, Denmark; Commonwealth Serum Laboratories, Australia; National Institutes of Health, USA; Lister Institute of Preventive Medicine, England

Reference Vaccine of the National Institutes of Health, Bethesda, Md.<sup>1</sup> Accelerated degradation tests have shown that the proposed international standard preparation is highly stable.<sup>1</sup> The Committee accordingly authorized the Statens Seruminstitut, Copenhagen, with the agreement of the participants, to define the unitage on the basis of the results of the collaborative assay, so that the International Unit for pertussis vaccine is equivalent to the protective unit used by the National Institutes of Health, and to establish the material as the International Standard for Pertussis Vaccine.

## 2. Typhoid Vaccines

The Committee considered the outcome of the field trial of both phenolized and alcoholized vaccines in Yugoslavia, and of the tests of these preparations carried out in several laboratories. Within the restricted circumstances of the field trial, only the phenolized vaccine could be shown to confer significant protection to man, a result which could not have been predicted from laboratory tests of antigenic potency; in the laboratory, the alcoholized vaccine proved the more effective in inducing the formation of Vi-agglutinins, and was at least as effective as the phenolized vaccine in active and passive protection tests.<sup>2</sup>

The Committee agreed that further research was needed on laboratory assay methods and on other types of vaccine, where possible in terms of a standard. Because of the relative instability of liquid vaccines, the Committee requested the Statens Seruminstitut, Copenhagen, to obtain a quantity of a stable, acetone-dried typhoid vaccine and to initiate studies of this material in collaboration with other interested organizations and laboratories. The Committee noted that sufficient quantities of the vaccines used in the Yugoslav field trials are still available for such collaborative studies.

## 3. Cholera Vaccines

The Committee noted that cholera vaccination has been widely practised during the past 50 years<sup>3</sup> and that the practice is increasing; but that laboratory tests of the protective value of cholera vaccines do not give results reproducible in different laboratories. The Committee also noted the report of the Committee on International Quarantine which "stressed the need for international standardization of anticholera vaccines

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<sup>1</sup> Maaløe, O., unpublished working document WHO/BS/338

<sup>2</sup> Maaløe, O., unpublished working document WHO/BS/340.

<sup>3</sup> WHO Secretariat, unpublished working document WHO/BS/342

and expressed the wish that the Expert Committee on Biological Standardization and other experts concerned would continue to study the matter".<sup>1</sup> The Committee emphasized the urgent need for further study of improved methods of testing cholera vaccines, and recommended the Secretariat to encourage and assist work directed to this end.

#### **4. Rabies Vaccine**

The Committee noted that studies of the proposed international reference preparation of rabies vaccine have shown that the material appears to be suitable,<sup>2</sup> and it endorsed the recommendation by the Secretariat to the Expert Committee on Rabies that a collaborative examination of its stability and suitability in assay should be arranged.

#### **5. Smallpox Vaccine**

The Committee noted that a sample of a very stable freeze-dried smallpox vaccine (sheep lymph)<sup>3</sup> has been offered by the Lister Institute of Preventive Medicine, London, for an international reference preparation, and asked the Statens Seruminstitut, Copenhagen, to arrange a collaborative examination of this material.

#### **6. Swine Erysipelas Vaccine**

The Committee noted the progress made by the Central Veterinary Laboratory, Weybridge, Surrey, in examining an adsorbed, freeze-dried preparation of swine erysipelas vaccine,<sup>4</sup> and asked the Laboratory, in conjunction with the Paul-Ehrlich-Institut, Frankfurt-on-Main, to arrange for a collaborative examination of the material for stability and suitability in assay, with a view to its establishment as the International Standard for Swine Erysipelas Vaccine.

#### **7. Japanese B Encephalitis Vaccine**

The Committee asked the Secretariat to assess the need for an international reference preparation of Japanese B encephalitis vaccine.

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<sup>1</sup> *Off. Rec. Wld Hlth Org.*, 1956, **72**, 36

<sup>2</sup> Kaplan, M., unpublished working document WHO/BS/372

<sup>3</sup> Cockburn, W. C. et al., unpublished working document WHO/BS/371

<sup>4</sup> Central Veterinary Laboratory, Standards Department, Weybridge, unpublished working document WHO/BS/344

### 8. Leptospirosis Vaccines

The Committee asked the Secretariat to assess the need for international reference preparations of leptospirosis vaccines.

### 9. Cardiolipin

The Committee noted that the collaborative study of the material for replacement of the present International Reference Preparation of Cardiolipin is nearly completed,<sup>1</sup> and authorized the Statens Seruminstitut, Copenhagen, with the agreement of the participants, to establish the material as the third International Reference Preparation of Cardiolipin.

### 10. Lecithins

The Committee noted that stocks of the International Reference Preparations of Egg and Beef Heart Lecithin are adequate for at least two years and that, since the general use of beef heart lecithin is decreasing, replacement of the corresponding International Reference Preparation will probably be unnecessary.<sup>1</sup> The Committee asked the Statens Seruminstitut, Copenhagen, to collect material for eventual replacement of the International Reference Preparation of Egg Lecithin.

## ANTIBODIES

### 11. Diphtheria Antitoxin for Flocculation Test

The Committee endorsed the establishment by the Statens Seruminstitut, Copenhagen, of the fourth International Standard for Diphtheria Antitoxin for the Flocculation Test.<sup>2</sup>

### 12. *Clostridium welchii* (Perfringens) Antitoxins

The Committee noted the progress made by the Central Veterinary Laboratory, Weybridge, Surrey,<sup>3</sup> in demonstrating that, when highly

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<sup>1</sup> International Serological Reference Laboratory, Statens Seruminstitut, Denmark, unpublished working document WHO/BS/360

<sup>2</sup> Statens Seruminstitut, Denmark, unpublished working document WHO/BS/359

<sup>3</sup> Central Veterinary Laboratory, Standards Department, Weybridge, unpublished working document WHO/BS/343

potent test toxins were used in the intravenous mouse assay, no discrepancies were apparent in relative potency determinations of several antitoxins, in terms of the corresponding International Reference Preparations of *Clostridium welchii* Antitoxins of Types B and D.

### 13. Gas Gangrene Antitoxin (*Vibrion Septique*)

The Committee noted that a collaborative examination<sup>1</sup> of the proposed replacement standard was almost completed.<sup>2</sup> It authorized the Statens Seruminstitut, Copenhagen, with the agreement of the participants, to define the unitage on the basis of the results of the collaborative assay, and to establish the preparation as the third International Standard for Gas Gangrene Antitoxin (*Vibrion septique*). The Committee noted that the standard will be distributed on request, and in freeze-dried form.

### 14. Staphylococcus $\beta$ Antitoxin

The Committee decided that the International Standard for Staphylococcus  $\beta$  Antitoxin should not be replaced and that its routine distribution should be discontinued. The remaining material will be available on request.<sup>3</sup>

### 15. Anti-Streptolysin O

The Committee noted the opinion of the Expert Committee on Rheumatic Diseases that an international standard for anti-streptolysin O serum is needed.<sup>4</sup> It asked the Statens Seruminstitut, Copenhagen, to obtain a quantity of antistreptolysin O serum, and to arrange for collaborative examination of the serum for its suitability as a standard preparation of anti-streptolysin O.

