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**EXPERT COMMITTEE ON
BIOLOGICAL STANDARDIZATION**

Thirteenth Report

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EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION

Geneva, 31 August-5 September 1959

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EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION

Thirteenth Report *

The Expert Committee on Biological Standardization met in Geneva from 31 August to 5 September 1959.

Dr P. Dorolle, Deputy Director-General, on behalf of the Director-General of the World Health Organization, welcomed the members of the Committee, the temporary advisers, and the representative of the Food and Agriculture Organization of the United Nations.

Recalling the long traditions of this Expert Committee, the Deputy Director-General surveyed the large range of substances of great importance in therapy and prophylaxis, which were included in the present agenda. The decisions of the Committee would affect the potency notation used by biological research workers and clinicians throughout the world, as well as the procedures of those whose task it is to control the biological drugs that are made available to the public. An item that required special consideration in this session was the proposal to make available, on a larger scale than hitherto, diagnostic reference reagents for direct routine use in laboratories engaged in the diagnosis of disease and in the identification of micro-organisms. This project must be based on standardization principles in order to ensure the specificity, potency, and stability of the diagnostic material that was to be provided.

PHARMACOLOGICAL

ANTIBIOTICS

1. Amphotericin B

The Committee noted that the National Institute for Medical Research, London, had obtained a quantity of amphotericin.¹ The Committee established this material as the International Reference Preparation of Amphotericin B.

* The Executive Board, at its twenty-fifth session, adopted the following resolution :
The Executive Board

1. NOTES the thirteenth 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 EB25.R2, *Off. Rec. Wld Hlth Org.*, 1960, 99, 5)

¹ Unpublished working document WHO/BS/478

2. Bacitracin

The Committee noted that the stock of the International Standard for Bacitracin would soon be exhausted,¹ and it requested the National Institute for Medical Research, London, to obtain suitable material for its replacement and to arrange a collaborative assay.

3. Gramicidin

The Committee was of the opinion that there is a need for an international reference preparation of gramicidin and it requested the National Institute for Medical Research, London, to obtain a quantity of gramicidin suitable for this purpose.

4. Kanamycin

The Committee noted that the National Institute for Medical Research, London, had obtained a quantity of kanamycin sulfate.² The Committee established this material as the International Reference Preparation of Kanamycin.

5. Leucomycin

The Committee noted that the quantity of leucomycin obtained by the National Institute for Medical Research, London,² was insufficient for serving as an international reference preparation. It requested the National Institute for Medical Research to reassess the need for an international reference preparation of this antibiotic.

6. Neomycin B

The Committee noted that investigation had indicated that the International Reference Preparation of Neomycin contained an antibiotic component which had not yet been identified.

The Committee also noted that the National Institute for Medical Research, London, had examined several samples of neomycin but had not yet been able to obtain a preparation sufficiently pure to serve as the international standard for neomycin B.³

¹ Unpublished working document WHO/BS/481

² Unpublished working document WHO/BS/478

³ Unpublished working document WHO/BS/491

7. Novobiocin

The Committee noted that the International Reference Preparation of Novobiocin had been found suitable to serve as an international standard and that a collaborative assay of this material was in progress.¹ It authorized the National Institute for Medical Research, London, to establish the International Standard for Novobiocin and to define the international unit with the agreement of the participants in the collaborative assay.

8. Nystatin

The Committee noted that progress was being made towards the replacement of the International Reference Preparation of Nystatin by an international standard.²

9. Oleandomycin

The Committee noted that the International Reference Preparation of Oleandomycin had been found suitable to serve as an international standard and that a collaborative assay of this material was in progress.³ It authorized the National Institute for Medical Research, London, to establish the international Standard for Oleandomycin and to define the international unit with the agreement of the participants in the collaborative assay.

10. Penicillin : Unit Notation

The Committee considered a published proposal of the Commission d'études des antibiotiques, France, that "for the administration of penicillin the doses of the antibiotic should no longer be expressed in units but in terms of weight of penicillin anion".⁴ The National Institute for Medical Research, London, had obtained the opinions of experts in different countries on this proposal and, although there had been no unanimity of opinion among the experts, the majority had expressed the view that a change in the present method of notation would be premature.

The Committee agreed with this view and decided 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. The Committee

¹ Unpublished working document WHO/BS/472

² Unpublished working document WHO/BS/476

³ Unpublished working document WHO/BS/477

⁴ France, Commission d'études des antibiotiques (1959) *Thérapie*, 14, 9

asked the National Institute for Medical Research to propose for the next meeting of the Committee an alternative definition of the International Unit of Penicillin in terms of theoretically pure penicillin acid.

11. Procaine Benzylpenicillin in Oil with Aluminium Monostearate (PAM)

The Committee considered the final report¹ on the collaborative study of various batches of PAM and noted that the National Institute for Medical Research, London, had been unable, because of the inconsistency of the results obtained in man, to establish an international reference preparation.

The Committee noted a report² on the results obtained during the last eight years in testing 600 samples of PAM by the blood-level duration test in man, as specified in the requirements³ adopted by the World Health Organization for the purpose of selecting batches of PAM for use in field projects. The Committee asked the National Institute for Medical Research, London, to obtain further details of these results and to subject them to an analysis on the basis of the responses to the injection of PAM that had been observed in individuals.

