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BIOLOGICAL STANDARDIZATION**

**Fourteenth Report**

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## EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION

Geneva, 26 September - 1 October 1960

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## **EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION**

### **Fourteenth Report**

The Expert Committee on Biological Standardization met in Geneva from 26 September to 1 October 1960.

Dr N. I. Grashchenkov, Assistant Director-General, on behalf of the Director-General, welcomed the members of the Committee and the representative of the Food and Agriculture Organization of the United Nations.

Reviewing the standardization work accomplished by the thirteen Expert Committees on Biological Standardization that have met under the auspices of the World Health Organization, and surveying the extensive agenda of the present Committee, the Assistant Director-General asked the members to aim both at continuity in the performance of this work and at results that will be as useful as possible to those who look to WHO for assistance and who are working in their national spheres under a great variety of conditions.

### **GENERAL**

The Committee discussed the scope and the usefulness of the work that is being conducted under its responsibility; it was generally agreed that the provision of International Standards and International Reference Preparations of biological substances, as well as the formulation of International Requirements for the manufacture and control of biological products were tasks that are of importance for orderly progress in human and veterinary medicine.

The Committee considered its procedures for the establishment, custody and distribution of the International Standards and International Reference Preparations. It was of the opinion that the elaborate and careful way in which numerous laboratories throughout the world contributed to the work of establishing International Standards and Reference Preparations, both by generous gifts of material and by the participation, without charge, in extensive collaborative studies, ensured a satisfactory basis for international biological standardization.

The International Laboratories for Biological Standards in the Statens Seruminstitut, Copenhagen, and in the National Institute for Medical

Research, London, have been the custodians of the standards for more than thirty-five years. In view of the expansion of its work, particularly in respect of substances of veterinary importance, the Committee requested the Secretariat to consult with the Food and Agriculture Organization concerning the possibility of nominating a third International Laboratory for Biological Standards with responsibility for the custody and distribution of those International Standards and International Reference Preparations that are primarily of veterinary importance.

As for the distribution of the International Standards and International Reference Preparations by the custodians, the Committee reiterated its opinion, stated in the seventh report,<sup>1</sup> that national governments should designate National Laboratories for Biological Standards qualified to deal with biological standardization in their own countries. These National Laboratories are entitled to receive supplies of the international standards and international reference preparations on request from the custodians in order to make these available to manufacturers and research workers in their countries. They should, nevertheless, be encouraged to prepare national standards when the demands for standard materials are large. The Committee recognized, however, that in some countries such National Laboratories cannot, at the present time, be designated or function adequately, and considered that the International Laboratories for Biological Standards should attempt to satisfy directly requests from individual laboratories in these countries.

The Committee was informed of the technical discussions that took place in connexion with the Thirteenth World Health Assembly,<sup>2</sup> and noted that these discussions, though they had acknowledged the usefulness of international biological standardization and of the formulation of international requirements in the control of vaccines and other biological products, had clearly indicated the difficulties which the responsible authorities in many countries experience in trying to establish appropriate laboratory control procedures. The Committee also noted the suggestion, made in the report on these discussions, that it would be of great value if the World Health Organization could assist in making facilities available for the control testing of vaccines on an international basis.

The Committee was of the opinion that each country should proceed with the establishment of a National Laboratory for Biological Standards which could control the biological preparations of medical importance made and offered to the public in its country, and it stressed that this is an important part of any national public health programme. The Committee realized, however, that many countries needed international assistance while such a system was being developed and it therefore asked the Secre-

<sup>1</sup> *Wld Hlth Org. techn. Ser.*, 1954, 86, Annex I

<sup>2</sup> Unpublished working document A13/Technical Discussions/5

tariat to consult with laboratories qualified in the control testing of various biological preparations and to compile a list of those that are willing to assist.

## PHARMACOLOGICAL

### ANTIBIOTICS

#### 1. Leucomycin

The Committee noted that the National Institute for Medical Research, London, had reassessed the need for an international reference preparation of leucomycin.<sup>1</sup> In view of the fact that leucomycin is not, at the present time, in widespread clinical use the Committee decided not to establish an international reference preparation of leucomycin, and asked the National Institute for Medical Research to distribute the material held to interested workers on request.

#### 2. Neomycin B

The Committee noted that the National Institute for Medical Research, London,<sup>2</sup> in collaboration with other laboratories, was continuing the examination of samples of neomycin but had not yet been able to obtain a preparation of neomycin B sufficiently pure to serve as an international standard and to replace the existing International Reference Preparation of Neomycin.

#### 3. Novobiocin

The Committee noted that the collaborative assay of the International Reference Preparation of Novobiocin had been completed,<sup>3</sup> and that the international standard of novobiocin would be established and the international unit defined by the National Institute for Medical Research, London, with the agreement of the participants in the collaborative assay.

#### 4. Nystatin

The Committee noted that the collaborative assay of the International Reference Preparation of Nystatin was in progress,<sup>4</sup> and authorized the

<sup>1</sup> Unpublished working document WHO/BS/520

<sup>2</sup> Unpublished working document WHO/BS/522

<sup>3</sup> Unpublished working document WHO/BS/521

<sup>4</sup> Unpublished working document WHO/BS/524

National Institute for Medical Research, London, to establish the international standard for nystatin and to define the international unit with the agreement of the participants in the collaborative assay.

### 5. Oleandomycin

The Committee noted that the collaborative assay of the International Reference Preparation of Oleandomycin had been completed,<sup>1</sup> and that the international standard for oleandomycin would be established and the international unit defined by the National Institute for Medical Research, London, with the agreement of the participants in the collaborative assay.

### 6. Penicillin : Unit Notation

The Committee reiterated its decision not to change the definition of the International Unit of Penicillin, which is the activity of 0.0005988 mg of the International Standard for Penicillin. In view of the fact that, for the purpose of clinical dosage, some workers desire to change the expression of potency of penicillin preparations from International Units to terms of weight, the Committee stated that, for all practical clinical purposes, the International Unit of Penicillin may be regarded as equivalent to 0.0006 mg of pure sodium benzylpenicillin or to 0.00056 mg of pure benzylpenicillin acid.<sup>2</sup>

### 7. Ristocetin

The Committee noted that the National Institute for Medical Research, London, had now obtained a quantity of ristocetin suitable for serving as an international reference preparation.<sup>3</sup> The Committee established this material as the International Reference Preparation of Ristocetin, and asked the National Institute for Medical Research to assess the need for establishing an international standard for ristocetin and, if the need is evident, to arrange collaborative assays.

### 8. Other Antibiotics

The Committee considered a number of antibiotics that had been brought to its notice by the Expert Committee on Antibiotics and by other workers in the antibiotics field.<sup>4</sup>

<sup>1</sup> Unpublished working document WHO/BS/521

<sup>2</sup> Unpublished working document WHO/BS/529

<sup>3</sup> Unpublished working document WHO/BS/518

<sup>4</sup> Unpublished working document WHO/BS/530

The Committee was of the opinion that there is a need for international reference preparations of griseofulvin, spiramycin and gramicidin S, and asked the National Institute for Medical Research, London, to obtain a quantity of each of these antibiotics. The Committee also asked the National Institute for Medical Research to assess the need for international reference preparations of other gramicidins, colistin, dimethylchlortetracycline, alpha-phenoxymethyl penicillin and sodium 6-(2,6-dimethoxybenzamide) penicillinate monohydrate.

## HORMONES, VITAMINS AND ENZYMES

### 9. Corticotrophin

The Committee noted that the collaborative assay of the proposed third international standard for corticotrophin had now been completed,<sup>1</sup> and that the National Institute for Medical Research, London, will establish this material as the third international standard for corticotrophin and define the international unit in accordance with the authorization given in the twelfth report.<sup>2</sup>

### 10. Chorionic Gonadotrophin

The Committee noted that the stock of the International Standard for Chorionic Gonadotrophin (established in 1939) was almost exhausted,<sup>3</sup> and asked the National Institute for Medical Research, London, to take steps, in consultation with experts in this field, to obtain material suitable for replacing this standard.

### 11. Serum Gonadotrophin

The Committee noted that the stock of the International Standard for Serum Gonadotrophin (established in 1939) was almost exhausted,<sup>3</sup> and asked the National Institute for Medical Research, London, to take steps, in consultation with experts in this field, to obtain material suitable for replacing this standard.

### 12. Human Menopausal Gonadotrophin

The Committee noted<sup>4, 5</sup> that the National Institute for Medical Research, London, had received a quantity of a preparation of human

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<sup>1</sup> Unpublished working document WHO/BS/526

<sup>2</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1959, 172

<sup>3</sup> Unpublished working document WHO/BS/519

<sup>4</sup> Unpublished working document WHO/BS/532

<sup>5</sup> Unpublished working document WHO/BS/533

menopausal gonadotrophin that was purer than the existing International Reference Preparation. The Committee also noted that the National Institute for Medical Research had distributed samples of this material to interested workers in order to obtain agreement concerning its suitability for serving as an international standard.

### 13. Prolactin

The Committee noted that the additional assays of the proposed second international standard for prolactin had now been completed and that the results permitted a satisfactory definition of the international unit.<sup>1</sup> The Committee also noted that, in accordance with the authorization given in the tenth report,<sup>2</sup> the second international standard for prolactin would be established and the international unit defined by the National Institute for Medical Research, London, with the agreement of the participants in the collaborative assay.