### 16. Antivenins

The Committee noted the progress made by the Instituto Butantan, São Paulo, in collecting samples of venom from *Bothrops jararaca* in

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<sup>1</sup> Participants: Statens Seruminstitut, Denmark; Paul-Ehrlich-Institut, Germany; Institute for the Control and Research of Immunological Substances, Yugoslavia; National Institutes of Health, USA

<sup>2</sup> Statens Seruminstitut, Denmark, unpublished working document WHO/BS/367

<sup>3</sup> Statens Seruminstitut, Denmark, unpublished working document WHO/BS/339

<sup>4</sup> Unpublished working document WHO/Rheum. Dis./21

different areas of Brazil, and in studying the toxicity and stability of these samples.<sup>1</sup>

The Committee emphasized that the principles of standardizing antivenins are analogous to those of standardizing antitoxins. It requested the Secretariat to investigate the possibility of obtaining, for each of the main genera of snakes (starting with *Bothrops* and *Naja*), sufficient quantities of potent antivenins, containing antibodies for the important toxic principles contained in the unmodified venom. It also requested the Secretariat to obtain representative samples of carefully dried snake venoms from different geographical areas, with a view to organizing collaborative studies of the suitability of the antivenins to serve as international standards.

### 17. Blood-Typing Sera

The Committee noted that the material proposed for use as the international standard for anti-Rh<sub>0</sub> (anti-D) blood-typing serum had proved unsuitable, and asked the International Blood-Group Reference Laboratory, London, to re-examine the need for an international standard for agglutinating ("saline-agglutinating") anti-Rh<sub>0</sub> (anti-D) blood-typing serum.

The Committee noted that the relative titres of albumin-potentiated anti-Rh<sub>0</sub> (anti-D) blood-typing sera had been shown to vary with the method of assay. It asked the International Blood-Group Reference Laboratory to carry out more extensive collaborative studies in order to prepare the ground for the establishment of an international standard for albumin-potentiated anti-Rh<sub>0</sub> (anti-D) blood-typing serum.

The Committee noted that the International Blood-Group Reference Laboratory, London, would attempt to obtain a quantity of agglutinating ("saline-agglutinating") anti-rh' (anti-C) and anti-rh" (anti-E) blood-typing sera to serve as international standards.<sup>2</sup>

### 18. Influenza Sera

The Committee endorsed the opinion of the World Influenza Centre, London,<sup>3</sup> that, in view of the variable antigenic constitution of influenza

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<sup>1</sup> Amaral, A. do, Schöttler, W. H. A. and the WHO Secretariat, unpublished working document WHO/BS/364; Amaral, A. do, unpublished working document WHO/BS/373

<sup>2</sup> Mourant, A. E., unpublished working document WHO/BS/366

<sup>3</sup> World Influenza Centre, National Institute for Medical Research, The Ridgeway, Mill Hill, London, N.W.7

virus strains isolated in epidemics, no useful purpose would be served by establishing international reference preparations for influenza sera at the present time.<sup>1</sup>

### 19. Poliomyelitis Sera

The Committee noted the plans of the Statens Seruminstitut, Copenhagen, to arrange a collaborative assay of the three proposed international standard sera (type-specific monkey sera)<sup>2</sup> by the international centres for epidemiological and laboratory studies of poliomyelitis (designated by WHO) and by other interested laboratories. These studies would comprise examination of the suitability of these sera to serve as standards for the determination of virus neutralizing potencies of sera, including therapeutic sera,<sup>3</sup> from various species of animals, when tested by different laboratory methods.

### 20. Typhoid and Paratyphoid Agglutinating Sera

The Committee considered the report of the Secretariat on the results so far received of the collaborative assay of the proposed international standards for typhoid and paratyphoid A and B agglutinating sera. All laboratories found closely similar titres for the proposed standard sera when tested both with locally prepared bacterial suspensions and with suspensions supplied by the Central Public Health Laboratory, Colindale. The relative potencies of human sera, however, determined by the various H-, O- and Vi-agglutination tests in the different laboratories, were widely discrepant.<sup>4</sup> The Committee decided that no action would be taken until the comments of participants have been received.

### 21. Syphilitic Human Serum

The Committee noted that the proposed reference preparation of syphilitic human serum has been studied in parallel with other syphilitic human sera,<sup>5</sup> and that the International Serological Reference Laboratory,

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<sup>1</sup> Payne, A. M.-M., unpublished working document WHO/BS/362

<sup>2</sup> Statens Seruminstitut, Denmark, unpublished working document WHO/BS/361

<sup>3</sup> Penso, G., unpublished working document WHO/BS/363

<sup>4</sup> WHO Secretariat, unpublished working document WHO/BS/346

<sup>5</sup> International Serological Reference Laboratory, Statens Seruminstitut, Denmark, unpublished working document WHO/BS/360

Copenhagen, is preparing a full report. The Committee decided to defer the establishment of the material as the international reference preparation for syphilitic human serum until the opinions of the participants have been considered.

## 22. Leptospirosis Sera

The Committee asked the Secretariat to ascertain whether international standards for leptospirosis sera are needed, in addition to the sera at present being prepared for typing purposes in the WHO/FAO Leptospirosis Reference Laboratories.<sup>1</sup>

# PHARMACOLOGICAL

## ANTIBIOTICS

### 23. Streptomycin

The Committee noted that a quantity of streptomycin sulfate is available for replacement of the International Standard for Streptomycin. This material contains a somewhat larger percentage of inert material than the existing International Standard.<sup>2</sup> The Committee considered, however, that this fact was irrelevant since the sole purpose of the standard is to serve as a means of defining antibiotic potency. It asked the National Institute for Medical Research, London, to arrange an international collaborative assay of the material and authorized it, with the agreement of the participants, to define the unitage on the basis of the results of the assay, and to establish the material as the second International Standard for Streptomycin.

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<sup>1</sup> Laboratory of the Department of Health and Home Affairs, Brisbane, Australia ; Institute for Tropical Hygiene and Geographical Pathology, Amsterdam, Netherlands ; Division of Veterinary Medicine, Walter Reed Army Institute of Research, Washington, D.C., USA ; The Wellcome Laboratories of Tropical Medicine, London, England ; Istituto Superiore di Sanità, Rome, Italy ; Department of Viral and Rickettsial Diseases, National Institute of Health, Tokyo, Japan

<sup>2</sup> National Institute for Medical Research, London, unpublished working document WHO/BS/369

#### 24. Tetracycline

The Committee noted that a quantity of tetracycline hydrochloride had been obtained and that a collaborative assay<sup>1</sup> has been carried out.<sup>2</sup> The Committee authorized the National Institute for Medical Research, London, with the agreement of the participants, and on the basis of the results of the collaborative assay, to assign the unitage so that the International Unit for tetracycline is equivalent to the activity of one microgram of the tetracycline hydrochloride in the standard used by the Food and Drug Administration, Department of Health, Education, and Welfare, Washington, D.C., and to establish the material as the International Standard for Tetracycline.

#### 25. Erythromycin

The Committee noted that the international collaborative assay<sup>3</sup> of the proposed international standard preparation of erythromycin was completed,<sup>4</sup> and authorized the National Institute for Medical Research, London, with the agreement of the participants, and on the basis of the results of the collaborative assay, to assign the unitage so that one International Unit is equivalent to the activity of one microgram of pure erythromycin base, and to establish this material as the International Standard for Erythromycin.