The Committee was informed that PAM was in continued and widespread use for the treatment of treponematoses in programmes involving millions of people; it therefore agreed that there was an urgent need for developing a more satisfactory method of evaluating the ability of PAM to provide a persistent concentration of penicillin in the circulating blood. It was recognized that this would involve extensive research by a group of scientists over a period of at least two years, but in view of the magnitude of the need the Committee recommended that the work be done. Considerable experience in the study of PAM has been accumulated by the National Institute for Medical Research, London, and the Committee therefore considered that it would be desirable if this Institute would undertake to arrange the further work.

12. Ristocetin

The Committee noted that the National Institute for Medical Research, London, had not yet been able to obtain a quantity of ristocetin suitable for serving as an international reference preparation.⁴

¹ Unpublished working document WHO/BS/484

² Unpublished working document WHO/INT/VDT/122 and Corr. 1

³ *Wld Hlth Org. techn. Rep. Ser.*, 1953, 63, 55

⁴ Unpublished working document WHO/BS/478

13. Vancomycin

The Committee noted that the National Institute for Medical Research, London, had obtained a quantity of vancomycin sulfate.¹ The Committee established this material as the International Reference Preparation of Vancomycin.

14. Viomycin

The Committee was of the opinion that there is a need for an international reference preparation of viomycin² and it established a quantity of this antibiotic offered by the National Institute for Medical Research, London, as the International Reference Preparation of Viomycin.

15. Other Antibiotics

On the basis of the information available to it, the Committee could not recommend the establishment of international reference preparations of other antibiotics. It invited responsible workers in the antibiotics field to submit information to the World Health Organization or to the International Laboratory for Biological Standards, National Institute for Medical Research, London, concerning other antibiotics in widespread clinical use for which international reference preparations are needed.

HORMONES

16. Corticotrophin

The Committee noted that progress was being made towards the establishment of the third international standard for corticotrophin as well as towards the preparation of a working standard.³

17. Human Menopausal Gonadotrophin

The Committee noted that, in accordance with the authorization given in its twelfth report,⁴ the National Institute for Medical Research, London, had established the International Reference Preparation of Human

¹ Unpublished working document WHO/BS/478

² Unpublished working document WHO/BS/493

³ Unpublished working document WHO/BS/473

⁴ *Wld Hlth Org. techn. Rep. Ser.*, 1959, **172**, 9

Menopausal Gonadotrophin, and had obtained a quantity of the unofficial reference preparation as requested.

18. Synthetic Oxytocin

The Committee considered the report prepared by the National Institute for Medical Research, London, on the possibility of replacing the International Standard for Oxytocic, Vasopressor and Antidiuretic Substances by preparations of synthetic peptides.¹ In agreement with this report, the Committee was of the opinion that such replacement at the present stage would not serve a useful purpose.

The Committee recognized the great value in research of synthetic peptides having hormone activity and suggested that the National Institute for Medical Research inform the Institute of Chemistry of the Czechoslovak Academy of Science, Prague, that their offer of synthetic oxytocin could be accepted for distribution to scientists working in this field.

19. Prolactin

The Committee noted that the second international standard for prolactin had not yet been established because of the wide variation in the results obtained in the collaborative assay.² It also noted that the National Institute for Medical Research, London, had arranged further assays in order to permit a satisfactory redefinition of the International Unit of Prolactin in terms of the second international standard.

VITAMINS

20. Vitamin A: Unit Notation

The Committee considered a request by the Chairman of the Vitamin Commission of the International Union of Pure and Applied Chemistry concerning the clarification of the definition of the International Unit of Vitamin A. Although there is no longer an international standard for vitamin A in terms of which the international unit can be defined, the term "international unit of vitamin A" is still being used extensively, and the Committee stated that this unit is equivalent to the activity of 0.000344 mg of pure all-*trans* vitamin A acetate.

¹ Unpublished working document WHO/BS/480

² Unpublished working document WHO/BS/492

21. Vitamin B₁₂

The Committee noted that, in accordance with the authorization given in its tenth report,¹ the International Reference Preparation of Vitamin B₁₂ has been established.² Since vitamin B₁₂ is a chemically defined substance, an international unit would not serve a useful purpose, and the Committee therefore decided not to classify this material as an international standard.

ENZYMES

22. Streptokinase-Streptodornase

The Committee considered that there was a need for an international reference preparation or an international standard suitable for use in determining the relative potency of streptokinase-streptodornase preparations for clinical use. It noted that the assay methods for streptokinase and streptodornase were different, but that there seems to be, at present, no advantage in having separate reference preparations or standards for these two enzymes.³ A joint standard or reference preparation should contain the two activities in relative proportions similar to those in which they are present in clinical preparations. The Committee therefore asked the National Institute for Medical Research, London, to examine the suitability of a number of preparations to serve as a reference for assay purposes.

23. Other Enzymes

The Committee considered the need for and the possibility of establishing international reference preparations or international standards for other enzymes that have widespread clinical application. It requested the National Institute for Medical Research, London, to obtain relevant information concerning penicillinase, trypsin and fibrinolysin.

The Committee noted that the International Union of Biochemistry had formed an International Commission on Enzymes which had undertaken to consider the definition of units of enzyme activity. The Committee was also informed of the formation of a Joint Sub-Commission on Clinical Enzyme Units by the International Union of Pure and Applied Chemistry and the International Union of Biochemistry in response to the request by the Federation of Clinical Chemists. In order to avoid duplication of efforts and possible confusion in notation, the Committee requested the

¹ *Wld Hlth Org. techn. Rep. Ser.*, 1957, **127**, 18

² Unpublished working document WHO/BS/458

³ Unpublished working document WHO/BS/479

National Institute for Medical Research to maintain the contact necessary to enable the Committee to base its future decisions regarding clinical enzymes on a close cooperation with the above-named groups.