### 14. Provitamin A: Unit Notation

The Committee considered the following recommendation by the Vitamin Assay Subdivision of the International Union of Pure and Applied Chemistry: "In view of the inadequacy of the evidence for establishing the equivalence of beta-carotene and Vitamin A in human nutrition, it is recommended that the results of analysis for this provitamin be expressed in weight units of beta-carotene or in International Units of Provitamin A, and that the problem of expressing the potency of beta-carotene in various foods in terms of International Units of Vitamin A be referred to the World Health Organization for further review."<sup>3, 4</sup>

The Committee was of the opinion that the problem of expressing the potency of beta-carotene in terms of International Units of Vitamin A did not concern the Expert Committee on Biological Standardization.

The Committee noted that the continued use of International Units of Provitamin A was included in the above recommendation, although there is no longer an international standard for provitamin A in terms of which the International Unit can be defined. The Committee therefore stated that the International Unit of Provitamin A is, for all practical purposes, equivalent to the activity of 0.0006 mg of pure all-*trans* beta-carotene.

<sup>1</sup> Unpublished working document WHO/BS/523

<sup>2</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1957, 127

<sup>3</sup> Unpublished working document WHO/BS/535

<sup>4</sup> International Union of Pure and Applied Chemistry, Applied Chemistry Section, Food Division, Vitamin Assay Subdivision (1959) *The vitamin A potency of beta-carotene*, London, Butterworth's

### 15. Streptokinase - Streptodornase

The Committee noted that the National Institute for Medical Research, London, had obtained a number of preparations of streptokinase-streptodornase, and that an examination of these materials was in progress, with a view to selecting the one most suitable for serving as an international standard.

### 16. Other Enzymes

The Committee noted that, following its request in the thirteenth report,<sup>1</sup> the National Institute for Medical Research, London, had consulted the International Commission on Enzymes of the International Union of Biochemistry concerning enzyme unitage. The Committee was informed that the following definition of the unit of enzyme activity had been formulated by the Commission and would be submitted for approval to the International Union of Biochemistry in 1961 :<sup>2</sup>

“ One *unit* (U) of any enzyme is defined as that amount which will catalyse the transformation of one micro-mole of substrate per minute or, where more than one bond of each substrate molecule is attacked, one micro-equivalent of the group concerned per minute, under defined conditions. The temperature should be stated, and it is suggested that where practicable it should be 25°C. The other conditions, including pH and substrate concentration, should where practicable be optimal. Where inconvenient numbers would otherwise be involved, terms such as milli-unit (mU), kilo-unit (kU), etc., may be used.”

Units thus defined are not based on material standards, and the Committee was of the opinion that, as far as any enzyme of medical importance is concerned, the time had not come to depart from its practice of defining the *International Unit* (I.U.) in terms of the activity contained in a given weight of a definite, stable preparation designated as the *International Standard*.

## IMMUNOLOGICAL

### ANTIGENS

#### 17. Anthrax Vaccine

The Committee noted that the Wellcome Research Laboratories, Beckenham, U.K., had offered a quantity of a freeze-dried, live, spore

<sup>1</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1960, 187

<sup>2</sup> Unpublished working document WHO/BS/534

suspension of the 34F2 strain of *Bacillus anthracis* to serve as a proposed international standard for anthrax vaccine,<sup>1</sup> and asked the Central Veterinary Laboratory, Weybridge, in collaboration with the Wellcome Research Laboratories, to examine the suitability of this material.

### 18. BCG Vaccine

The Committee noted that further progress had been made in the WHO studies directed towards the elaboration of reliable methods of determining the protective value of BCG vaccines. The Committee was informed that similar studies were in progress under the auspices of the International Union against Tuberculosis. The Committee asked the Secretariat to consult with these two groups of workers with the object of assessing the combined results of their studies.

The Committee was of the opinion that the establishment of an international reference preparation of BCG vaccine could now be initiated and that such a preparation would serve a useful purpose in the evaluation of both intracutaneous and oral BCG<sup>2</sup> vaccines.

The Committee noted that the Institut Pasteur, Paris, had offered to prepare a large, homogeneous batch of stable freeze-dried BCG vaccine using the original bacillus of Calmette and Guérin, and to distribute this material into several thousand ampoules. The Committee accepted this offer and asked the Statens Seruminstitut, Copenhagen, in consultation with the Institut Pasteur, to arrange for a collaborative assay of this material, with a view to determining its suitability to serve as an international reference preparation.

The Committee requested the Secretariat to make arrangements, as early as possible, for the formulation of international requirements, for the manufacture and control of BCG vaccines.

### 19. *Clostridium Oedematiens* (Alpha) Toxoid

The Committee was informed that the Commonwealth Serum Laboratories, Melbourne, Australia, had offered a quantity of *Clostridium oedematiens* (alpha) toxoid to serve as a proposed international standard. The Committee asked the Central Veterinary Laboratory, Weybridge, in collaboration with the Commonwealth Serum Laboratories, to make preliminary studies of the suitability of this material and, if it should be found suitable, to arrange a collaborative assay.

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<sup>1</sup> Unpublished working document WHO/BS/527

<sup>2</sup> Unpublished working document WHO/BS/513

## 20. Influenza Virus Vaccine

The Committee reconsidered the statement in its eighth report<sup>1</sup> that there were insuperable technical difficulties in providing an international reference preparation of influenza virus vaccine, and asked the National Institute for Medical Research, London, to re-assess this problem in consultation with the World Influenza Centre and with others working in the influenza field.

## 21. Newcastle Disease Vaccines

The Committee noted that the Central Veterinary Laboratory, Weybridge, had investigated the usefulness of establishing an international standard for inactivated Newcastle disease vaccine.<sup>2</sup> Several experts had expressed the opinion that it is practicable to set up such a standard for use in the determination of the relative potencies of other preparations of inactivated Newcastle disease vaccine. The Committee also noted that the Paul-Ehrlich-Institut, Frankfurt, had offered a quantity of material suitable for serving as the proposed international standard. This material is a preparation of infected allantoid fluid containing a mixture of nine strains of formalin-inactivated Newcastle disease virus adsorbed on to aluminium hydroxide and freeze-dried. The unit that is in use in Germany has been defined as the activity contained in 1 mg of this material. The Committee accepted this offer and asked the Central Veterinary Laboratory, in consultation with the Paul-Ehrlich-Institut, to arrange collaborative assays.

The Committee also noted that the experts consulted had agreed that a standard preparation of inactivated vaccine could not be used for the accurate assay of a live vaccine. The Committee therefore asked the Central Veterinary Laboratory to try to obtain a preparation of dried, stable, live Newcastle disease vaccine and to arrange preliminary tests of its suitability to serve as an international standard in assays of other preparations of live Newcastle disease vaccine.

## 22. Poliomyelitis Vaccine (Inactivated)

The Committee noted that the collaborative assay of inactivated poliomyelitis vaccines was nearly completed,<sup>3</sup> and that the preliminary results indicated that an international standard vaccine would serve a useful purpose in reducing the variability of the results of potency determinations between

<sup>1</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1955, 96

<sup>2</sup> Unpublished working document WHO/BS/528 and Addendum 1

<sup>3</sup> Unpublished working document WHO/BS/537

laboratories. The full analysis of this collaborative assay will also furnish information helpful in the selection of the most reliable and practical assay methods. The Committee was of the opinion, however, that none of the materials included in the collaborative assay would be entirely satisfactory as an international reference preparation. The freeze-dried material had been shown to contain only very little antigenic activity of type 1 poliovirus; the liquid material had to be kept in the frozen state, which was a disadvantage in its distribution to users. The Committee asked the Statens Seruminstitut, Copenhagen, to make the materials used in the collaborative studies available to interested workers on request.

The Committee noted that the collaborative assays<sup>1</sup> have shown that it is possible to prepare a freeze-dried poliomyelitis vaccine that is antigenic. The Committee was informed that further work on the freeze-drying of inactivated poliomyelitis vaccine was in progress in the Institute for Poliomyelitis Prophylactics, Moscow, and that purified preparations of inactivated poliomyelitis vaccine were being prepared by Merck, Sharp and Dohme, West Point, Pennsylvania. The Committee requested the Secretariat to consult with these two laboratories with a view to arranging for the freeze-drying of a purified vaccine.

The Committee noted that arrangements had been made by the Secretariat to formulate international requirements for the manufacture and control of live, attenuated poliovirus vaccines.

### **23. Purified Protein Derivative (PPD) of Mammalian Tuberculin**

The Committee noted that the studies by the Statens Seruminstitut, Copenhagen,<sup>2</sup> aimed at the redefinition of the International Unit of PPD of Mammalian Tuberculin, had shown that assays of PPD preparations against the International Standard for PPD of Mammalian Tuberculin and against the International Standard for Old Tuberculin were affected not only by the variable loss of specific material through interface adsorption, but also by numerous other factors.

In view of the fact that the assays carried out originally for the purpose of defining the International Unit of PPD of Mammalian Tuberculin were done at a time when the adsorption effect was not known, the Committee was of the opinion that those assays were invalid. The Committee therefore decided that the existing definition of the International Unit of PPD of Mammalian Tuberculin shall no longer apply. Moreover, the data at present available did not provide a sufficient basis for a redefinition of an international unit of PPD, similar in activity to the International Unit of Old Tuberculin.

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<sup>1</sup> Unpublished working document WHO/BS/537

<sup>2</sup> Unpublished working document WHO/BS/525

The Committee also considered the question whether the potency of the International Standard of Old Tuberculin had remained stable during the twenty-five years that have now elapsed since this standard was established. The Committee asked the Statens Seruminstitut to examine this question, but retained the definition of the International Unit of Old Tuberculin as the activity contained in 0.01 mg of the International Standard for Old Tuberculin.