#### 26. Neomycin

The Committee agreed that an international standard for neomycin is needed. It noted that a quantity of neomycin sulfate is available for this

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<sup>1</sup> Participants : Laboratory of Hygiene, Department of National Health and Welfare, Canada ; Statens Seruminstitut, Denmark ; Research Institute for the Pharmaceutical Industry, Hungary ; Hindustan Antibiotics, Pimpri, Bombay State, India ; Istituto Superiore di Sanità, Italy ; National Institute for Medical Research, Great Britain ; Food and Drug Administration, Department of Health, Education, and Welfare, USA ; Messrs. Chas. Pfizer & Co., Inc., USA

<sup>2</sup> National Institute for Medical Research, London, unpublished working document WHO/BS/370

<sup>3</sup> Participants : Laboratory of Hygiene, Department of National Health and Welfare, Canada ; Statens Seruminstitut, Denmark ; Istituto Superiore di Sanità, Italy ; Distillers Company Ltd., Liverpool and Epsom, England ; National Institute for Medical Research, Great Britain ; Eli Lilly & Co., USA ; Food and Drug Administration, Department of Health, Education, and Welfare, USA ; State Control Institute, Ministry of Health, USSR

<sup>4</sup> National Institute for Medical Research, London, unpublished working document WHO/BS/368

purpose,<sup>1</sup> and asked the National Institute for Medical Research, London, to examine this material for suitability as a standard preparation, with a view to arranging an international collaborative assay in terms of the standard used by the Food and Drug Administration, Department of Health, Education, and Welfare, Washington, D.C.

#### **27. Novobiocin**

The Committee, noting that a need for an international standard for novobiocin might arise,<sup>1</sup> asked the National Institute for Medical Research, London, to obtain further opinions about this need and to investigate whether material suitable for an international standard preparation could be obtained.

#### **28. Carbomycin (Magnamycin), Spiromycin, Albomycin, Nystatin (Mycostatin)**

The Committee was of the opinion that, at the present time, international standards are not needed for carbomycin (magnamycin), spiromycin, albomycin, or nystatin (mycostatin).<sup>1</sup>

#### **29. Phenoxymethylpenicillin**

The Committee noted that phenoxymethylpenicillin cannot be validly assayed against the International Standard for Penicillin (benzylpenicillin), and agreed that an international standard for phenoxymethylpenicillin is needed. The Committee further noted that a highly purified preparation is available which has been found to be suitable for this purpose.<sup>1</sup> The Committee asked the National Institute for Medical Research, London, to arrange for a collaborative assay in terms of the standard used by the Food and Drug Administration, Department of Health, Education, and Welfare, Washington, D.C.

#### **30. Procaine Benzylpenicillin in Oil with Aluminium Monostearate (PAM)**

The Committee considered the work done by the National Institute for Medical Research, London, in devising an animal test for persistence of penicillin in circulating blood after administration of long-acting peni-

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<sup>1</sup> National Institute for Medical Research, London, unpublished working document WHO/BS/347

cillin preparations.<sup>1</sup> Since animal tests of persistence now appear to be practicable, the Committee agreed that a standard preparation of the long-acting penicillin (PAM) was needed. It accordingly asked the National Institute for Medical Research to obtain material suitable for an international reference preparation of PAM and to arrange for this material to be tested, in parallel with other preparations of PAM of differing efficacies, in man as well as in laboratory animals.

### 31. Assay Methods for Penicillin in Serum

The Committee discussed a report from the National Institute for Medical Research, London, on the assay of small amounts of penicillin in human and rabbit serum.<sup>2</sup> It noted that a suitable method is available for use in tests of persistence of penicillin in circulating blood and recommended that it be considered by the Expert Committee on Venereal Diseases and Treponematoses.

## HORMONES

### 32. Oxytocic, Vasopressor and Antidiuretic Substances

The Committee noted that a collaborative assay<sup>3</sup> of the material which had been collected for replacement of the International Standard for Posterior Pituitary Lobe had been carried out.<sup>4</sup> It authorized the National Institute for Medical Research, London, with the agreement of

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<sup>1</sup> Humphrey, J. H., Lightbown, J. W. & Mussett, M. V., unpublished working document WHO/BS/358 Rev.1

<sup>2</sup> Lightbown, J. W. & Sulitzeanu, D., unpublished working document WHO/BS/349 Rev.1

<sup>3</sup> Participants: Commonwealth Serum Laboratories, Australia; Food and Drug Directorate, Department of National Health and Welfare, Canada; Statens Serum-institut, Denmark; Laboratoire national de Contrôle des Médicaments, France; Medizinische Forschungsanstalt, Germany; Rijks Instituut voor de Volksgezondheid, Netherlands; Central Drugs Laboratory, India; The Wellcome Research Laboratories, England; School of Pharmacy, London, England; Department of Pharmacology, University of Oxford, England; Pharmacological Laboratory, University College, London, England; Department of Pharmacology, University of Bristol, England; National Institute for Medical Research, Great Britain; The Armour Laboratories, USA; Wilson Laboratories, USA; Parke, Davis & Co., USA; Eli Lilly & Co., USA; Food and Drug Administration, Department of Health, Education, and Welfare, USA; Department of Pharmacology, University of Zagreb, Yugoslavia

<sup>4</sup> National Institute for Medical Research, London, unpublished working document WHO/BS/351

the participants, to assign to the material a unitage for each of the substances (oxytocic, vasopressor and antidiuretic) for which it is to serve as the standard, on the basis of the results of the collaborative assay, and to establish this material as the third International Standard.

The Committee decided to change the name of this standard to International Standard for Oxytocic, Vasopressor and Antidiuretic Substances, thereby emphasizing that the material is to serve as the standard for three distinct, and not necessarily related activities.<sup>1</sup> The Committee further decided that, pending isolation or synthesis of pure active peptides in sufficient quantities, a single preparation should continue to serve as the standard for oxytocic, vasopressor and antidiuretic substances.

### 33. Corticotrophin

The Committee noted that the existing International Standard had been found to be unsuitable for the assay of such highly purified preparations of corticotrophin as are now coming into clinical use.<sup>2</sup> It asked the National Institute for Medical Research, London, to obtain further opinions on the need for a new standard and, if this need is confirmed, to obtain material of high potency, suitable for a standard preparation.

### 34. Prolactin

The Committee noted that a preparation of prolactin suitable for replacing the International Standard had been obtained, and that a collaborative assay would be organized.<sup>3</sup> It authorized the National Institute for Medical Research, London, with the agreement of the participants, to define the unitage on the basis of the results of the collaborative assay, and to establish this material as the second International Standard for Prolactin.

### 35. Insulin

The Committee noted that the international collaborative assay<sup>4</sup> of the replacement standard for insulin was completed except for the final

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<sup>1</sup> National Institute for Medical Research, London, unpublished working document WHO/BS/352

<sup>2</sup> National Institute for Medical Research, London, unpublished working document WHO/BS/356

<sup>3</sup> National Institute for Medical Research, London, unpublished working document WHO/BS/350

<sup>4</sup> Participants: Commonwealth Serum Laboratories, Australia; Nordisk Insulinlaboratorium, Denmark; Novo Terapeutisk Laboratorium A/S, Denmark; Farbwerke

analysis of the results.<sup>1</sup> It authorized the National Institute for Medical Research, London, with the agreement of the participants to define the unitage on the basis of the results of the collaborative assay and to establish this material as the fourth International Standard for Insulin.

## MISCELLANEOUS

### 36. Dextran Sulfate

The Committee noted that material suitable for an international standard had been obtained,<sup>2</sup> and that a collaborative assay against the existing author's preparation is being arranged. It authorized the National Institute for Medical Research, London, with the agreement of the participants, to define the unitage of the material in terms of the existing International Unit<sup>3</sup> on the basis of the results of the collaborative assay, and to establish it as the International Standard for Dextran Sulfate.

### 37. Heparin

The Committee noted that material suitable for replacement of the International Standard had been obtained,<sup>4</sup> and that an international collaborative assay would be organized. It authorized the National Institute for Medical Research, London, with the agreement of the participants, to define the unitage on the basis of the results of the collaborative assay, and to establish this material as the second International Standard for Heparin.