IMMUNOLOGICAL

ANTIGENS

24. BCG Vaccine

The Committee noted reports^{1, 2} on the WHO studies directed towards the elaboration of a reliable method for the assay of BCG vaccine and the establishment of an international reference preparation. Several laboratories are at present taking part in collaborative studies which include the determination of the viable count of both fluid and freeze-dried BCG vaccines and an investigation of their immunogenic effects in laboratory animals and in man.

The Committee asked the Statens Seruminstitut, Copenhagen, to collect the necessary data on the basis of which the Committee could decide on the establishment of an international reference preparation and on the formulation of minimum requirements.

25. Cholera Vaccine

The Committee was informed that the further studies on cholera vaccine envisaged in its twelfth report³ had not been initiated.

The Committee agreed that the procedures for field and laboratory work directed towards the ultimate standardization of cholera vaccine should follow the pattern adopted for typhoid vaccine, as outlined in section 32 of the present report.

The Committee asked the Secretariat to obtain the co-operation of the Indian Council of Medical Research in this matter. Even if a decision on details in the planning of field trials cannot yet be made, the preparation of the large quantities of vaccines could be undertaken and laboratory studies be arranged as soon as there is a reasonable certainty that these vaccines will be included in future field trials.

¹ Unpublished working document WHO/BS/455

² World Health Organization, Tuberculosis Research Office (1958) *Co-operative studies of methods for assay of BCG vaccine*, First Series (unpublished mimeographed report)

³ *Wld Hlth Org. techn. Rep. Ser.*, 1959, 172, 12

26. Egg Lecithin

The Committee noted that the analysis of the results of the collaborative assay had been completed,¹ and that, in accordance with the authorization given in its twelfth report,² the third International Reference Preparation of Egg Lecithin had now been established.

27. Poliomyelitis Vaccine

The Committee noted that the Statens Seruminstitut, Copenhagen, had now obtained a large quantity of freeze-dried trivalent poliomyelitis vaccine from the Institute for Poliomyelitis Prophylactics, Moscow, and a similar quantity of fluid trivalent poliomyelitis vaccine in the frozen state from the National Institutes of Health, Bethesda, and that both these preparations were included in the collaborative assay that was being arranged.³

Since stability is an important factor in the selection of an international reference preparation, and freeze-dried preparations have in the past presented advantages over fluid preparations, the Committee asked the Statens Seruminstitut, Copenhagen, to undertake a study employing accelerated deterioration tests of the stability of the freeze-dried vaccine it had obtained.

28. Purified Protein Derivative of Mammalian Tuberculin (PPD)

The Committee considered the recently published observations concerning the adsorption of purified tuberculin derivatives to the walls of vessels containing high dilutions of this material.^{4, 5} The fraction of material lost by adsorption depends on the concentration of PPD, the size of the interface in dilution vessels and injection syringes, the time and temperature of exposure, and the nature of the diluent. Solutions containing only a few International Units of PPD per ml in buffered saline may lose as much as two-thirds of the specific material, whereas no loss appears to occur from the same dilutions in a diluent containing Tween 80.

This adsorption effect was not known when the International Unit of Purified Protein Derivative of Mammalian Tuberculin was defined in 1952 as the activity of 0.000028 mg of the International Standard on the

¹ Unpublished working document WHO/BS/456

² *Wld Hlth Org. techn. Rep. Ser.*, 1959, **172**, 14

³ Unpublished working documents WHO/BS/466 and Addenda 1 & 2

⁴ Unpublished working document WHO/BS/488

⁵ *Bull. Wld Hlth Org.*, 1958, **19**, 759

basis of a biological activity similar to one International Unit of Old Tuberculin.

The Committee considered it necessary to draw the attention of the users of the International Standard for PPD of Mammalian Tuberculin to the fact that the International Unit was defined on the basis of assays in which the International Standard was diluted in phosphate-buffered saline. Therefore, dilutions of the International Standard should be made up in this same diluent when assays are conducted for the purpose of determining the potency of other preparations.

Since, however, the results of such assays are affected by variations in the adsorption effect, the Committee was of the opinion that there was an urgent need for a redefinition of the International Unit on the basis of assays employing the system in which the loss of specific material through interface adsorption is negligible; this redefinition should be based on the unit of activity of Old Tuberculin. The Committee therefore asked the Statens Seruminstitut, Copenhagen, to arrange collaborative studies for this purpose, and also to investigate whether it would be useful to replace the present International Standard for PPD of Mammalian Tuberculin by a different preparation.

The Committee also requested the Central Veterinary Laboratory, Weybridge, in consultation with the Statens Seruminstitut, to investigate whether the adsorption effect necessitated similar steps with respect to the International Standard for PPD of Avian Tuberculin.

29. Rabies Vaccine

The Committee noted that, in accordance with the recommendations made in its eleventh report,¹ a quantity of dried rabies vaccine had been obtained from the National Institutes of Health, Bethesda, suitable for serving as an international reference preparation. The Committee also noted that a collaborative assay of this material had been arranged by the Expert Committee on Rabies,² and that the Expert Committee on Biological Standardization would be asked to consider the results of this assay with a view to establishing an international reference preparation of rabies vaccine.