The Committee recommended that the expression of the potency of preparations of PPD of mammalian tuberculin should for the present be in terms of International Units of Old Tuberculin, on the basis of assays performed under defined conditions. The Committee recognized the urgency of establishing a more satisfactory basis for the potency notation of tuberculin preparations, and asked the Statens Seruminstitut, in consultation with the Institut Pasteur, Paris, the International Union against Tuberculosis, and WHO, to carry out further studies with the object of providing the necessary data.

The Committee also noted a report<sup>1</sup> on the influence of the adsorption effect on the evaluation of preparations of PPD of avian tuberculin, and asked the Central Veterinary Laboratory, Weybridge, in consultation with the Statens Seruminstitut, to examine whether similar steps should be taken in respect of the International Unit and the International Standard for PPD of Avian Tuberculin.

#### 24. Rabies Vaccine

The Committee noted the results of the collaborative studies of the proposed international reference preparation of rabies vaccine which had been arranged by the Expert Committee on Rabies.<sup>2, 3, 4, 5, 6</sup> Although these results have shown the suitability of this material in assay, no data are yet available showing the degree of reproducibility between laboratories of determinations of relative potency of unknown vaccines in terms of the proposed international reference preparation. The Committee therefore decided to establish this material as the International Reference Preparation of Rabies Vaccine, but asked the Secretariat to arrange further work in order to provide a sufficient basis for the establishment of an international standard and the definition of an international unit.

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<sup>1</sup> Unpublished working document WHO/BS/504 and Addendum 1

<sup>2</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1960, 201

<sup>3</sup> Unpublished working document WHO/Rabies/111

<sup>4</sup> Unpublished working document WHO/Rabies/123

<sup>5</sup> Unpublished working document WHO/Rabies/146

<sup>6</sup> Unpublished working document WHO/BS/507 and Correction 1

The Committee also noted that the long-term stability of dried rabies vaccine preparations was in doubt and asked the Secretariat to arrange accelerated degradation tests of the International Reference Preparation.

#### **25. Sheep Pox Vaccine**

The Committee was informed that the Razi Institute, Teheran, Iran, had offered a quantity of sheep pox vaccine to serve as a proposed international standard, and requested the Central Veterinary Laboratory, Weybridge, to ask workers in countries where sheep pox vaccine is widely used whether they would be willing to participate in a collaborative study.

#### **26. Smallpox Vaccine**

The Committee noted that the collaborative assay of the proposed international reference preparation of smallpox vaccine had now been completed,<sup>1</sup> and that the results obtained were being analysed.

The Committee also noted that a preliminary examination of the results had indicated that the proposed international reference preparation satisfies the international requirements for smallpox vaccine, and that accelerated degradation tests<sup>2</sup> had shown that the material was highly stable.

The Committee therefore authorized the Statens Seruminstitut, Copenhagen, after final evaluation of the results of the collaborative assay and with the agreement of the participants, to establish this material as the International Reference Preparation of Smallpox Vaccine.

#### **27. Swine Erysipelas Vaccine**

The Committee noted that the participants in the collaborative assay<sup>3</sup> had now agreed on the definition of the international unit. Accordingly, the Committee defined the International Unit of Swine Erysipelas Vaccine as the activity contained in 0.50 mg of the International Standard for Swine Erysipelas Vaccine; the International Unit has been shown to be equivalent to the unit<sup>4</sup> used in Germany.

#### **28. Tetanus Toxoid, Adsorbed**

The Committee noted that the Paul-Ehrlich-Institut, Frankfurt, had performed a number of assays in guinea pigs, and in mice, of a preliminary

<sup>1</sup> Unpublished working document WHO/BS/536

<sup>2</sup> Unpublished working document WHO/BS/500

<sup>3</sup> Unpublished working document WHO/BS/512 and Correction 1

<sup>4</sup> Unpublished working document WHO/BS/486 and Adendum 1

preparation of freeze-dried tetanus toxoid adsorbed on to aluminium hydroxide, and that the preparation appeared suitable for assaying the potency of other adsorbed preparations.<sup>1</sup>

The Committee also noted that further studies of this material were in progress in the Paul-Ehrlich-Institut and in the Rijks Instituut voor de Volksgezondheid, Utrecht. The Committee was informed that, if the results of these further studies were satisfactory and if the preparation proved sufficiently stable in accelerated degradation tests, the Paul-Ehrlich-Institut would prepare a larger, homogeneous batch of this preparation to serve as a proposed international standard for tetanus toxoid, adsorbed. The Committee noted that in the preparation of this batch, in order to obtain a dry product which is both stable and easy to reconstitute, an equal volume of normal rabbit serum would be added to the adsorbed toxoid before freeze-drying, and the Committee had no objection to this procedure.

The Committee asked the Rijks Instituut voor de Volksgezondheid, in collaboration with the Paul-Ehrlich-Institut, and in consultation with the Statens Seruminstitut, Copenhagen, to arrange a collaborative assay as soon as the proposed international standard has been prepared.

### 29. Typhoid Vaccine

The Committee noted that the Walter Reed Army Institute of Research, Washington, had now prepared large quantities of two preparations of typhoid vaccine, one a heat-killed, phenolized and freeze-dried vaccine, and the other an acetone-killed and dried vaccine,<sup>2</sup> part of which had been received in the Statens Seruminstitut, Copenhagen, together with a number of ampoules containing the seed strain from which these vaccines were made.

The Committee also noted that the Statens Seruminstitut was arranging collaborative laboratory studies of these vaccine preparations, and that a large number of laboratories would participate in this work, using a variety of assay methods.<sup>3</sup>

The Committee was informed that the same two vaccine preparations have already been used for human immunization in field trials that were initiated this year in British Guiana and Yugoslavia, and that one of these preparations will be included in a field trial of several preparations of typhoid vaccine that will take place in Poland. The Committee asked the Statens Seruminstitut to obtain quantities of all typhoid vaccine preparations that will be used in the field trials in Poland, so that these materials may be included in the collaborative laboratory studies.

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<sup>1</sup> Unpublished working document WHO/BS/510

<sup>2</sup> Unpublished working document WHO/BS/505

<sup>3</sup> Unpublished working document WHO/BS/515

The Committee was of the opinion that it would be useful, while this work is in progress, if workers in countries in which experience has accumulated of the efficacy of various typhoid vaccine preparations, including products consisting of antigenic fractions of typhoid bacilli, were to provide relevant information to WHO so as to permit an assessment of the present work in a wider context.

The Committee requested the Secretariat to make arrangements, as early as possible, for the formulation of international requirements for the manufacture and control of typhoid vaccines.

## ANTIBODIES

### 30. Anti-Echinococcus Human Serum

The Committee noted that the Department of Tropical Medicine of the American University, Beirut, Lebanon, had undertaken to collect and pool sera from human cases of surgically proven hydatidosis, and that the Statens Seruminstitut, Copenhagen, would be asked to freeze-dry this serum pool.<sup>1</sup> The Committee also noted that the Secretariat would then arrange for a collaborative assay of this material by a flocculation test, a complement fixation test, and a haemagglutination test, in comparison with samples of individual anti-echinococcus human sera, with a view to establishing an international standard and defining an international unit.

### 31. Anti-Leptospira Sera

The Committee noted that the Statens Seruminstitut, Copenhagen, now held stocks of all 19 International Reference Preparations of Anti-Leptospira sera that were established in 1958, but that the stock of one of these, the International Reference Preparation of Anti-*Leptospira semaranga* serum, was nearly exhausted and should be replaced.<sup>2</sup>

The Committee was informed that the collaborative study of the additional collection of 18 anti-leptospira sera, prepared by the WHO/FAO International Leptospira Reference Laboratories, was now nearly completed<sup>3</sup> and that the participants in the collaborative study would examine the results and would report to the Committee on the suitability of these sera to serve as international reference preparations.

<sup>1</sup> Unpublished working document WHO/BS/542

<sup>2</sup> Unpublished working document WHO/BS/508

<sup>3</sup> Unpublished working document WHO/BS/543

### 32. Anti-Measles Serum

The Committee noted that the Statens Seruminstitut, Copenhagen, had obtained the unanimous agreement of a number of experts that there is a need for an international standard for anti-measles serum.<sup>1</sup> The Committee therefore asked the Statens Seruminstitut to investigate whether a human serum or a monkey serum<sup>2</sup> should be selected for this purpose and to obtain suitable material for a collaborative assay.

### 33. Anti-Poliovirus Sera

The Committee noted that the Statens Seruminstitut, Copenhagen, had arranged a collaborative assay of the proposed international standards for anti-poliovirus sera of types 1, 2 and 3, with a view to replacing the International Reference Preparations.<sup>3</sup> The Committee authorized the Statens Seruminstitut to establish these materials as the International Standards for Anti-Poliovirus Sera of Types 1, 2 and 3 and to define the International Units with the agreement of the participants in the collaborative assay.

### 34. Anti-Streptolysin O

The Committee noted that the Statens Seruminstitut, Copenhagen, in accordance with the request made in the thirteenth report,<sup>4</sup> and with the agreement of the participants in the collaborative assay, had defined the International Unit of Anti-Streptolysin O as the activity contained in 0.0213 mg of the International Standard for Anti-Streptolysin O.<sup>5</sup> The Committee also noted that the International Unit is equivalent to the unit originally adopted by workers in the United Kingdom.

### 35. Anti-Swine Fever Serum

The Committee was informed that the Central Veterinary Laboratory, Weybridge, had prepared a quantity of anti-swine fever serum and would arrange a collaborative assay of this material in order to determine its suitability for serving as an international standard.