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Hoechst, Germany; Rijks Instituut voor de Volksgezondheid, Netherlands; N. V. Organon, Netherlands; Central Drugs Laboratory, India; British Drug Houses Ltd, England; British Schering Research Laboratories, Alderley Ridge, England; Boots Pure Drug Co., Ltd, Nottingham, England; Burroughs Wellcome & Co., England; Evans Biological Institute, Runcorn, England; National Institute for Medical Research, Great Britain; Insulin Committee, University of Toronto, Canada; Food and Drug Directorate, Department of National Health and Welfare, Canada; The Armour Laboratories, USA; Eli Lilly & Co., USA; Food and Drug Administration, Department of Health, Education, and Welfare, USA; Sharp & Dohme, USA; Squibb & Sons, USA

<sup>1</sup> National Institute for Medical Research, London, unpublished working document WHO/BS/357

<sup>2</sup> National Institute for Medical Research, London, unpublished working document WHO/BS/354

<sup>3</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1956, **108**, 18

<sup>4</sup> National Institute for Medical Research, London, unpublished working document WHO/BS/353

### 38. Vitamin B<sub>12</sub>

The Committee noted that the proposed international standard preparation for Vitamin B<sub>12</sub> had been made in a satisfactory tablet form,<sup>1</sup> and asked the National Institute for Medical Research, London, to proceed with a collaborative examination of this material. It authorized the National Institute for Medical Research, with the agreement of the participants, to define the unitage on the basis of the results of the collaborative examination, so that the International Unit is equivalent to the activity of one microgram of pure Vitamin B<sub>12</sub>, and to establish this material as the International Standard for Vitamin B<sub>12</sub>.

### 39. Pyrogens

The Committee noted that the collaborative examination<sup>2</sup> of two pyrogen preparations was completed and that the majority of the participants had confirmed that an international reference preparation of pyrogen is needed.<sup>3</sup> In view of the difficulties of accurately determining the relative potencies of pyrogen preparations, the Committee asked the National Institute for Medical Research, London, to obtain a quantity of pyrogen sufficient for distribution as a working standard to interested laboratories, as well as to serve as an international reference preparation of pyrogen, and to collect opinions on its usefulness.

## GENERAL

### 40. Collection of Authentic Chemical Substances

The Committee reaffirmed its previous decision to offer the following substances, now held at the National Institute for Medical Research,

<sup>1</sup> National Institute for Medical Research, London, unpublished working document WHO/BS/355

<sup>2</sup> Participants: Department of National Health and Welfare, Canada; Statens Seruminstitut, Denmark; Danmarks Apotekers Kontrollaboratorium, Denmark; Institut Pasteur, Paris, France; Rijks Instituut voor de Volksgezondheid, Netherlands; N. V. Organon, Netherlands; Central Drugs Research Institute, India; Bengal Immunity Research Institute, India; Boots Pure Drug Co., Ltd, Nottingham, England; The Crookes Laboratories, England; National Institute for Medical Research, Great Britain; Baxter Laboratories, Inc., USA; Eli Lilly & Co., USA; National Institutes of Health, USA; The Upjohn Company, USA

<sup>3</sup> National Institute for Medical Research, London, unpublished working document WHO/BS/365

London,<sup>1</sup> to the Expert Committee on the International Pharmacopoeia for inclusion in the Collection of Authentic Chemical Substances, which WHO has established at Stockholm: <sup>2</sup> chloramphenicol; <sup>3</sup> melarsen; <sup>4</sup> ouabain; <sup>4</sup> progesterone; <sup>5</sup> tubocurarine.<sup>6</sup>

The Committee decided also to offer, for the same purpose, the following substances, which have ceased to be international standards but are still held at the National Institute for Medical Research: <sup>7</sup> oestrone; <sup>8</sup> oestradiol monobenzoate; <sup>8</sup> androsterone; <sup>9</sup> vitamin A acetate.<sup>4</sup>

The Committee decided that the following have ceased to be International Standards: the International Standard for Provitamin A; <sup>10</sup> the International Standard for Vitamin B<sub>1</sub>; <sup>11</sup> the International Standard for Vitamin C; <sup>12</sup> and the International Standard for Vitamin E.<sup>13</sup> The Committee offered the remaining stocks of these materials, held at the National Institute for Medical Research,<sup>7</sup> to the Expert Committee on the International Pharmacopoeia for inclusion in the Collection of Authentic Chemical Substances.

#### 41. Biological Assay Methods for the International Pharmacopoeia

The Committee decided that, in view of their heavy commitments, expert committees on biological standardization, as currently convened, were unable to give the detailed consideration necessary for approval of the methods of biological assay for publication in the second edition of the *Pharmacopoea Internationalis*. It agreed that approval by a committee could be given if the methods were first drawn up by correspondence or at meetings of a working party whose members could be drawn from

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<sup>1</sup> National Institute for Medical Research, London, unpublished working document WHO/BS/348

<sup>2</sup> Collection of Authentic Chemical Substances, Apotekens Kontrollaboratorium, Lindhagensgatan 128, Stockholm K, Sweden

<sup>3</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1954, **86**, 15

<sup>4</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1955, **96**, 16

<sup>5</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1956, **108**, 17

<sup>6</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1956, **108**, 19

<sup>7</sup> National Institute for Medical Research, London, unpublished working document WHO/BS/348

<sup>8</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1950, **2**, 9

<sup>9</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1951, **36**, 8

<sup>10</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1950, **3**, 6

<sup>11</sup> *Bull. Hlth Org. L. o. N.*, 1938, **7**, 882

<sup>12</sup> *Quart. Bull. Hlth Org. L. o. N.*, 1934, **3**, 436

<sup>13</sup> *Bull. Hlth Org. L. o. N.*, 1940/41, **9**, 443

appropriate WHO Expert Advisory Panels, such as those on Biological Standardization and on the International Pharmacopoeia and Pharmaceutical Preparations.

#### 42. List of International Biological Standards

The Committee welcomed the publication, in the first edition of the *Pharmacopoea Internationalis*,<sup>1</sup> of a complete list of International Biological Standards and Reference Preparations, which had helped to make information about the standards available on a world-wide scale. It asked the Secretariat to revise the list, for publication in the forthcoming supplement to the *Pharmacopoea Internationalis*.

The Committee also decided that an up-to-date list of International Biological Standards and Reference Preparations should be annexed to the present report (see Annex, page 21), so that copies of the list would be available to national centres for biological standards and other interested institutions.

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<sup>1</sup> World Health Organization (1955) *Pharmacopoea Internationalis*, Geneva, Editio prima, vol. II, p. 254 (Appendix 10)

**Annex**

**INTERNATIONAL BIOLOGICAL STANDARDS  
AND REFERENCE PREPARATIONS**

## A. IMMUNOLOGICAL

*Held by the International Laboratory for Biological Standards,*

Substances	International Unit of present standard (mg)	Form in which dispensed
<b>ANTIGENS</b>		
Old tuberculin	0.0100	Ampoules containing 2 ml of Old tuberculin (100 000 International Units (I.U.) per ml)
Purified protein derivative of mammalian tuberculin	0.0000280	Ampoules containing 10 mg of PPD plus 4 mg of salts (500 000 I.U. per ampoule)
Purified protein derivative of avian tuberculin	0.0000726	Ampoules containing 10 mg of PPD plus 26.3 mg of salts (500 000 I.U. per ampoule)
Tetanus toxoid	0.03	Ampoules containing 25 mg (420 Lf) of alcohol purified tetanus toxoid plus glycine (833 I.U. per ampoule)
Diphtheria toxoid, plain	0.50	Ampoules containing 50 mg (1730 Lf) of alcohol purified diphtheria toxoid plus glycine (100 I.U. per ampoule)
Diphtheria toxoid, adsorbed	0.75	Ampoules containing 80 mg (50 Lf) of diphtheria toxoid adsorbed to aluminium hydroxide, dried, plus lactose (107 I.U. per ampoule)
Schick test toxin (diphtheria)	0.0042	Ampoules containing 0.005 mg (0.9 Lf) of purified diphtheria toxin plus 1 mg of bovine albumin and 2.74 mg of phosphate buffer salts (900 I.U. per ampoule)
Cholera antigen (Inaba)	—	Ampoules containing approximately 100 mg of dried antigen
Cholera antigen (Ogawa)	—	Ampoules containing approximately 100 mg of dried antigen