30. Smallpox Vaccine

The Committee noted that a collaborative assay of the proposed international reference preparation of smallpox vaccine was now in progress³

¹ *Wld Hlth Org. techn. Rep. Ser.*, 1958, 147, 12

² Unpublished working document WHO/BS/490

³ Unpublished working document WHO/BS/467

and that it included the methods for potency determination which were recommended by the Study Group on Requirements for Smallpox vaccine.¹

31. Tetanus Toxoid, Adsorbed

The Committee noted that, in accordance with a request made in its twelfth report,² opinions had been obtained from experts concerning the need for an international standard for tetanus toxoid, adsorbed.^{3, 4, 5} The Committee decided, in agreement with these opinions, that the establishment of such a standard would serve a useful purpose from the point of view of evaluating the potency of preparations of tetanus toxoid containing adjuvants.

The Committee requested the Rijks Instituut voor de Volksgezondheid, Utrecht, in collaboration with the Paul-Ehrlich Institut, Frankfurt, to obtain a sufficient quantity of tetanus toxoid, adsorbed on aluminium phosphate or aluminium hydroxide and prepared in a freeze-dried, stable and homogeneous form, suitable for adoption as an international standard.

32. Typhoid Vaccine

The Committee noted that the Walter Reed Army Institute of Research, Washington, had studied certain technical points preliminary to the preparation of two large batches of typhoid vaccine. One of these will be a heat-killed, phenolized and freeze-dried vaccine, and the other an acetone-killed and dried vaccine. These vaccines will be prepared from the same single pool of harvest, derived from a seed culture of the Ty 2 strain, and freeze-dried in a large number of ampoules. An adequate number of these ampoules will be offered to the World Health Organization to serve as seed for any subsequent vaccines required or for use in research. The Committee also noted that the Walter Reed Army Institute of Research, Washington, was studying the possibility of dispensing these large quantities of vaccine in tablet form which might facilitate their use both in field trials and for standardization purposes. Each batch will be sufficiently large to serve in a number of field trials and in extensive laboratory investigations, after setting aside adequate quantities for possible use as international reference preparations.

The Committee was informed that field trials of typhoid vaccine were being organized in British Guiana and in Yugoslavia by the national

¹ *Wld Hlth Org. techn. Rep. Ser.*, 1959, **180**, 6, 19

² *Wld Hlth Org. techn. Rep. Ser.*, 1959, **172**, 14

³ Unpublished working document WHO/BS/452

⁴ Unpublished working document WHO/BS/468 and Addendum 1

⁵ Unpublished working document WHO/BS/469

health authorities in co-operation with the World Health Organization, and that agreement had been obtained on the inclusion in these trials of the vaccines mentioned above. Since these trials may prove the protective power in man of one or both of these vaccines, the Committee requested the Statens Seruminstitut, Copenhagen, to arrange collaborative laboratory studies of these same vaccines by a variety of methods in an attempt ultimately to select a laboratory assay which will predict the protective value of typhoid vaccine in man. The Committee recognized that further field trials involving various vaccines will be necessary in order to obtain a valid foundation for the laboratory evaluation of typhoid vaccines; it nevertheless considered that the establishment of an international reference preparation of proven protective value in man would be a major achievement.

ANTIBODIES

33. Anti-Leptospira Sera

The Committee noted that the Statens Seruminstitut, Copenhagen, has already received a stock of 12 of the 19 International Reference Preparations of Anti-Leptospira Sera that were established in 1958,¹ and that a further collection of 18 anti-leptospira sera has been prepared by the WHO/FAO International Leptospira Reference Laboratories. The Committee also noted that a collaborative study of the suitability of these sera for use as international reference preparations is in progress and that the Committee would be asked to consider the results of this investigation.

34. Anti-Poliomyelitis Sera

The Committee noted that the Statens Seruminstitut, Copenhagen, had obtained materials suitable for serving as international standards for anti-poliomyelitis sera of types 1, 2 and 3, to replace the existing International Reference Preparations.² It asked the Statens Seruminstitut to arrange a collaborative assay for this purpose.

35. Anti-Streptolysin O

The Committee noted the final report on the collaborative assay of the proposed international standard for anti-streptolysin O,³ and established

¹ Unpublished working documents WHO/BS/462 & WHO/BS/489

² Unpublished working document WHO/BS/483

³ Unpublished working document WHO/BS/482, Rev. 1

this preparation as the International Standard for Anti-Streptolysin O. The Committee asked the Statens Seruminstitut, Copenhagen, to define the international unit with the agreement of the participants in the collaborative assay.

36. Anti-Tick-Borne-Encephalitis Serum

The Committee considered the opinions obtained by the Statens Seruminstitut, Copenhagen, from a number of experts concerning the selection of material suitable for use as an international reference preparation of anti-tick-borne-encephalitis serum.¹ The Committee agreed that it would be useful to establish one reference serum for the characterization of this whole group of viruses, and it asked the Statens Seruminstitut to collect immune sera from several animal species and to distribute these sera for a limited investigation to various laboratories in order to obtain agreement on the selection of the most suitable material.

37. Anti-Toxoplasma Serum

The Committee was informed of the discussions concerning the establishment of an international reference preparation of anti-toxoplasma serum which took place at a conference held in Copenhagen in 1959 on the Laboratory Diagnosis of Toxoplasmosis in Man and Animals.² It noted that the selection of a serum suitable for use in the Sabin-Feldman dye-test, as well as in the complement fixation test and the haemagglutination test would necessitate a collaborative study of sera obtained from human cases as well as from experimental animals infected with various strains of toxoplasma. The Committee asked the Statens Seruminstitut, Copenhagen, to proceed with the collection of suitable sera for this study.