### 36. Anti-Tick-Borne-Encephalitis Serum

The Committee noted that the Statens Seruminstitut, Copenhagen, had obtained a quantity of freeze-dried anti-tick-borne-encephalitis sheep serum

<sup>1</sup> Unpublished working document WHO/BS/539

<sup>2</sup> Unpublished working document WHO/BS/544

<sup>3</sup> Unpublished working document WHO/BS/516

<sup>4</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1960, 187

<sup>5</sup> Unpublished working document WHO/BS/517, Correction 1

prepared in the Institute of Experimental Medicine, Leningrad ; that further offers of material had been made by institutes in Bratislava, Copenhagen, and Moscow ; and that studies were being undertaken with the object of selecting material suitable for serving as an international reference preparation for the identification of the group of tick-borne-encephalitis viruses.<sup>1</sup> The Committee was informed that a WHO Study Group on Arthropod-borne-viruses had met, and that the Secretariat was now considering the problems of providing international reference sera for the grouping and typing of arthropod-borne viruses.

### 37. Anti-Toxoplasma Serum

The Committee noted that the Toxoplasma Subcommittee of the International Association of Microbiological Societies had asked the Statens Seruminstitut, Copenhagen, to arrange an international assay of preparations of anti-toxoplasma human sera,<sup>2</sup> and that a collaborative study of one human serum was now in progress. The Committee also noted that further arrangements had been made, in consultation with the Secretariat, to obtain samples of other anti-toxoplasma human sera and of anti-toxoplasma sera from a number of different species of animals.

### 38. Anti-Trichinella Human Serum

The Committee noted that the Communicable Disease Centre, Chamblee, Georgia, USA, had undertaken to collect and pool sera from human cases of trichinosis, confirmed, when necessary, by muscle biopsy, and to freeze-dry this serum pool.<sup>3</sup>

The Committee also noted that the Secretariat would then arrange for a collaborative assay of this material in comparison with samples of individual antitrichinella human sera, with a view to establishing an international standard and defining an international unit.

### 39. Anti-Yellow-Fever Serum

The Committee noted that a collaborative assay is now in progress<sup>4</sup> of a preparation of anti-yellow-fever serum as proposed by the Expert Committee on Yellow Fever Vaccine<sup>5</sup> and by the Study Group on Require-

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<sup>1</sup> Unpublished working document WHO/BS/511

<sup>2</sup> Unpublished working document WHO/BS/538

<sup>3</sup> Unpublished working document WHO/BS/542

<sup>4</sup> Unpublished working document WHO/BS/506

<sup>5</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1957, 136

ments for Yellow Fever Vaccine.<sup>1</sup> This serum is intended to serve<sup>2</sup> as an international reference preparation of immune serum in the determination by a mouse protection test of the neutralizing power of other anti-yellow-fever sera in the control of yellow fever vaccines. The Committee also noted that stability tests of this material had been performed.

#### 40. Naja Antivenin

The Committee noted that, in accordance with the request in its thirteenth report,<sup>3</sup> the School of Tropical Medicine, Calcutta, had collected several samples of Naja antivenin and Naja venom from different parts of the world and had conducted a preliminary collaborative antivenin assay with these materials. The results of this study had shown that the use of a standard serum would considerably reduce the variability of potency determinations.<sup>4, 5</sup>

The Committee also noted a report<sup>6</sup> from the South African Institute for Medical Research, Johannesburg, on certain aspects of antivenin assays, and was informed that this institute had offered a quantity of Naja antivenin of high potency which might serve as a proposed international standard. The Committee accepted this offer and asked the South African Institute for Medical Research to distribute this serum into ampoules in the freeze-dried state and, in consultation with the participants in the preliminary studies, to arrange collaborative assays.

The Committee further noted an offer from the Queen Saovabha Memorial Institute, Bangkok,<sup>7</sup> of a purified, freeze-dried preparation of Naja venom, and was of the opinion that this preparation should be included in the collaborative assays as one of the test venoms from different Naja species.

#### 41. Syphilitic Human Serum

The Committee noted that a collaborative investigation had shown that the International Standard for Syphilitic Human Serum was suitable for use also in the *Treponema pallidum* immobilization test.<sup>8</sup>

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<sup>1</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1959, 179

<sup>2</sup> Unpublished working document WHO/BS/514

<sup>3</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1960, 187

<sup>4</sup> Unpublished working document WHO/BS/501

<sup>5</sup> Unpublished working document WHO/BS/502 and Addendum 1

<sup>6</sup> Unpublished working document WHO/BS/503

<sup>7</sup> Unpublished working document WHO/BS/541

<sup>8</sup> Unpublished working document WHO/BS/509

## MISCELLANEOUS

### 42. Opacity Reference Preparation

The Committee noted that the stock of the International Opacity Reference Preparation was almost exhausted.<sup>1</sup> The Committee therefore asked the Statens Seruminstitut, Copenhagen, to obtain material for replacement, and to arrange collaborative studies with the object of equating the opacity of this material with the opacity of the present International Opacity Reference Preparation and determining its suitability for estimating the opacity of bacterial suspensions.

### 43. Staphylococcal Products

The Committee noted that, following a request made in its thirteenth report,<sup>2</sup> the National Institute for Medical Research, London, had examined the question of providing reference material for staphylococcus leucocidins and anti-leucocidins.<sup>3</sup> The Committee decided not to take steps, at the present time, towards the establishment of international standards or international reference preparations for these staphylococcal products.

The Committee was informed that data concerning the prophylactic and therapeutic value of staphylococcus toxoids were available in the Institut Pasteur, Paris, and the Institute of Epidemiology and Microbiology, Moscow, and asked the National Institute for Medical Research to collect this information and to obtain opinions from others working in this field.

### 44. Further Substances for Veterinary Use

The Committee asked the Secretariat to consult with the Food and Agriculture Organization concerning the need for, and the practicability of, establishing international reference preparations or international standard preparations of foot-and-mouth disease vaccine, type-specific anti-foot-and-mouth-disease sera, african horse sickness vaccine, type-specific anti-african-horse-sickness sera, and rinderpest vaccine.

<sup>1</sup> Unpublished working document WHO/BS/531

<sup>2</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1960, 187

<sup>3</sup> Unpublished working document WHO/BS/540

**Annex**

**I. INTERNATIONAL BIOLOGICAL STANDARDS  
AND  
INTERNATIONAL BIOLOGICAL REFERENCE PREPARATIONS  
1961**

The primary purpose underlying the establishment of International Biological Standards and International Biological Reference Preparations is to provide a means of ensuring uniformity throughout the world in the designation of potency of preparations which are used in the prophylaxis, therapy, or diagnosis of human and animal disease, and which cannot be characterized adequately by chemical and physical means. A secondary purpose in the provision of International Biological Standards is the facilitation of research work out of which clinical application may arise. The substances listed to which an International Unit has been assigned are International Biological Standards. Those listed without designation of an International Unit are International Biological Reference Preparations.

The International Laboratories for Biological Standards at the Statens Seruminstitut, Copenhagen, Denmark, and at the National Institute for Medical Research, London, England, are custodians of all International Biological Standards and International Biological Reference Preparations, and distribute samples of these preparations, free of charge, to national laboratories for biological standards, as well as to other biological laboratories in countries where national laboratories for biological standards do not function. Such samples are intended for use in laboratory assays only and must not be administered to humans unless by special authorization.

## A. IMMUNOLOGICAL

*Held and distributed by the International Laboratory for Biological Standards,*

Substance	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	—	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, plain	0.03	Ampoules containing 420 Lf of alcohol-purified tetanus toxoid plus glycine (25 mg = 833 I.U. per ampoule)
Diphtheria toxoid, plain	0.50	Ampoules containing 1730 Lf of alcohol-purified diphtheria toxoid plus glycine (50 mg = 100 I.U. per ampoule)
Diphtheria toxoid, adsorbed	0.75	Ampoules containing 50 Lf of diphtheria toxoid adsorbed to aluminium hydroxide, plus an equal part of guinea-pig serum dried (80 mg = 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)
Pertussis vaccine	1.5	Ampoules containing 52 mg of dried vaccine (34.7 I.U. per ampoule)

## SUBSTANCES

*Statens Seruminstitut, Amager Boulevard, 80, Copenhagen, Denmark*

Years of establishment (in brackets, unitage of previous standards)	References (WHO/BS refers to unpublished working documents of the WHO Expert Committees 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; 1958, <b>19</b> , 759; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1952, <b>56</b> , 6; 1960, <b>187</b> , 13; 1961, <b>222</b> , 14; WHO/BS 3, 16, 28, 64, 106, 120, 127, 173, 181, 488
1st Standard 1954	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1955, <b>96</b> , 11; 1960, <b>187</b> , 13; 1961, <b>222</b> , 15; WHO/BS 126, 181, 227, 293, 293 Add. 1 and 2, 504, 504 Add. 1
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, 382
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 Standard 1957	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1957, <b>127</b> , 5; 1958, <b>147</b> , 11; WHO/BS 5, 54, 62, 81, 88, 96, 123, 203, 216, 251, 259, 282, 287, 302, 338, 401, 408

Substance	International Unit of present standard (mg)	Form in which dispensed
<b>Antigens (contd)</b>		
Cholera antigen (Inaba)	—	Ampoules containing approximately 100 mg of dried antigen
Cholera antigen (Ogawa)	—	Ampoules containing approximately 100 mg of dried antigen
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	—	Ampoules containing 4 ml, 8 ml or 16 ml of a solution of purified cardiolipin in ethanol (6.4 mg cardiolipin per ml, as calculated from the phosphorus content)
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)	—	Ampoules containing 4 ml, 8 ml or 16 ml of a solution of purified egg lecithin in ethanol (26.7 mg of lecithin per ml as calculated from the phosphorus content)
Rabies vaccine	—	Ampoules containing 38 mg of a freeze-dried suspension of rabbit-brain infected with fixed rabies virus and inactivated by ultra-violet irradiation
Swine erysipelas vaccine	0.50	Ampoules containing 499 mg of dried vaccine, derived from formalin-treated <i>Erysipelas rhusiopathiae</i> type B, adsorbed to aluminium hydroxide