## SUBSTANCES

*Statens Seruminstitut, Copenhagen*

Years of establishment of standards (in brackets, unitage of previous standards)	References (WHO/BS refers to unpublished working documents of the Expert Committee on Biological Standardization)
1st Standard 1931 (0.0100 mg) 2nd Standard 1935	<i>Off. Rec. Wld Hlth Org.</i> , 1948, <b>11</b> , 10; <i>Bull. Wld Hlth Org.</i> , 1952, <b>7</b> , 171; 1954, <b>10</b> , 989; 1955, <b>12</b> , 179; <i>Bull. Hlth Org. L. o. N.</i> , 1935, <b>4</b> , 475, 514; <i>Pharmacopoea Internationalis</i> , 1951, Vol. I, 257, 354; WHO/BS 3, 16, 28, 64, 120
1st Standard 1951	<i>Bull. Wld Hlth Org.</i> , 1952, <b>7</b> , 171; 1954, <b>10</b> , 989; 1955, <b>12</b> , 179; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1952, <b>56</b> , 6; WHO/BS 3, 16, 28, 64, 106, 120, 127, 173, 181
1st Standard 1954	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1955, <b>96</b> , 11; WHO/BS 126, 181, 227, 293, 293 Add.1 and 2
1st Standard 1951	<i>Bull. Wld Hlth Org.</i> , 1953, <b>9</b> , 837, 843; 1955, <b>12</b> , 761; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1952, <b>56</b> , 5; WHO/BS 25, 37, 48, 68, 83, 92, 125, 192, 194, 214
1st Standard 1951	<i>Bull. Wld Hlth Org.</i> , 1949, <b>2</b> , 49; 1953, <b>9</b> , 829, 843; 1955, <b>12</b> , 751; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1952, <b>56</b> , 4; 1953, <b>61</b> , 1; WHO/BS 4, 13, 19, 32, 48, 68, 79, 83, 86, 102, 108, 113, 191, 193, 214, 215, 248, 288, 330, 331
1st Standard 1955	<i>Bull. Wld Hlth Org.</i> , 1949, <b>2</b> , 49; 1953, <b>9</b> , 829, 843; 1954, <b>10</b> , 951, 983; 1955, <b>12</b> , 751; 1955, <b>13</b> , 473; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1953, <b>61</b> , 1; 1956, <b>108</b> , 8; WHO/BS 4, 13, 19, 32, 48, 68, 79, 83, 86, 102, 108, 113, 191, 193, 214, 215, 248, 288, 330, 331
1st Standard 1954	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1955, <b>96</b> , 7; WHO/BS 229, 247, 274, 275, 275 Add.1 and 2
1st Reference Preparation 1953	<i>Bull. Wld Hlth Org.</i> , 1955, <b>12</b> , 945; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1954, <b>86</b> , 7; WHO/BS 52, 130, 167, 222, 255
1st Reference Preparation 1953	<i>Bull. Wld Hlth Org.</i> , 1955, <b>12</b> , 945; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1954, <b>86</b> , 7; WHO/BS 52, 130, 167, 222, 255

Substances	International Unit of present standard (mg)	Form in which dispensed
<b>Antigens (cont.)</b>		
Cholera vaccine (Inaba)	—	Ampoules containing 20 mg of dried vaccine ( $1.6 \times 10^{10}$ organisms per ampoule)
Cholera vaccine (Ogawa)	—	Ampoules containing 20 mg of dried vaccine ( $1.6 \times 10^{10}$ organisms per ampoule)
Cardiolipin	—	Bottles containing 10 ml of a solution of purified sodium cardiolipin in ethanol (8.57 mg of cardiolipin per ml)
Lecithin (beef heart)	—	Bottles containing 30 ml of a solution of purified beef heart lecithin in ethanol (30.3 mg of lecithin per ml)
Lecithin (egg)	—	Bottles containing 30 ml of a solution of purified egg lecithin in ethanol (33.7 mg of lecithin per ml)
<b>ANTIBODIES</b>		
Tetanus antitoxin	0.3094	Bottles containing 10 ml of a solution of dried hyperimmune horse serum in saline, containing 66% v/v of glycerol (5 I.U. per ml)
Diphtheria antitoxin	0.0628	Bottles containing 10 ml of a solution of dried hyperimmune horse serum in saline, containing 66% v/v of glycerol (10 I.U. per ml)
Diphtheria antitoxin for flocculation test	—	Bottles containing 10 ml of a dilution of hyperimmune horse serum in phosphate buffered saline, containing 0.01% w/v of thiomersal (500 I.U. per ml)

Years of establishment of standards (in brackets, unitage of previous standards)	References (WHO/BS refers to unpublished working documents of the Expert Committee on Biological Standardization)
<i>1st Reference Preparation</i> 1953	<i>Bull. Wld Hlth Org.</i> , 1950, <b>3</b> , 43; 1955, <b>12</b> , 945; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1954, <b>86</b> , 7; WHO/BS 23, 36, 41, 52, 69, 82, 87, 87 Add.1, 107, 130, 222, 255
<i>1st Reference Preparation</i> 1953	<i>Bull. Wld Hlth Org.</i> , 1950, <b>3</b> , 43; 1955, <b>12</b> , 945; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1954, <b>86</b> , 7; WHO/BS 23, 36, 41, 52, 69, 82, 87, 87 Add.1, 107, 130, 222, 255
1st Reference Preparation 1951 <i>2nd Reference Preparation</i> 1953	<i>Bull. Wld Hlth Org.</i> , 1951, <b>4</b> , 151; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1952, <b>56</b> , 8; <i>Cardiolipin antigens</i> , 1951 (WHO Monograph No. 6); WHO/BS 72, 117, 238, 278, 278 Add.1, 305
1st Reference Preparation 1951 <i>2nd Reference Preparation</i> 1953	<i>Bull. Wld Hlth Org.</i> , 1951, <b>4</b> , 151; 1955, <b>13</b> , 323; 1956, <b>14</b> , 567, 577; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1952, <b>56</b> , 8; <i>Cardiolipin antigens</i> , 1951 (WHO Monograph No. 6); WHO/BS 72, 238, 278, 278 Add.1, 305
1st Reference Preparation 1951 <i>2nd Reference Preparation</i> 1953	<i>Bull. Wld Hlth Org.</i> , 1951, <b>4</b> , 151; 1955, <b>13</b> , 323; 1956, <b>14</b> , 567, 577; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1952, <b>56</b> , 8; <i>Cardiolipin antigens</i> , 1951 (WHO Monograph No. 6); WHO/BS 72, 238, 278, 278 Add.1, 305
<i>1st Standard</i> 1928	<i>Bull. Wld Hlth Org.</i> , 1949, <b>2</b> , 59; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1950, <b>2</b> , 5; <i>Bull. Hlth Org. L. o. N.</i> , 1935, <b>4</b> , 506; 1936, <b>5</b> , 702; 1938, <b>7</b> , 684, 713, 733, 739, 770, 776, 783; 1940/41, <b>9</b> , 447, 452; 1942/43, <b>10</b> , 104, 113; 1945/46, <b>12</b> , 14; <i>Pharmacopoea Internationalis</i> , 1951, Vol. I, 210, 338; WHO/BS 37, 44
<i>1st Standard</i> 1922	<i>Bull. Hlth Org. L. o. N.</i> , 1935, <b>4</b> , 505; 1938, <b>7</b> , 711, 853; 1945/46, <b>12</b> , 12; <i>Pharmacopoea Internationalis</i> , 1951, Vol. I, 208, 324; WHO/BS 68, 77
1st Standard 1935 2nd Standard 1938 3rd Standard 1945 <i>4th Standard</i> 1956	<i>Bull. Wld Hlth Org.</i> , 1947/48, <b>1</b> , 9; <i>Bull. Hlth Org. L. o. N.</i> , 1936, <b>5</b> , 577, 695; 1938, <b>7</b> , 712, 859; 1945/46, <b>12</b> , 12; WHO/BS 318