38. Anti-Vaccinia Gamma Globulin

The Committee noted that the Study Group on Requirements for Smallpox Vaccine had expressed the opinion that there is a need for the provision of an international standard for anti-vaccinia gamma globulin.³ It also noted the opinion expressed on this matter by the Lister Institute of Preventive Medicine, Elstree, Herts.⁴ The Committee asked the National Institute for Medical Research, London, in consultation with the Lister

¹ Unpublished working document WHO/BS/463

² Unpublished working document WHO/BS/496

³ *Wld Hlth Org. techn. Rep. Ser.*, 1959, **180**, 5

⁴ Unpublished working document WHO/BS/454

Institute of Preventive Medicine, the Metchnikov Institute, Moscow, the National Institutes of Health, Bethesda, and the Rijks Instituut voor de Volksgezondheid, Utrecht, to obtain a preparation, either of serum or of gamma globulin, suitable for use in assays of anti-vaccinia gamma globulin intended for the prophylaxis and treatment of smallpox and post-vaccination complications, and to arrange a collaborative study on the methods of titration of virus neutralizing antibodies.

39. Anti-Yellow-Fever Serum

The Committee noted the progress made by the Statens Seruminstitut, Copenhagen, and the West African Council for Medical Research, Lagos, Nigeria, in arranging the collaborative examination of the proposed international reference preparation of anti-yellow-fever serum.¹

40. Blood-Typing Sera

The Committee noted a report from the International Blood Group Reference Laboratory, London,² on a collaborative assay of six albumin-potentiated anti-Rh₀ (Anti-D) blood-typing sera carried out in ten laboratories. The report expressed concern about the low degree of consistency in the results of tests carried out by laboratories known to maintain the highest possible standards of accuracy. The Committee also noted that a preliminary analysis of the results had indicated that the variation among laboratories was less for relative potencies than for actual titres. The Committee therefore decided to ask the National Institute for Medical Research, London, to consult with the International Blood Group Reference Laboratory concerning the establishment of an international standard for albumin-potentiated anti-Rh₀ (Anti-D) blood-typing serum on the basis of these findings.

41. *Clostridium Botulinum*, Types A, B, C, D, and E Antitoxins

The Committee was of the opinion that there was a need for international standards for *Clostridium botulinum* antitoxins of types A, B, C, D and E. The Committee noted that the National Institute for Medical Research, London,³ had obtained suitable quantities of sera which might serve as international standards for each of these five antitoxins, and it asked the National Institute for Medical Research to arrange collaborative assays.

¹ Unpublished working documents WHO/BS/464 and Addendum 1

² Unpublished working document WHO/BS/453 Rev. 1, Addendum 1

³ Unpublished working document WHO/BS/485

42. *Clostridium welchii* (*Cl. perfringens*) Type A Antitoxin

The Committee noted that the stock of the fourth International Standard for *Clostridium welchii* (*Cl. perfringens*) type A antitoxin was almost exhausted, and that material suitable for its replacement had been obtained by the National Institute for Medical Research, London. The Committee requested the National Institute for Medical Research to arrange a collaborative assay.

43. *Naja* Antivenin

The Committee noted that, following the request made in its tenth report,¹ the World Health Organization had received offers of quantities of *Naja* antivenins as well as samples of dried *Naja* venoms from different geographical areas. The Committee also noted a report² from the School of Tropical Medicine, Calcutta, on the need for the establishment of an international standard for *Naja* antivenin which may be used in the assay of the potency of *Naja* antivenin preparations against venoms of the genus *Naja*. The Committee requested the School of Tropical Medicine, in consultation with the Secretariat, to obtain a sufficient quantity of *Naja* antivenin suitable for serving as an international standard, as well as samples of other *Naja* antivenins and venoms, and to arrange an international collaborative assay.

44. *Staphylococcus* Toxins and Antitoxins

The Committee noted a suggestion of the President of the International Association of Microbiological Societies that an investigation should be initiated into the practicability of establishing international standards based on *staphylococcus* leucocidins and antileucocidins. In view of the importance of *staphylococcus* problems at the present time, the Committee was of the opinion that the question concerning the establishment of further international standards and reference preparations for *staphylococcal* products should be assessed, and it therefore asked the National Institute for Medical Research, London, to examine this question in consultation with the Sir William Dunn School of Pathology, Oxford, and with other institutes working in this field.

¹ *Wld Hlth Org. techn. Rep. Ser.*, 1957, 127, 10

² Unpublished working document WHO/BS/471

45. Syphilitic Human Serum

The Committee noted that a collaborative investigation was in progress concerning the suitability of the International Standard for Syphilitic Human Serum for use in the *Treponema pallidum* immobilization test.¹

46. Trichinosis and Echinococcosis Sera

The Committee noted that there is a need for international reference preparations of trichinosis and echinococcosis sera for diagnostic purposes,² and it asked the Statens Seruminstitut, Copenhagen, to investigate the possibility of obtaining suitable material.

VETERINARY STANDARDS

47. Newcastle Disease Vaccine

The Committee noted a request by the Sixteenth International Veterinary Congress held in Madrid in 1959 for an international standard for Newcastle disease vaccine. Since both live and killed vaccines are in widespread use the Committee asked the Central Veterinary Laboratory, Weybridge, to consult with the Statens Seruminstitut, Copenhagen, the State Control Institute of Veterinary Biological Preparations, Moscow, the Paul-Ehrlich Institut, Frankfurt, and the United States Department of Agriculture, Agricultural Research Service, Beltsville, Maryland, concerning the practicability of using one preparation for the assay of both types of vaccine. In the event of an affirmative decision, the Committee also requested the Central Veterinary Laboratory to obtain suitable material and to arrange a collaborative assay.