Years of establishment (in brackets, unitage of previous standards)	References (WHO/BS refers to unpublished working documents of the WHO Expert Committees on Biological Standardization)
<i>1st Reference Preparation</i> 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
<i>1st Reference Preparation</i> 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
<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; 1959, <b>179</b> , 10, 33, 43; 1960, <b>187</b> , 12; WHO/BS 23, 36, 41, 52, 69, 82, 87, 87 Add. 1, 107, 130, 222, 255, 342, 410; WHO/BS/IR/58
<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; 1959, <b>179</b> , 10, 33, 43; 1960, <b>187</b> , 12; WHO/BS 23, 36, 41, 52, 69, 82, 87, 87 Add. 1, 107, 130, 222, 255, 342, 410; WHO/BS/IR/58
<i>1st Reference Preparation</i> 1951 <i>2nd Reference Preparation</i> 1953 <i>3rd Reference Preparation</i> 1958	<i>Bull. Wld Hlth Org.</i> , 1951, <b>4</b> , 151; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1952, <b>56</b> , 8; 1958, <b>147</b> , 14; <i>Cardiolipin antigens</i> , 1955 (WHO Monograph No. 6); WHO/BS 72, 117, 238, 278, 278 Add. 1, 305, 360, 414, 420
<i>1st Reference Preparation</i> 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> , 1955 (WHO Monograph No. 6); WHO/BS 72, 238, 278, 278 Add. 1, 305
<i>1st Reference Preparation</i> 1951 <i>2nd Reference Preparation</i> 1953 <i>3rd Reference Preparation</i> 1959	<i>Bull. Wld Hlth Org.</i> , 1951, <b>4</b> , 151; 1955, <b>13</b> , 323; 1956, <b>14</b> , 567, 577; 1961, <b>24</b> , 265; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1952, <b>56</b> , 8; 1959, <b>172</b> , 14; 1960, <b>187</b> , 13; <i>Cardiolipin antigens</i> , 1955 (WHO Monograph No. 6); WHO/BS 72, 238, 278, 278 Add. 1, 305, 360, 440, 456
<i>1st Reference Preparation</i> 1960	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1960, <b>201</b> ; 1961, <b>222</b> , 15; WHO/BS/372, 411, 411 Annex 1, 490, 507, 507 Corr. 1; WHO/Rabies/111, 123, 146
<i>1st Standard</i> 1959	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1960, <b>187</b> , 20; 1961, <b>222</b> , 16; WHO/BS 344, 377, 435, 436, 486, 486 Add. 1, 512, 512 Corr. 1

Substance	International Unit of present standard (mg)	Form in which dispensed
<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)
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>vibrion septique</i> )	0.118	Ampoule containing 59 mg of a dried 1 : 3 dilution of hyperimmune horse serum in phosphate-buffered saline (500 I.U. per ampoule)
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)

Years of establishment (in brackets, unitage of previous standards)	References (WHO/BS refers to unpublished working documents of the WHO Expert Committees on Biological Standardization)
<i>1st Standard 1928</i>	<i>Bull. Wld Hlth Org.</i> , 1949, 2, 59; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1950, 2, 5; <i>Bull. Hlth Org. L. o. N.</i> , 1935, 4, 506; 1936, 5, 702; 1938, 7, 684, 713, 733, 739, 770, 776, 783; 1940/41, 9, 447, 452; 1942/43, 10, 104, 113; 1945/46, 12, 14; <i>Pharmacopoea Internationalis</i> , 1951, Vol. I, 210, 338; WHO/BS 37, 44
<i>1st Standard 1922</i>	<i>Bull. Hlth Org. L. o. N.</i> , 1935, 4, 505; 1938, 7, 711, 853; 1945/46, 12, 12; <i>Pharmacopoea Internationalis</i> , 1951, Vol. I, 208, 324; WHO/BS 68, 77
<i>1st Standard 1928</i>	<i>Bull. Wld Hlth Org.</i> , 1951, 4, 111; <i>Bull. Hlth Org. L. o. N.</i> , 1935, 4, 508; 1945/46, 12, 20
1st Standard 1931 (0.3220 mg) 2nd Standard 1935 (0.2660 mg) 3rd Standard 1943 (0.3477 mg) <i>4th Standard 1953</i>	<i>Bull. Wld Hlth Org.</i> , 1947/48, 1, 9; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1956, 108, 7; <i>Bull. Hlth Org. L. o. N.</i> , 1935, 4, 510; 1938, 7, 695, 802, 818; 1939, 8, 797; 1942/43, 10, 97; 1945/46, 12, 22; <i>Pharmacopoea Internationalis</i> , 1951, Vol. I, 209, 332; WHO/BS 281, 495
<i>1st Standard 1954</i>	<i>Bull. Wld Hlth Org.</i> , 1956, 14, 557; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1955, 96, 6; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1956, 108, 7; 1957, 127, 8; WHO/BS 281, 283, 298, 303, 343
<i>1st Standard 1954</i>	<i>Bull. Wld Hlth Org.</i> , 1956, 14, 557; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1955, 96, 6; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1956, 108, 7; 1957, 127, 8; WHO/BS 281, 283, 298, 303, 343
1st Standard 1934 (0.2377 mg) 2nd Standard 1947 (0.0974 mg) <i>3rd Standard 1957</i>	<i>Bull. Wld Hlth Org.</i> , 1947/48, 1, 9; <i>Bull. Hlth Org. L. o. N.</i> , 1935, 4, 1, 13, 511; 1938, 7, 699, 815; 1942/43, 10, 97; 1945/46, 12, 26; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1956, 108, 7; 1957, 127, 9; 1958, 147, 15; <i>Pharmacopoea Internationalis</i> , 1951, Vol. I, 210, 334; WHO/BS 318, 367, 384
1st Standard 1934 (0.2681 mg) <i>2nd Standard 1952</i>	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1953, 68, 11; <i>Bull. Hlth Org. L. o. N.</i> , 1935, 4, 3, 42, 511; 1942/43, 10, 97; 1945/46, 12, 26; <i>Pharmacopoea Internationalis</i> , 1951, Vol. I, 209, 328

Substance	International Unit of present standard (mg)	Form in which dispensed
<b>Antibodies (contd)</b>		
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)
Anti-streptolysin O	0.0213	Ampoules containing 46 mg of dried human serum
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)

Years of establishment (in brackets, unitage of previous standards)	References (WHO/BS refers to unpublished working documents of the WHO Expert Committees on Biological Standardization)
1st Standard 1935 (0.3575 mg) 2nd Standard 1951	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1952, 56, 17; <i>Bull. Hlth Org. L. o. N.</i> , 1936, 5, 576, 659; 1945/46, 12, 21; WHO/BS 91, 131
<i>1st Standard</i> 1938	<i>Bull. Hlth Org. L. o. N.</i> , 1938, 7, 698, 807; 1939, 8, 856; 1945/46, 12, 21
1st Standard 1934 (0.5000 mg) 2nd Standard 1938	<i>Bull. Hlth Org. L. o. N.</i> , 1935, 4, 6, 68, 514; 1938, 7, 702, 845; 1945/46, 12, 32
<i>1st Standard</i> 1952	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1953, 68, 11; WHO/BS 38, 60, 84, 150, 225
<i>1st Standard</i> 1959	<i>Bull. Wld Hlth Org.</i> , 1961, 24, 271; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1960, 187, 16; 1961, 222, 19; WHO/BS/402, 443, 482, Rev. 1., 482, Rev. 1, Corr. 1, 517, 517, Corr. 1
<i>1st Standard</i> 1954	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1955, 96, 10; 1956, 108, 12; WHO/BS 246, 297, 300
<i>1st Standard</i> 1934	<i>Bull. Hlth Org. L. o. N.</i> , 1935, 4, 4, 48, 512
<i>1st Standard</i> 1934	<i>Bull. Hlth Org. L. o. N.</i> , 1935, 4, 5, 65, 512
<i>1st 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>1st 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

Substance	International Unit of present standard (mg)	Form in which dispensed
<b>Antibodies (contd)</b>		
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)
Syphilitic human serum	3.617	Ampoules containing 177.4 mg of dried human serum (49 I.U. per ampoule)
Cholera agglutinating serum (Inaba)	—	Ampoules containing 0.6 ml of monospecific serum
Cholera agglutinating serum (Ogawa)	—	Ampoules containing 0.6 ml of monospecific serum
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)
Antityphoid serum (provisional)	—	Ampoules containing 5 ml of hyperimmune horse serum, dried
Antipoliomyelitis serum (type 1)	—	Ampoules containing 1 ml of a 1 : 100 dilution of hyperimmune monkey serum in a 6% solution of dextran in distilled water, dried
Antipoliomyelitis serum (type 2)	—	Ampoules containing 1 ml of a 1 : 100 dilution of hyperimmune monkey serum in a 6% solution of dextran in distilled water, dried
Antipoliomyelitis serum (type 3)	—	Ampoules containing 1 ml of a 1 : 100 dilution of hyperimmune monkey serum in a 6% solution of dextran in distilled water, dried