Substances	International Unit of present standard (mg)	Form in which dispensed
<b>Antibodies (cont.)</b>		
Antidysentery serum (Shiga)	0.05	Bottles containing 10 ml of a solution of dried hyperimmune horse serum in saline, containing 66% v/v of glycerol (200 I.U. per ml)
Gas-gangrene antitoxin (perfringens) ( <i>Clostridium welchii</i> type A antitoxin)	0.1132	Bottles containing 10 ml of a solution of dried hyperimmune horse serum in saline, containing 66% v/v of glycerol (20 I.U. per ml)
<i>Clostridium welchii</i> (perfringens) type B antitoxin	0.0137	Ampoules containing 68.5 mg of dried hyperimmune horse serum (5000 I.U. per ampoule)
<i>Clostridium welchii</i> (perfringens) type D antitoxin	0.0657	Ampoules containing 65.7 mg of dried hyperimmune horse serum (1000 I.U. per ampoule)
Gas-gangrene antitoxin ( <i>vibrio septique</i> )	0.0974	Bottles containing 10 ml of a solution of dried hyperimmune horse serum in saline, containing 66% v/v of glycerol (50 I.U. per ml)
Gas-gangrene antitoxin (oedematiens)	0.1135	Bottles containing 10 ml of a solution of dried hyperimmune horse serum in saline, containing 66% v/v of glycerol (20 I.U. per ml)
Gas-gangrene antitoxin (histolyticus)	0.2	Bottles containing 10 ml of a solution of dried hyperimmune horse serum in saline, containing 66% v/v of glycerol (20 I.U. per ml)
Gas-gangrene antitoxin (Sordelli)	0.1334	Bottles containing 10 ml of a solution of dried hyperimmune horse serum in saline, containing 66% v/v of glycerol (20 I.U. per ml)
Staphylococcus $\alpha$ antitoxin	0.2376	Bottles containing 10 ml of a solution of dried hyperimmune horse serum in phosphate buffered saline, containing 0.01% w/v of thiomersal (20 I.U. per ml)
Scarlet fever streptococcus antitoxin	0.049	Ampoules containing 490 mg of dried hyperimmune horse serum (10 000 I.U. per ampoule)

Years of establishment of standards (in brackets, unitage of previous standards)	References (WHO/BS refers to unpublished working documents of the Expert Committee on Biological Standardization)
<i>1st Standard</i> 1928	<i>Bull. Wld Hlth Org.</i> , 1951, <b>4</b> , 111; <i>Bull. Hlth Org. L. o. N.</i> , 1935, <b>4</b> , 508; 1945/46, <b>12</b> , 20
1st Standard 1931 (0.3220 mg) 2nd Standard 1935 (0.2660 mg) 3rd Standard 1943 (0.3477 mg) 4th Standard 1953	<i>Bull. Wld Hlth Org.</i> , 1947/48, <b>1</b> , 9; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1956, <b>108</b> , 7; <i>Bull. Hlth Org. L. o. N.</i> , 1935, <b>4</b> , 510; 1938, <b>7</b> , 695, 802, 818; 1939, <b>8</b> , 797; 1942/43, <b>10</b> , 97; 1945/46, <b>12</b> , 22; <i>Pharmacopoea Internationalis</i> , 1951, Vol. I, 209, 332; WHO/BS 281
<i>1st Reference Preparation</i> 1954	<i>Bull. Wld Hlth Org.</i> , 1956, <b>14</b> , 557; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1955, <b>96</b> , 6; WHO/BS 281, 283, 298, 303
<i>1st Reference Preparation</i> 1954	<i>Bull. Wld Hlth Org.</i> , 1956, <b>14</b> , 557; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1955, <b>96</b> , 6; WHO/BS 281, 283, 298, 303
1st Standard 1934 (0.2377 mg) 2nd Standard 1947	<i>Bull. Wld Hlth Org.</i> , 1947/48, <b>1</b> , 9; <i>Bull. Hlth Org. L. o. N.</i> , 1935, <b>4</b> , 1, 13, 511; 1938, <b>7</b> , 699, 815; 1942/43, <b>10</b> , 97; 1945/46, <b>12</b> , 26; <i>Pharmacopoea Internationalis</i> , 1951, Vol. I, 210, 334; WHO/BS 318
1st Standard 1934 (0.2681 mg) 2nd Standard 1952	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1953, <b>68</b> , 11; <i>Bull. Hlth Org. L. o. N.</i> , 1935, <b>4</b> , 3, 42, 511; 1942/43, <b>10</b> , 97; 1945/46, <b>12</b> , 26; <i>Pharmacopoea Internationalis</i> , 1951, Vol. I, 209, 328
1st Standard 1935 (0.3575 mg) 2nd Standard 1951	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1952, <b>56</b> , 17; <i>Bull. Hlth Org. L. o. N.</i> , 1936, <b>5</b> , 576, 659; 1945/46, <b>12</b> , 21; WHO/BS 91, 131
<i>1st Standard</i> 1938	<i>Bull. Hlth Org. L. o. N.</i> , 1938, <b>7</b> , 698, 807; 1939, <b>8</b> , 856; 1945/46, <b>12</b> , 21
1st Standard 1934 (0.5000 mg) 2nd Standard 1938	<i>Bull. Hlth Org. L. o. N.</i> , 1935, <b>4</b> , 6, 68, 514; 1938, <b>7</b> , 702, 845; 1945/46, <b>12</b> , 32
<i>1st Standard</i> 1952	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1953, <b>68</b> , 11; WHO/BS 38, 60, 84, 150, 225

Substances	International Unit of present standard (mg)	Form in which dispensed
<b>Antibodies (cont.)</b>		
Swine erysipelas serum (anti-N)	0.14	Ampoules containing 87.9 mg of dried hyperimmune horse serum (628 I.U. per ampoule)
Antipneumococcus serum (type 1)	0.0886	Bottles containing 10 ml of a solution of dried hyperimmune horse serum in saline, containing 66% v/v of glycerol (200 I.U. per ml)
Antipneumococcus serum (type 2)	0.0894	Bottles containing 10 ml of a solution of dried hyperimmune horse serum in saline, containing 66% v/v of glycerol (200 I.U. per ml)
Anti- <i>Brucella abortus</i> serum	0.091	Ampoules containing 91 mg of dried bovine serum (1000 I.U. per ampoule)
Anti-Q-fever serum	0.1017	Ampoules containing 101.7 mg of dried bovine serum (1000 I.U. per ampoule)
Antirabies serum	1.0	Ampoules containing 86.6 mg of dried hyperimmune horse serum (86.6 I.U. per ampoule)
Anti-A blood-typing serum	0.3465	Ampoules containing 88.7 mg of dried human serum (256 I.U. per ampoule)
Anti-B blood-typing serum	0.3520	Ampoules containing 90.1 mg of dried human serum (256 I.U. per ampoule)
Antityphoid serum (provisional)	—	Ampoules containing 5 ml of hyperimmune horse serum, dried
Cholera agglutinating serum (Inaba)	—	Ampoules containing 0.6 ml of monospecific serum
Cholera agglutinating serum (Ogawa)	—	Ampoules containing 0.6 ml of monospecific serum
<b>MISCELLANEOUS</b>		
Opacity reference preparation	—	Ampoules containing 20 ml of a suspension of pyrex-glass particles in water (10 I.U. of opacity per ml)