48. Swine Erysipelas Vaccine

The Committee noted that the laboratory which had obtained discordant results in the collaborative assay of swine erysipelas vaccine had repeated its tests and that the results now available from all the five participating laboratories were in agreement.³ The Committee therefore established the

¹ Unpublished working document WHO/BS/465

² Unpublished working document WHO/BS/470

³ Unpublished working documents WHO/BS/486 and Addendum 1

material as the International Standard for Swine Erysipelas Vaccine and asked the Statens Seruminstitut, Copenhagen, in consultation with the Central Veterinary Laboratory, Weybridge, and the Paul-Ehrlich Institut, Frankfurt, and with the agreement of the participants in the collaborative assay, to define as the international unit for swine erysipelas vaccine the quantity of the International Standard which has been shown to have the same activity as the existing German unit.

49. Other Immunological Substances for Veterinary Use

The Committee noted a request¹ by the Sixteenth International Veterinary Congress, held in Madrid in 1959, for the establishment of international standards for a number of toxoids, antitoxins and vaccines. The Committee agreed with the suggestion that priority should be given to anthrax vaccine, sheep pox vaccine, *Clostridium oedematiens* (alpha) toxoid, and anti-swine-fever serum.

The Committee asked the Central Veterinary Laboratory, Weybridge, to investigate, in consultation with the Statens Seruminstitut, Copenhagen, whether this request could be implemented and, in the event of an affirmative decision, to obtain suitable material and to arrange collaborative assays.

BIOLOGICAL DIAGNOSTIC REAGENTS

50. Diagnostic Reagents

The Committee was informed of the plans that have been made for increasing WHO activities in the field of medical research, an important part of which would be the servicing of research throughout the world by providing certain materials such as reagents used in the diagnosis of disease. Though these projects might involve the preparation and large-scale distribution of a wide variety of reagents, the Committee would be asked to concern itself exclusively with the specification and standardization aspects. International standards or reference preparations are needed in order to relate the results of laboratory tests carried out in various parts of the world and to enable batches of diagnostic reagents produced in different laboratories for distribution within particular geographical areas to be calibrated against a common standard.

The Expert Committee on Biological Standardization has already established several international standards and reference preparations for

¹ Unpublished working document WHO/BS/487

biological substances used in diagnosis and, though the Committee realized that the proposed distribution of diagnostic reagents might be on a much larger scale, it expressed its willingness to accept responsibility for this WHO service.

The Committee stressed that the standardization of diagnostic reagents must be dealt with according to the principles followed for other substances. The preparation of material proposed for adoption as an international standard or reference preparation should be undertaken only by laboratories which have shown special competence in the particular field; further, before any material can be established as an international standard or reference preparation it should be submitted to stability tests and a collaborative assay by a number of expert laboratories, and an analysis of the results examined by an Expert Committee on Biological Standardization. A laboratory designated by the World Health Organization should then hold a stock of the established international standard or reference preparation in order to ensure continuity of purity, potency, and specificity. To enable the Committee to cope with this extensive task, the advice of groups of experts in the standardization aspects of the necessary preliminary work would have to be sought. These experts would present the Committee with an analysis of the collaborative investigations on which the Committee would base the establishment of international standards or reference preparations for diagnostic reagents.

The Committee recognized that the number of different diagnostic reagents which might be required included a great variety of substances, such as sera against various micro-organisms, other diagnostic sera, bacterial and viral antigens, bacteriophages, microbial strains, and cell lines for tissue culture. The Committee agreed, however, that the programme should initially be confined to reagents used in epidemiological studies of viral diseases, since the need for such reagents is becoming increasingly urgent and in many countries they are difficult to prepare or obtain. The Committee also agreed that in any antigen-antibody system used in the identification of viruses, the standard or reference preparation should be the antibody. Most sera are stable, especially in the freeze-dried form, and they can be prepared in large, homogeneous quantities. Antigens which may be needed in relation to these sera should be controlled by means of the appropriate serum standard or reference preparation. The Committee recommended, therefore, that in the first place the work should be directed towards the provision of international standards or reference preparations for sera used in the grouping and typing of a large number of viruses.

REQUIREMENTS FOR BIOLOGICAL SUBSTANCES

51. Requirements for Smallpox Vaccine

The Committee studied the requirements for smallpox vaccine formulated by a study group,¹ and suggested a few minor amendments. The Committee agreed that these requirements represented a useful contribution towards the effective control of smallpox vaccine produced in different laboratories throughout the world.

Acting on a recommendation of the study group, the Committee made the necessary arrangements for the establishment of an international standard for anti-vaccinia gamma globulin, as outlined in section 38 of the present report (page 17).

52. General Requirements for the Sterility of Biological Substances

The Committee studied the General Requirements for the Sterility of Biological Substances formulated by a study group,² and suggested a few minor amendments. The Committee agreed that the text represented a satisfactory formulation of the general requirements for sterility which should be met by biological substances used in human medicine.