Years of establishment (in brackets, unitage of previous standards)	References (WHO/BS refers to unpublished working documents of the WHO Expert Committees on Biological Standardization)
<i>1st Standard</i> 1955	<i>Bull. Wld Hlth Org.</i> , 1954, <b>10</b> , 781 ; 1955, <b>13</b> , 747, 773 ; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1956, <b>108</b> , 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, 375  <i>Bull. Wld Hlth Org.</i> , 1950, <b>3</b> , 301 ; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1951, <b>36</b> , 10 ; WHO/BS 42, 49, 74
<i>1st Standard</i> 1950	<i>Bull. Wld Hlth Org.</i> , 1950, <b>3</b> , 301 ; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1951, <b>36</b> , 10 ; WHO/BS 42, 49, 74
<i>1st Standard</i> 1958	<i>Bull. Wld Hlth Org.</i> , 1961, <b>24</b> , 271 ; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1958, <b>147</b> , 16 ; 1961, <b>222</b> , 21 ; WHO/BS 239, 289 Rev. 1, 304, 341, 379, 380 Rev. 1, 439, 465, 509
<i>1st Reference Preparation</i> 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 ; 1959, <b>179</b> , 33, 45 ; WHO/BS 40, 98, 130, 167, 222, 255
<i>1st Reference Preparation</i> 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 ; 1959, <b>179</b> , 33, 45 ; WHO/BS 40, 98, 130, 167, 222, 255
1st Reference Preparation 1935 2nd Reference Preparation 1938 3rd Reference Preparation 1945 4th Reference Preparation 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, 359
<i>1st Reference Preparation</i> 1952	<i>Bull. Wld Hlth Org.</i> , 1954, <b>10</b> , 911 ; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1953, <b>68</b> , 10 ; WHO/BS 182, 226
<i>1st Reference Preparation</i> 1958	<i>Bull. Wld Hlth Org.</i> , 1961, <b>25</b> (in press) ; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1959, <b>172</b> , 15 ; 1959, <b>178</b> , 18 ; WHO/BS 313, 361, 363, 385, 433, 444, 475, 483, 516
<i>1st Reference Preparation</i> 1958	<i>Bull. Wld Hlth Org.</i> , 1961, <b>25</b> (in press) ; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1959, <b>172</b> , 15 ; 1959, <b>178</b> , 18 ; WHO/BS 313, 361, 363, 385, 433, 444, 475, 483, 516
<i>1st Reference Preparation</i> 1958	<i>Bull. Wld Hlth Org.</i> , 1961, <b>25</b> (in press) ; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1959, <b>172</b> , 15 ; 1959, <b>178</b> , 18 ; WHO/BS 313, 361, 363, 385, 433, 444, 475, 483, 516

Substance	International Unit of present standard (mg)	Form in which dispensed
<b>Antibodies (contd)</b>		
Anti- <i>Leptospira saxkoebing</i> serum <sup>1</sup>	—	Ampoules containing 0.5 ml or 1.0 ml of hyperimmune rabbit serum, dried
Anti- <i>Leptospira ballum</i> AB serum <sup>1</sup>	—	
Anti- <i>Leptospira canicola</i> serum <sup>1</sup>	—	
Anti- <i>Leptospira sejroe</i> serum <sup>1</sup>	—	
Anti- <i>Leptospira mini</i> AB serum <sup>1</sup>	—	
Anti- <i>Leptospira grippotyphosa</i> serum <sup>1</sup>	—	
Anti- <i>Leptospira australis</i> A serum <sup>1</sup>	—	
Anti- <i>Leptospira icterohaemorrhagiae</i> AB serum <sup>1</sup>	—	
Anti- <i>Leptospira icterohaemorrhagiae</i> A serum <sup>1</sup>	—	
Anti- <i>Leptospira hyos</i> serum <sup>1</sup>	—	
Anti- <i>Leptospira autumnalis</i> AB serum <sup>1</sup>	—	
Anti- <i>Leptospira autumnalis</i> A serum <sup>1</sup>	—	
Anti- <i>Leptospira pomona</i> serum <sup>1</sup>	—	
Anti- <i>Leptospira bataviae</i> serum <sup>1</sup>	—	
Anti- <i>Leptospira semaranga</i> serum <sup>1</sup>	—	

<sup>1</sup> The WHO/FAO Leptospirosis Reference Laboratories are co-custodians of these International Reference Sera. Samples can be obtained only by application to the following:

Laboratory of the Queensland Department of Health and Home Affairs, Brisbane, Queensland, Australia; Istituto Superiore di Sanità, Viale Regina Elena 299, Rome,

Years of establishment (in brackets, unitage of previous standards)	References (WHO/BS refers to unpublished working documents of the WHO Expert Committees on Biological Standardization)
<p><i>1st Reference Preparation 1958</i></p>	<p><i>Wld Hlth Org. techn. Rep. Ser., 1956, 113; 1959, 172, 17; WHO/BS 413, 437, 508</i></p>

Italy; Department of Viral and Rickettsial Diseases, National Institute of Health, Tokyo, Japan; Institute for Tropical Hygiene and Geographical Pathology (Royal Tropical Institute), Mauritskade, 57A, Amsterdam, Netherlands; The Wellcome Laboratories of Tropical Medicine, The Wellcome Building, Euston Road, London N.W.1., England; Division of Veterinary Medicine, Walter Reed Army Institute of Research, Walter Reed Army Medical Centre, Washington 12, DC, USA.

Substance	International Unit of present standard (mg)	Form in which dispensed
<b>Antibodies (contd)</b>		
Anti- <i>Leptospira hebdomadis</i> serum <sup>1</sup>	—	Ampoules containing 0.5 ml or 1.0 ml of hyperimmune rabbit serum, dried
Anti- <i>Leptospira andamana</i> serum <sup>1</sup>	—	
Anti- <i>Leptospira javanica</i> serum <sup>1</sup>	—	
Anti- <i>Leptospira pyrogenes</i> serum <sup>1</sup>	—	
<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)

<sup>1</sup> The WHO/FAO Leptospirosis Reference Laboratories are co-custodians of these International Reference Sera. Samples can be obtained only by application to the following:

Laboratory of the Queensland Department of Health and Home Affairs, Brisbane, Queensland, Australia; Istituto Superiore di Sanità, Viale Regina Elena 299, Rome,

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Substance	International Unit (mg)	Adopted	Discontinued
Arsphenamine	—	1925	1935
Ouabain	—	1928	1954
Provitamin A ( $\beta$ -carotene)	0.0006	1931	1956
Vitamin B (synthetic vitamin B <sub>1</sub> )	0.003	1931	1956
*Oestrone	0.0001	1932	1949
Vitamin C	0.05	1934	1956
Oestradiol monobenzoate	0.0001	1935	1949
Androsterone	0.1	1935	1950
*Progesterone	1.0	1935	1955
Vitamin E ( $\alpha$ -tocopheryl acetate)	1.0	1941	1956
*Vitamin A (vitamin A acetate)	0.000344	1949	1954
*Tubocurarine ( <i>d</i> -tubocurarine chloride)	1.0	1951	1955
Staphylococcus $\beta$ antitoxin	2.623	1952	1956
*Chloramphenicol	—	1953	1956

## B. PHARMACOLOGICAL SUBSTANCES

Substance	References (WHO/BS refers to unpublished working documents of the WHO Expert Committees on Biological Standardization)
Gramicidin S Griseofulvin	} <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1961, 222, 9; WHO/BS/530
Procaine benzylpenicillin in oil with aluminium monostearate	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1953, 63, 55; WHO/BS/324, 349 Rev. 1, 358 Rev. 1, 403, 404, 484
Spiramycin	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1961, 222, 9; WHO/BS/530
Human urinary menopausal gonadotrophins	WHO/BS/532
Streptodornase	WHO/BS/479
Streptokinase	WHO/BS/479

## III. DISCONTINUED INTERNATIONAL BIOLOGICAL STANDARDS

The International Biological Standards for the following substances which can either now be characterized completely by chemical or physical tests, or for which there has been little demand, have been discontinued. (References : *Wld Hlth Org. techn. Rep. Ser.*, 1952, 56, 14; 1953, 68, 25; 1957, 127, 9, 19)

Samples of the substances marked with an asterisk are now available at the WHO Centre for Authentic Chemical Substances, Apotekens Kontrolllaboratorium, 128 Lindhagensgatan, Stockholm, Sweden.