Years of establishment of standards (in brackets, unitage of previous standards)	References (WHO/BS refers to unpublished working documents of the Expert Committee on Biological Standardization)
<i>Ist Standard</i> 1954	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1955, 96, 10; WHO/BS 246, 297, 300
<i>Ist Standard</i> 1934	<i>Bull. Hlth Org. L. o. N.</i> , 1935, 4, 4, 48, 512
<i>Ist Standard</i> 1934	<i>Bull. Hlth Org. L. o. N.</i> , 1935, 4, 5, 65, 512
<i>Ist Standard</i> 1952	<i>Bull. Wld Hlth Org.</i> , 1950, 3, 309; 1953, 9, 385, 399; 1954, 10, 927; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1953, 68, 9; WHO/BS 128, 162, 223, 224, 228
<i>Ist Standard</i> 1953	<i>Bull. Wld Hlth Org.</i> , 1955, 13, 807; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1954, 86, 10; WHO/BS 177, 230, 276, 276 Add.1, 296
<i>Ist Standard</i> 1955	<i>Bull. Wld Hlth Org.</i> , 1954, 10, 781; 1955, 13, 747, 773; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1956, 108, 11; <i>Laboratory techniques in rabies</i> , 1954 (WHO Monograph No. 23); WHO/BS 231, 277, 277 Add.1, 294, 295, 329, 329 Add.1, 335
<i>Ist Standard</i> 1950	<i>Bull. Wld Hlth Org.</i> , 1950, 3, 301; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1951, 36, 10; WHO/BS 42, 49, 74
<i>Ist Standard</i> 1950	<i>Bull. Wld Hlth Org.</i> , 1950, 3, 301; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1951, 36, 10; WHO/BS 42, 49, 74
<i>Ist Standard</i> 1952	<i>Bull. Wld Hlth Org.</i> , 1954, 10, 911; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1953, 68, 10; WHO/BS 181, 226
<i>Ist Reference Preparation</i> 1953	<i>Bull. Wld Hlth Org.</i> , 1955, 12, 945; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1954, 86, 7; WHO/BS 40, 98, 130, 167, 222, 255
<i>Ist Reference Preparation</i> 1953	<i>Bull. Wld Hlth Org.</i> , 1955, 12, 945; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1954, 86, 7; WHO/BS 40, 98, 130, 167, 222, 255
<i>Ist Reference Preparation</i> 1953	<i>Bull. Wld Hlth Org.</i> , 1955, 12, 769; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1954, 86, 14; WHO/BS 54, 62, 124, 172, 198, 256

## B. PHARMACOLOGICAL

*Held by the International Laboratory for Biological Standards,*

Substances	International Unit of present standard (mg)	Form in which dispensed
<b>ANTIBIOTICS</b>		
Penicillin	0.0005988	Ampoules containing 30 mg of sodium benzylpenicillin (1670 I.U. per mg)
Penicillin K	—	Ampoules containing 20 mg of 89.9% pure sodium <i>n</i> -heptylpenicillin, with 9.6% penicillin dihydro F and 0.5% penicillin F
Streptomycin	0.001282	Ampoules containing 25 mg of streptomycin sulfate (780 I.U. per mg)
Dihydrostreptomycin	0.001316	Ampoules containing 70 mg of dihydrostreptomycin sulfate (760 I.U. per mg)
Bacitracin	0.0182	Ampoules containing 50 mg of bacitracin (55 I.U. per mg)
Chlortetracycline	0.001	Ampoules containing 60 mg of chlortetracycline hydrochloride (1000 I.U. per mg)
Oxytetracycline	0.00111	Ampoules containing 100 mg of oxytetracycline base dihydrate (900 I.U. per mg)
Polymyxin B	0.000127	Ampoules containing 19 mg of purified polymyxin B sulfate (7874 I.U. per mg)
<b>HORMONES</b>		
Oxytocic, vasopressor and anti-diuretic substances (previously named : posterior pituitary lobe)	0.5	Ampoules containing 30 mg of acetone dried powder of whole posterior ox pituitary gland (2 oxytocic, 2 vasopressor, and 2 antidiuretic I.U. per mg)

## SUBSTANCES

*National Institute for Medical Research, London*

Years of establishment of standards (in brackets, unitage of previous standards)	References (WHO/BS refers to unpublished working documents of the Expert Committee on Biological Standardization)
1st Standard 1944 (0.0006000 mg) 2nd Standard 1952	<i>Bull. Wld Hlth Org.</i> , 1953, 9, 15; <i>Bull. Hlth Org. L. o. N.</i> , 1945/46, 12, 181; <i>Pharmacopoea Internationalis</i> , 1955, Vol. II, 23, 277; WHO/BS 10, 15, 67, 94, 121, 170
1st Reference Preparation 1951	<i>Bull. Wld Hlth Org.</i> , 1954, 10, 895; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1952, 56, 11; WHO/BS 132
1st Standard 1950	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1951, 36, 9; <i>Pharmacopoea Internationalis</i> , 1955, Vol. II, 198, 279; WHO/BS 11, 67, 76
1st Standard 1953	<i>Bull. Wld Hlth Org.</i> , 1954, 10, 901; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1954, 86, 15; <i>Pharmacopoea Internationalis</i> , 1955, Vol. II, 89, 277; WHO/BS 122, 146, 241, 242
1st Standard 1953	<i>Bull. Wld Hlth Org.</i> , 1953, 9, 861; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1954, 86, 15; WHO/BS 122, 144, 236
1st Standard 1953	<i>Bull. Wld Hlth Org.</i> , 1953, 9, 851; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1954, 86, 14; <i>Pharmacopoea Internationalis</i> , 1955, Vol. II, 37, 276; WHO/BS 122, 143, 245
1st Standard 1955	<i>Bull. Wld Hlth Org.</i> , 1955, 13, 903; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1956, 108, 14; <i>Pharmacopoea Internationalis</i> , 1955, Vol. II, 179; WHO/BS 122, 145, 211, 285, 307
1st Standard 1955	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1956, 108, 14; WHO/BS 263, 326
1st Standard 1925 (0.5 mg) 2nd Standard 1942	<i>Bull. Wld Hlth Org.</i> , 1947/48, 1, 9; <i>Bull. Hlth Org. L. o. N.</i> , 1935, 4, 530; 1936, 5, 572; 1942/43, 10, 89; 1945/46, 12, 42; <i>Pharmacopoea Internationalis</i> , 1951, Vol. I, 191, 342