¹ *Wld Hlth Org. techn. Rep. Ser.*, 1959, **180**

² Unpublished working document WHO/BS/IR/76



Annex

**I. INTERNATIONAL BIOLOGICAL STANDARDS
AND
INTERNATIONAL BIOLOGICAL REFERENCE PREPARATIONS
1960**

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 in all countries. Such samples are intended for use in laboratory assays only and must not be administered to humans unless by special authorization.

A. IMMUNOLOGICAL

Held by the International Laboratory for Biological Standards,

Substance	International Unit of present standard (mg)	Form in which dispensed
ANTIGENS		
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, 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)
Cholera antigen (Inaba)	—	Ampoules containing approximately 100 mg of dried antigen

SUBSTANCES

Statens Seruminstitut, 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, 11 , 10; <i>Bull. Wld Hlth Org.</i> , 1952, 7 , 171; 1954, 10 , 989; 1955, 12 , 179; <i>Bull. Hlth Org. L. o. N.</i> , 1935, 4 , 475, 514; <i>Pharmacopoea Internationalis</i> , 1951, Vol. I, 257, 354; WHO/BS 3, 16, 28, 64, 120
<i>Ist Standard</i> 1951	<i>Bull. Wld Hlth Org.</i> , 1952, 7 , 171; 1954, 10 , 989; 1955, 12 , 179; 1958, 19 , 759; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1952, 56 , 6; 1960, 187 , 13; WHO/BS 3, 16, 28, 64, 106, 120, 127, 173, 181, 488
<i>Ist Standard</i> 1954	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1955, 96 , 11; 1960, 187 , 13; WHO/BS 126, 181, 227, 293, 293 Add. 1 and 2
<i>Ist Standard</i> 1951	<i>Bull. Wld Hlth Org.</i> , 1953, 9 , 837, 843; 1955, 12 , 761; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1952, 56 , 5; WHO/BS 25, 37, 48, 68, 83, 92, 125, 192, 194, 214, 382
<i>Ist Standard</i> 1951	<i>Bull. Wld Hlth Org.</i> , 1949, 2 , 49; 1953, 9 , 829, 843; 1955, 12 , 751; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1952, 56 , 4; 1953, 61 , 1; WHO/BS 4, 13, 19, 32, 48, 68, 79, 83, 86, 102, 108, 113, 191, 193, 214, 215, 248, 288, 330, 331
<i>Ist Standard</i> 1955	<i>Bull. Wld Hlth Org.</i> , 1949, 2 , 49; 1953, 9 , 829, 843; 1954, 10 , 951, 983; 1955, 12 , 751; 1955, 13 , 473; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1953, 61 , 1; 1956, 108 , 8; WHO/BS 4, 13, 19, 32, 48, 68, 79, 83, 86, 102, 108, 113, 191, 193, 214, 215, 248, 288, 330, 331
<i>Ist Standard</i> 1954	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1955, 96 , 7; WHO/BS 229, 247, 274, 275, 275 Add. 1 and 2
<i>Ist Standard</i> 1957	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1957, 127 , 5; 1958, 147 , 11; WHO/BS 5, 54, 62, 81, 88, 96, 123, 203, 216, 251, 259, 282, 287, 302, 338, 401, 408
<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 52, 130, 167, 222, 255

Substance	International Unit of present standard (mg)	Form in which dispensed
Antigens (contd)		
Cholera antigen (Ogawa)	—	Ampoules containing approximately 100 mg of dried antigen
Cholera vaccine (Inaba)	—	Ampoules containing 20 mg of dried vaccine (1.6×10^{10} organisms per ampoule)
Cholera vaccine (Ogawa)	—	Ampoules containing 20 mg of dried vaccine (1.6×10^{10} organisms per ampoule)
Cardiolipin	—	Ampoules containing 4 ml, 8 ml or 16 ml of a solution of purified cardiolipin in ethanol.
Lecithin (beef heart)	—	(6.4 mg cardiolipin per ml, as calculated from the phosphorus content).
Lecithin (egg)	—	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)
Swine erysipelas vaccine	—	Ampoules containing 510 mg of dried vaccine, derived from formalin-treated <i>Erysipelas rhusiopathiae</i> type B, adsorbed to aluminium hydroxide
ANTIBODIES		
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)

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, 12 , 945; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1954, 86 , 7; WHO/BS 52, 130, 167, 222, 255
<i>1st Reference Preparation</i> 1953	<i>Bull. Wld Hlth Org.</i> , 1950, 3 , 43; 1955, 12 , 945; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1954, 86 , 7; 1959, 179 , 10, 33, 43; 1960, 187 , 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, 3 , 43; 1955, 12 , 945; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1954, 86 , 7; 1959, 179 , 10, 33, 43; 1960, 187 , 12; WHO/BS 23, 36, 41, 52, 69, 82, 87, 87 Add.1, 107, 130, 222, 255, 342, 410; WHO/BS/IR/58
1st Reference Preparation 1951 2nd Reference Preparation 1953 3rd Reference Preparation 1958	<i>Bull. Wld Hlth Org.</i> , 1951, 4 , 151; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1952, 56 , 8; 1958, 147 , 14; <i>Cardiolipin antigens</i> , 1955 (WHO Monograph No. 6); WHO/BS 72, 117, 238, 278, 278 Add.1, 305, 360, 414, 420
1st Reference Preparation 1951 2nd Reference Preparation 1953	<i>Bull. Wld Hlth Org.</i> , 1951, 4 , 151; 1955, 13 , 323; 1956, 14 , 567, 577; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1952, 56 , 8, <i>Cardiolipin antigens</i> , 1955 (WHO Monograph No. 6); WHO/BS 72, 238, 278, 278 Add.1, 305
1st Reference Preparation 1951 2nd Reference Preparation 1953 3rd Reference Preparation 1959	<i>Bull. Wld Hlth Org.</i> , 1951, 4 , 151; 1955, 13 , 323; 1956, 14 , 567, 577; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1952, 56 , 8; 1959, 172 , 14; 1960, 187 , 13; <i>Cardiolipin antigens</i> , 1955 (WHO Monograph No. 6); WHO/BS 72, 238, 278, 278 Add.1, 305, 360, 440, 456
<i>1st Standard</i> 1959	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1960, 187 , 20; WHO/BS 344, 377, 435, 436, 486, 486 Add.1
<i>1st Standard</i> 1928	<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</i> 1922	<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