Although there are no longer international standards for vitamin A or for provitamin A, the international units for these substances are still used extensively. The Expert Committee on Biological Standardization has therefore redefined the International Unit for Vitamin A as the activity of 0.000344 mg of pure all-*trans* vitamin A acetate,<sup>1</sup> and the International Unit for Provitamin A as the activity of 0.0006 mg of pure all-*trans* beta carotene.<sup>2</sup>

<sup>1</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1960, 187, 10

<sup>2</sup> *Wld Hlth Org. techn. Rep. Ser.*, 1961, 222, 10

Substance	References (WHO/BS refers to unpublished working documents of the WHO Expert Committees on Biological Standardization)
Anti- <i>Leptospira poi</i> serum	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1956, 113; 1961, 222, 18; WHO/BS 437, 489, 543
Anti- <i>Leptospira sarmin</i> serum	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1956, 113; 1961, 222, 18; WHO/BS 437, 489, 543
Anti- <i>Leptospira schüffneri</i> serum	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1956, 113; 1961, 222, 18; WHO/BS 437, 489, 543
Anti- <i>Leptospira bangkinang</i> serum	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1956, 113; 1961, 222, 18; WHO/BS 437, 489, 543
Anti- <i>Leptospira celledoni</i> serum	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1956, 113; 1961, 222, 18; WHO/BS 437, 489, 543
Anti- <i>Leptospira cynopteri</i> serum	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1956, 113; 1961, 222, 18; WHO/BS 437, 489, 543
Anti- <i>Leptospira hardjo</i> serum	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1956, 113; 1961, 222, 18; WHO/BS 437, 489, 543
Anti- <i>Leptospira kremastos</i> serum	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1956, 113; 1961, 222, 18; WHO/BS 437, 489, 543
Anti- <i>Leptospira wolffi</i> serum	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1956, 113; 1961, 222, 18; WHO/BS 437, 489, 543
Anti- <i>Leptospira zannoni</i> ( <i>australis</i> B) serum	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1956, 113; 1961, 222, 18; WHO/BS 437, 489, 543
Anti- <i>Leptospira benjamin</i> serum	WHO/BS 437, 489
Anti- <i>Leptospira djasiman</i> serum	WHO/BS 437, 489
Anti- <i>Leptospira medanensis</i> serum	WHO/BS 437, 489
Anti- <i>Leptospira paidjan</i> serum	WHO/BS 437, 489
Anti- <i>Leptospira sentot</i> serum	WHO/BS 437, 489

Substance	References (WHO/BS refers to unpublished working documents of the WHO Expert Committees on Biological Standardization)
<i>Clostridium botulinum</i> Type D anti-toxin	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1960, 187, 18; WHO/BS/485
<i>Clostridium botulinum</i> Type E anti-toxin	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1960, 187, 18; WHO/BS/485
<i>Bothrops</i> antivenin	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1957, 127, 9; WHO/BS/316, 317, 333, 334, 364, 373
<i>Naja</i> antivenin	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1960, 187, 19; 1961, 222, 21; WHO/BS 316, 317, 333, 334, 364, 373, 471, 501, 502, 502 Add. 1, 503, 541
Anti-Rh <sub>0</sub> (anti-D) albumin-potentiated blood-typing serum	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1950, 2, 12; WHO/BS 46, 165, 213, 328, 366, 407, 453 Rev. 1, 453 Add. 1
Anti-rh' (anti-C) blood-typing serum	WHO/BS 46, 165, 366, 407
Anti-rh" (anti-E) blood-typing serum	WHO/BS 46, 165, 366, 407
Anti-vaccinia gamma globulin	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1959, 180, 5; WHO/BS 454
Anti-measles serum	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1961, 222, 19; WHO/BS/539, 544
Anti-toxoplasma human serum	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1961, 222, 20; WHO/BS/447, 496, 538
Anti-tick-borne encephalitis serum	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1961, 222, 19; WHO/BS/463, 511
Anti-yellow-fever serum	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1957, 136, 9; 1959, 179, 12; 1961, 222, 20; WHO/BS/416, 438, 464, 464 Add. 1, 506, 514
Anti-trichinella human serum	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1961, 222, 20; WHO/BS/470, 542
Anti-echinococcus human serum	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1961, 222, 18; WHO/BS/470, 542
Anti- <i>Leptospira mankarso</i> serum	<i>Wld Hlth Org. techn. Rep. Ser.</i> 1956, 113; 1961, 222, 18; WHO/BS 437, 489, 543
Anti- <i>Leptospira muenchen</i> serum	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1956, 113; 1961, 222, 18; WHO/BS 437, 489, 543
Anti- <i>Leptospira naam</i> serum	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1956, 113; 1961, 222, 18; WHO/BS 437, 489, 543

**II. PROPOSED INTERNATIONAL BIOLOGICAL STANDARDS  
AND  
INTERNATIONAL BIOLOGICAL REFERENCE PREPARATIONS**

**A. IMMUNOLOGICAL SUBSTANCES**

Substance	References (WHO/BS refers to unpublished working documents of the WHO Expert Committees on Biological Standardization)
Anthrax vaccine	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1961, <b>222</b> , 11; WHO/BS/527
BCG-vaccine	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1960, <b>187</b> , 12; 1961, <b>222</b> , 12; WHO/BS/455, 513
Clostridium oedematiens (alpha) toxoid	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1961, <b>222</b> , 12
Newcastle disease vaccine (inactivated)	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1960, <b>187</b> , 20; 1961, <b>222</b> , 13; WHO/BS/528, 528 Add. 1
Newcastle disease vaccine (live)	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1961, <b>222</b> , 13; WHO/BS/528, 528 Add. 1
Poliomyelitis vaccine (inactivated)	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1959, <b>178</b> , 5, 18; 1961, <b>222</b> , 13; WHO/BS/235, 260, 321, 376, 376 Annex 1, 449, 459, 460, 466, 466 Add. 1, 537
Smallpox vaccine	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1961, <b>222</b> , 16; WHO/BS/14, 73, 105, 371, 381, 383, 417, 442, 461, 467, 500, 536
Tetanus toxoid, adsorbed	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1961, <b>222</b> , 16; WHO/BS/452, 468, 468 Add. 1, 469, 510
Typhoid vaccine	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1958, <b>147</b> , 11; 1960, <b>187</b> , 15; 1961, <b>222</b> , 17; WHO/BS 217, 291, 301, 340, 378, 409, 441, 505, 515
<i>Clostridium botulinum</i> Type A anti-toxin	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1960, <b>187</b> , 18; WHO/BS/485
<i>Clostridium botulinum</i> Type B anti-toxin	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1960, <b>187</b> , 18; WHO/BS/485
<i>Clostridium botulinum</i> Type C anti-toxin	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1960, <b>187</b> , 18; WHO/BS/485

Years of establishment (in brackets, unitage of previous standards)	References (WHO/BS refers to unpublished working documents of the WHO Expert Committees on Biological Standardization)
<i>1st Reference Preparation 1954</i>	<i>Wld Hlth Org. techn. Rep. Ser., 1955, 96, 14; WHO/BS 261</i>
<i>1st Reference Preparation 1958</i>	<i>Wld Hlth Org. techn. Rep. Ser., 1958, 147, 11; WHO/BS 90, 147, 206, 264, 312, 365, 400, 425</i>

Substance	International Unit of present standard (mg)	Form in which dispensed
<b>Miscellaneous (contd)</b>		
Protamine	—	Ampoules containing 60 mg of protamine
Pyrogen	—	Ampoules containing 2 mg of dried purified 'O' somatic antigen of <i>Shigella dysenteriae</i>

Years of establishment (in brackets, unitage of previous standards)	References (WHO/BS refers to unpublished working documents of the WHO Expert Committees on Biological Standardization)
1st Standard 1931 (0.1 mg) [Irradiated ergosterol] 2nd Standard 1949	<i>Bull. Wld Hlth Org.</i> , 1954, 10, 875; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1950, 3, 7; <i>Bull. Hlth Org. L. o. N.</i> , 1940/41, 9, 425; 1945/46, 12, 54; <i>Pharmacopoea Internationalis</i> , 1951, Vol. I, 369; WHO/BS 8
1st Reference Preparation 1959	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1960, 187, 11; WHO/BS/34, 58, 61, 118, 142, 164, 209, 268, 355, 389, 458
1st Standard 1955	<i>Bull. Wld Hlth Org.</i> , 1957, 16, 291; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1956, 108, 18; WHO/BS 78, 135, 160, 163, 232, 271, 306
1st Standard 1926 (100.0 mg) 2nd Standard 1936 (80.0 mg) 3rd Standard 1949	<i>Bull. Wld Hlth Org.</i> , 1950, 2, 655; <i>Bull. Hlth Org. L. o. N.</i> , 1935, 4, 522; 1936, 5, 574; 1945/46, 12, 41; <i>Pharmacopoea Internationalis</i> , 1951, Vol. I, 93, 357; WHO/BS 33, 51
1st Reference Preparation 1925 2nd Reference Preparation 1935 3rd Reference Preparation 1940	<i>Bull. Wld Hlth Org.</i> , 1947/48, 1, 9; <i>Bull. Hlth Org. L. o. N.</i> , 1935, 4, 528; 1936, 5, 573; 1945/46, 12, 40; <i>Pharmacopoea Internationalis</i> , 1951, Vol. I, 147, 347; WHO/BS 26
1st Reference Preparation 1925 2nd Reference Preparation 1936 3rd Reference Preparation 1951	<i>Bull. Wld Hlth Org.</i> , 1951, 4, 563; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1952, 56, 17; <i>Bull. Hlth Org. L. o. N.</i> , 1935, 4, 528; 1936, 5, 573; 1945/46, 12, 40; <i>Pharmacopoea Internationalis</i> , 1951, Vol. I, 234, 351; WHO/BS 110
1st Reference Preparation 1951	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1952, 56, 7; <i>Pharmacopoea Internationalis</i> , 1955, Vol. II, 176; WHO/BS 133, 174
1st Reference Preparation 1954	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1955, 96, 16; WHO/BS 134, 148, 202, 273
1st Reference Preparation 1954	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1955, 96, 16; WHO/BS 134, 148, 202, 273
1st Reference Preparation 1952	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1953, 68, 18; <i>Pharmacopoea Internationalis</i> , 1955, Vol. II, 91, 122, 280; WHO/BS 159

Substance	International Unit of present standard (mg)	Form in which dispensed
<b>MISCELLANEOUS</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)
Vitamin B <sub>12</sub>	—	Ampoules containing ten 20-mg tablets of cyanocobalamin
Hyaluronidase	0.1	Ampoules containing ten 20-mg tablets of dried bovine testicular hyaluronidase diluted with lactose (approximately 200 I.U. per tablet)
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