Substances	International Unit of present standard (mg)	Form in which dispensed
<b>Hormones (cont.)</b>		
Prolactin	0.1	Ampoules containing ten 10-mg tablets of dried active principle from anterior ox pituitary gland (approximately 100 I.U. per tablet)
Corticotrophin (previously named: adrenocorticotrophic hormone)	0.88	Ampoules containing 28 mg of crude corticotrophin from anterior pig pituitary gland (1.14 I.U. per mg)
Thyrotrophin	13.5	Ampoules containing ten 20-mg tablets of a blend of 1 part purified thyrotrophin from anterior ox pituitary gland and 19 parts lactose (approximately 1.48 I.U. per tablet)
Growth hormone	1.0	Ampoules containing 30 mg of dried active principle from anterior pituitary gland (1 I.U. per mg)
Serum gonadotrophin	0.25	Ampoules containing ten 25-mg tablets of dried active principle from serum of pregnant mares, diluted with lactose (approximately 100 I.U. per tablet)
Chorionic gonadotrophin	0.1	Ampoules containing twenty-five 10-mg tablets of dried active principle from human urine of pregnancy, diluted with lactose (approximately 100 I.U. per tablet)
Insulin	0.04082	Ampoules containing 20 mg of purified insulin, largely from the ox (24.5 I.U. per mg)
Heparin	0.0077	Ampoules containing 50 mg of sodium salt of purified active principle from bovine tissue (130 I.U. per mg)
<b>VITAMINS, ENZYMES</b>		
Vitamin D <sub>3</sub>	0.000025	Bottles containing 10 g of a solution of vitamin D <sub>3</sub> in vegetable oil (1000 I.U. per g)

Years of establishment of standards (in brackets, unitage of previous standards)	References (WHO/BS refers to unpublished working documents of the Expert Committee on Biological Standardization)
<i>1st Standard</i> 1939	<i>Bull. Hlth Org. L. o. N.</i> , 1939, <b>8</b> , 901; 1942/43, <b>10</b> , 96; 1945/46, <b>12</b> , 62; WHO/BS 208, 310
1st Standard 1950 (1.00 mg) <i>2nd Standard</i> 1955	<i>Bull. Wld Hlth Org.</i> , 1956, <b>14</b> , 543; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1951, <b>36</b> , 7; WHO/BS 85, 156, 158, 249, 262, 308
<i>1st Standard</i> 1954	<i>Bull. Wld Hlth Org.</i> , 1955, <b>13</b> , 917; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1955, <b>96</b> , 14; WHO/BS 155, 158, 210, 284, 309
<i>1st Standard</i> 1955	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1956, <b>108</b> , 16; WHO/BS 140, 158, 250, 320
<i>1st Standard</i> 1939	<i>Bull. Hlth Org. L. o. N.</i> , 1939, <b>8</b> , 887, 898; 1945/46, <b>12</b> , 60; <i>Pharmacopoea Internationalis</i> , 1955, Vol. II, 98, 263
<i>1st Standard</i> 1939	<i>Bull. Hlth Org. L. o. N.</i> , 1939, <b>8</b> , 862, 884; 1945/46, <b>12</b> , 60; <i>Pharmacopoea Internationalis</i> , 1955, Vol. II, 98, 261; WHO/BS 93, 141
1st Standard 1925 (0.12500 mg) <i>2nd Standard</i> 1935 (0.04550 mg) <i>3rd Standard</i> 1952	<i>Bull. Wld Hlth Org.</i> , 1952, <b>7</b> , 445; <i>Bull. Hlth Org. L. o. N.</i> , 1935, <b>4</b> , 525; 1936, <b>5</b> , 575, 584; 1945/46, <b>12</b> , 44; <i>Pharmacopoea Internationalis</i> , 1955, Vol. II, 130, 264; WHO/BS 89, 116, 119, 137, 138, 204, 205, 267, 311
<i>1st Standard</i> 1942	<i>Bull. Wld Hlth Org.</i> , 1947/48, <b>1</b> , 9; <i>Bull. Hlth Org. L. o. N.</i> , 1942/43, <b>10</b> , 144, 151; 1495/46, <b>12</b> , 46; <i>Pharmacopoea Internationalis</i> , 1951, Vol. I, 104, 341; 1955, Vol. II, 126
1st Standard 1931 (0.1 mg) [Irradiated ergosterol] <i>2nd Standard</i> 1949	<i>Bull. Wld Hlth Org.</i> , 1954, <b>10</b> , 875; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1950, <b>3</b> , 7; <i>Bull. Hlth Org. L. o. N.</i> , 1940/41, <b>9</b> , 425; 1945/46, <b>12</b> , 54; <i>Pharmacopoea Internationalis</i> , 1951, Vol. I, 369; WHO/BS 8

Substances	International Unit of present standard (mg)	Form in which dispensed
<b>Vitamins, enzymes (cont.)</b>		
Hyaluronidase	0.1	Ampoules containing ten 20-mg tablets of dried bovine testicular hyaluronidase diluted with lactose (approximately 200 I.U. per tablet)
<b>MISCELLANEOUS</b>		
Digitalis	76.0	Ampoules containing 2500 mg of dry powdered leaves of <i>Digitalis purpurea</i> (0.01316 I.U. per mg)
Neoarsphenamine	—	Ampoules containing 300 mg of neoarsphenamine
Sulfarsphenamine	—	Ampoules containing 300 mg of sulfarsphenamine
Oxophenarsine	—	Sets of three ampoules containing (a) 120 mg of oxophenarsine hydrochloride, (b) 100 mg of anhydrous sodium carbonate, and (c) 500 mg of anhydrous sucrose
Mel B	—	Ampoules containing 100 mg of melaminyl-4-phenylarseno-dithioglycerol
MSb	—	Ampoules containing 500 mg of sodium <i>p</i> -melaminylphenylstibonate polymer
Dimercaprol	—	Ampoules containing 2 ml of 2,3-dimercaptopropanol
Protamine	—	Ampoules containing 60 mg of protamine

Years of establishment of standards (in brackets, unitage of previous standards)	References (WHO/BS refers to unpublished working documents of the Expert Committee on Biological Standardization)
<i>1st Standard</i> 1955	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1956, <b>108</b> , 18; WHO/BS 78, 135, 163, 232, 271, 306
1st Standard 1926 (100.0 mg) 2nd Standard 1936 (80.0 mg) <i>3rd Standard</i> 1949	<i>Bull. Wld Hlth Org.</i> , 1950, <b>2</b> , 655; <i>Bull. Hlth Org. L. o. N.</i> , 1935, <b>4</b> , 522; 1936, <b>5</b> , 574; 1945/46, <b>12</b> , 41; <i>Pharmacopoea Internationalis</i> , 1951, Vol. I, 93, 357; WHO/BS 33, 51
1st Standard 1925 2nd Standard 1935 <i>3rd Standard</i> 1940	<i>Bull. Wld Hlth Org.</i> , 1947/48, <b>1</b> , 9; <i>Bull. Hlth Org. L. o. N.</i> , 1935, <b>4</b> , 528; 1936, <b>5</b> , 573; 1945/46, <b>12</b> , 40; <i>Pharmacopoea Internationalis</i> , 1951, Vol. I, 147, 347; WHO/BS 26
1st Standard 1925 2nd Standard 1936 <i>3rd Standard</i> 1951	<i>Bull. Wld Hlth Org.</i> , 1951, <b>4</b> , 563; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1952, <b>56</b> , 17; <i>Bull. Hlth Org. L. o. N.</i> , 1935, <b>4</b> , 528; 1936, <b>5</b> , 573; 1945/46, <b>12</b> , 40; <i>Pharmacopoea Internationalis</i> , 1951, Vol. I, 234, 351; WHO/BS 110
<i>1st Standard</i> 1951	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1952, <b>56</b> , 7; <i>Pharmacopoea Internationalis</i> , 1955, Vol. II, 176; WHO/BS 133, 174
<i>1st Reference Preparation</i> 1954	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1955, <b>96</b> , 16; WHO/BS 134, 148, 202, 273
<i>1st Reference Preparation</i> 1954	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1955, <b>96</b> , 16; WHO/BS 134, 148, 202, 273
<i>1st Standard</i> 1952	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1953, <b>68</b> , 18; <i>Pharmacopoea Internationalis</i> , 1955, Vol. II, 91, 122, 280; WHO/BS 159
<i>1st Reference Preparation</i> 1954	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1955, <b>96</b> , 14; WHO/BS 261

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