Years of establishment (in brackets, unitage of previous standards)	References (WHO/BS refers to unpublished working documents of the WHO Expert Committees on Biological Standardization)
<i>1st Standard 1939</i>	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1957, <b>127</b> , 16; <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, 350, 405, 446, 492
<i>1st Standard 1950 (1.00 mg)</i> <i>2nd Standard 1955</i>	<i>Bull. Wld Hlth Org.</i> , 1956, <b>14</b> , 543; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1951, <b>36</b> , 7; 1958, <b>147</b> , 8; WHO/BS 85, 156, 158, 249, 262, 308, 356, 386, 387, 432, 473, 526
<i>1st Standard 1954</i>	<i>Bull. Wld Hlth Org.</i> , 1955, <b>13</b> , 917; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1955, <b>96</b> , 14; 1956, <b>108</b> , 16; WHO/BS 1955, 158, 210, 284, 309
<i>1st Standard 1955</i>	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1956, <b>108</b> , 16; WHO/BS 140, 158, 250, 320
<i>1st Reference Preparation 1959</i>	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1959, <b>172</b> , 9; 1960, <b>187</b> , 9; WHO/BS 392, 434, 474, 532, 533
<i>1st Standard 1939</i>	<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, 519
<i>1st Standard 1939</i>	<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, 519
<i>1st Standard 1925 (0.12500 mg)</i> <i>2nd Standard 1935 (0.04550 mg)</i> <i>3rd Standard 1952 (0.04082 mg)</i> <i>4th Standard 1958</i>	<i>Bull. Wld Hlth Org.</i> , 1952, <b>7</b> , 445; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1958, <b>147</b> , 9; <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, 357, 388, 427
<i>1st Standard 1942 (0.0077 mg)</i> <i>2nd Standard 1958</i>	<i>Bull. Wld Hlth Org.</i> , 1947/48, <b>1</b> , 9; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1958, <b>147</b> , 10; <i>Bull. Hlth Org. L. o. N.</i> , 1942/43, <b>10</b> , 144, 151; 1945/46, <b>12</b> , 46; <i>Pharmacopoea Internationalis</i> , 1951, Vol. I, 104, 341; 1955, Vol. II, 126 WHO/BS 353, 390, 424

Substance	International Unit of present standard (mg)	Form in which dispensed
<b>Hormones (contd)</b>		
Prolactin	0.1	Ampoules containing ten 10-mg tablets of dried active principle from anterior pituitary gland of the ox (approximately 100 I.U. per tablet)
Corticotrophin (previously named : adrenocorticotrophic hormone)	0.88	Ampoules containing 28 mg of crude corticotrophin from anterior pituitary gland of the pig (1.14 I.U. per mg)
Thyrotrophin	13.5	Ampoule containing ten 20-mg tablets of a blend of 1 part purified thyrotrophin from anterior pituitary gland of the ox 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)
Human menopausal gonadotrophin	—	Ampoules containing 22 mg of dried active principle from urine of post-menopausal women
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	0.04167	Ampoules containing 110-125 mg of purified insulin, 52% from bovine and 48% from porcine pancreas (24 I.U. per mg)
Heparin	0.0077	Ampoules containing 20 mg of sodium salt of purified active principle from bovine tissue (130 I.U. per mg)

Years of establishment (in brackets, unitage of previous standards)	References (WHO/BS refers to unpublished working documents of the WHO Expert Committees on Biological Standardization)
<i>1st Standard</i> 1955	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1956, <b>108</b> , 14; WHO/BS 263, 326
<i>1st Reference Preparation</i> 1959	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1960, <b>187</b> , 5; WHO/BS/450, 478
<i>1st Reference Preparation</i> 1959	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1960, <b>187</b> , 6; WHO/BS/450, 478
<i>1st Reference Preparation</i> 1959	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1960, <b>187</b> , 9; WHO/BS 450, 478
<i>1st Reference Preparation</i> 1959	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1960, <b>187</b> , 9; WHO/BS/493
<i>1st Reference Preparation</i> 1951	<i>Bull. Wld Hlth Org.</i> , 1954, <b>10</b> , 895; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1952, <b>56</b> , 11; WHO/BS 132
<i>1st Reference Preparation</i> 1958	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1958, <b>147</b> , 6; WHO/BS 347, 398, 428, 491
<i>1st Reference Preparation</i> 1958	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1958, <b>147</b> , 8; WHO/BS 347, 429, 476, 524
<i>1st Reference Preparation</i> 1958	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1958, <b>147</b> , 6; WHO/BS/394, 431, 472
<i>1st Reference Preparation</i> 1958	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1958, <b>147</b> , 8; WHO/BS 430, 477
<i>1st Reference Preparation</i> 1960	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1961, <b>222</b> , 8; WHO/BS/450, 478, 518
1st Standard 1925 (0.5 mg) 2nd Standard 1942 (0.5 mg) 3rd Standard 1957	<i>Bull. Wld Hlth Org.</i> , 1947/48, <b>1</b> , 9; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1957, <b>127</b> , 15; 1958, <b>147</b> , 8; <i>Bull. Hlth Org. L. o. N.</i> , 1935, <b>4</b> , 530; 1936, <b>5</b> , 572; 1942/43, <b>10</b> , 89; 1945/46, <b>12</b> , 42; <i>Pharmacopoea Internationalis</i> , 1951, Vol. I, 191, 342; WHO/BS 351, 352, 395, 480

Substance	International Unit of present standard (mg)	Form in which dispensed
<b>Antibiotics (contd)</b>		
Polymyxin B	0.000127	Ampoules containing 19 mg of purified polymyxin B sulfate (7874 I.U. per mg)
Amphotericin B	—	Ampoules in preparation
Kanamycin	—	Ampoules containing 50 mg of kanamycin sulfate
Vancomycin	—	Ampoules containing 50 mg of vancomycin sulfate
Viomycin	—	Ampoules containing 35 mg of viomycin sulfate
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
Neomycin	—	Ampoules containing 100 mg of neomycin sulfate
Nystatin	—	Ampoules containing 75 mg of nystatin
Novobiocin	—	Ampoules containing 150 mg of sodium novobiocin
Oleandomycin	—	Ampoules containing 75 mg of oleandomycin chloroform adduct
Ristocetin	—	Ampoules containing 45 mg of ristocetin
<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 pituitary gland of the ox (2 oxytocic, 2 vasopressor, and 2 antidiuretic I.U. per mg)

## SUBSTANCES

*National Institute for Medical Research, Mill Hill, London, N.W. 7, England*

Years of establishment (in brackets, unitage of previous standards)	References (WHO/BS refers to unpublished working documents of the WHO Expert Committees on Biological Standardization)
1st Standard 1944 (0.0006000 mg) 2nd Standard 1952	<i>Bull. Wld Hlth Org.</i> , 1953, <b>9</b> , 15; <i>Bull. Hlth Org. L. o. N.</i> , 1945/46, <b>12</b> , 181; <i>Pharmacopoea Internationalis</i> , 1955, Vol. II, 23, 277; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1960, <b>187</b> , 7; WHO/BS 10, 15, 67, 94, 211, 170, 349 Rev. 1, 404, 529
1st Standard 1957	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1957, <b>127</b> , 14; 1958, <b>147</b> , 7; WHO/BS 399
1st Standard 1950 (0.001282mg) 2nd Standard 1958	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1951, <b>36</b> , 9; 1958, <b>147</b> , 5; <i>Pharmacopoea Internationalis</i> , 1955, Vol. II, 198, 279; WHO/BS 11, 67, 76, 369, 393, 421
1st Standard 1953	<i>Bull. Wld Hlth Org.</i> , 1954, <b>10</b> , 901; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1954, <b>86</b> , 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, <b>9</b> , 861; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1954, <b>86</b> , 15; WHO/BS 122, 144, 236, 481
1st Standard 1957	<i>Bull. Wld Hlth Org.</i> , 1957, <b>17</b> , 521; <i>Wld Hlth Org. tech. Rep. Ser.</i> , 1957, <b>127</b> , 13; 1958, <b>147</b> , 6; WHO/BS 323, 370, 396, 396 Annex 1
1st Standard 1953	<i>Bull. Wld Hlth Org.</i> , 1953, <b>9</b> , 851; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1954, <b>86</b> , 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, <b>13</b> , 903; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1956, <b>108</b> , 14; <i>Pharmacopoea Internationalis</i> , 1955, Vol. II, 179; WHO/BS 122, 145, 211, 285, 307
1st Standard 1957	<i>Bull. Wld Hlth Org.</i> , 1957, <b>17</b> , 527; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1957, <b>127</b> , 13; 1958, <b>147</b> , 6; WHO/BS 322, 368, 397, 397 Annex 1

## B. PHARMACOLOGICAL

*Held and distributed by the International Laboratory for Biological Standards,*

Substance	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)
Phenoxymethylpenicillin	0.00059	Ampoules containing 75 mg of phenoxymethylpenicillin (1695 I.U. per mg)
Streptomycin	0.001282	Ampoules containing 175 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)
Tetracycline	0.00101	Ampoules containing 200 mg of tetracycline hydrochloride (990 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)
Erythromycin	0.001053	Ampoules containing 200 mg of erythromycin dihydrate (950 I.U. per mg)

Years of establishment (in brackets, unitage of previous standards)	References (WHO/BS refers to unpublished working documents of the WHO Expert Committees on Biological Standardization)
<i>1st Reference Preparation 1958</i>	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1956, <b>113</b> ; 1959, <b>172</b> , <b>17</b> ; WHO/BS 413, 437
<i>1st Reference Preparation 1953</i>	<i>Bull. Wld Hlth Org.</i> , 1955, <b>12</b> , 769 ; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1954, <b>86</b> , 14 ; WHO/BS 124, 172, 198, 256

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