Substance	International Unit of present standard (mg)	Form in which dispensed
Antibodies (contd)		
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)
Clostridium welchii (perfringens) type B antitoxin	0.0137	Ampoules containing 68.5 mg of dried hyperimmune horse serum (5000 I.U. per ampoule)
Clostridium welchii (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>)	0.118	Ampoules 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)
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 α 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)

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> 1928	<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</i> 1953	<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</i> 1954	<i>Bull. Wld Hlth Org.</i> , 1956, 14 , 557; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1955, 96 , 6; WHO/BS 281, 283, 298, 303, 343
<i>1st Standard</i> 1954	<i>Bull. Wld Hlth Org.</i> , 1956, 14 , 557; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1955, 96 , 6; WHO/BS 281, 283, 298, 303, 343
1st Standard 1934 (0.2377 mg) 2nd Standard 1947 (0.0974 mg) <i>3rd Standard</i> 1957	<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>Pharmacopoea Internationalis</i> , 1951, Vol. I, 210, 334; WHO/BS 318, 367, 384
1st Standard 1934 (0.2681 mg) <i>2nd Standard</i> 1952	<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
1st Standard 1935 (0.3575 mg) <i>2nd Standard</i> 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) <i>2nd Standard</i> 1938	<i>Bull. Hlth Org. L. o. N.</i> , 1935, 4 , 6, 68, 514; 1938, 7 , 702, 845; 1945/46, 12 , 32

Substance	International Unit of present standard (mg)	Form in which dispensed
Antibodies (contd)		
Scarlet fever streptococcus anti-toxin	0.049	Ampoules containing 490 mg of dried hyper-immune horse serum (10 000 I.U. per ampoule)
Anti-streptolysin O	—	Ampoules containing 46 mg of dried human serum
Swine erysipelas serum (anti-N)	0.14	Ampoules containing 87.9 mg of dried hyper-immune 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 hyper-immune 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

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> 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>Wld Hlth Org. techn. Rep. Ser.</i> , 1960, 187, 16; WHO/BS/402, 443, 482, Rev. 1.
<i>1st Standard</i> 1954	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1955, 96, 10; 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
<i>1st 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, 375
<i>1st 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>1st 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>1st Standard</i> 1958	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1958, 147, 16; WHO/BS 239, 289 Rev.1, 304, 341, 379, 380 Rev.1, 439, 465
<i>1st Reference Preparation</i> 1953	<i>Bull. Wld Hlth Org.</i> , 1955, 12, 945; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1954, 86, 7; 1959, 179, 33, 45; WHO/BS 40, 98, 130, 167, 222, 255

Substance	International Unit of present standard (mg)	Form in which dispensed
Antibodies (contd)		
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
Anti- <i>Leptospira saxkoebing</i> serum	—	
Anti- <i>Leptospira ballum</i> AB serum	—	
Anti- <i>Leptospira canicola</i> serum	—	
Anti- <i>Leptospira sejroe</i> serum	—	Ampoules containing 0.5 ml or 1.0 ml of hyperimmune rabbit serum, dried
Anti- <i>Leptospira mini</i> AB serum	—	
Anti- <i>Leptospira grippityphosa</i> serum	—	
Anti- <i>Leptospira australis</i> A serum	—	

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, 12 , 945; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1954, 86 , 7; 1959, 179 , 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, 1 , 9; <i>Bull. Hlth Org. L. o. N.</i> , 1936, 5 , 577, 695; 1938, 7 , 712, 859; 1945/46, 12 , 12; WHO/BS 318, 359
<i>1st Reference Preparation</i> 1952	<i>Bull. Wld Hlth Org.</i> , 1954, 10 , 911; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1953, 68 , 10; WHO/BS 182, 226
<i>1st Reference Preparation</i> 1958	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1959, 172 , 15; 1959, 178 , 18; WHO/BS 313, 361, 363, 385, 433, 444, 475, 483
<i>1st Reference Preparation</i> 1958	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1959, 172 , 15; 1959, 178 , 18; WHO/BS 313, 361, 363, 385, 433, 444, 475, 483
<i>1st Reference Preparation</i> 1958	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1959, 172 , 15; 1959, 178 , 18; WHO/BS 313, 361, 363, 385, 433, 444, 475, 483
<i>1st Reference Preparation</i> 1958	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1956, 113 ; WHO/BS 413, 437

Substance	International Unit of present standard (mg)	Form in which dispensed
Antibodies (contd)		
Anti- <i>Leptospira icterohaemorrhagiae</i> AB serum	---	Ampoules containing 0.5 ml or 1.0 ml of hyperimmune rabbit serum, dried
Anti- <i>Leptospira icterohaemorrhagiae</i> A serum	---	
Anti- <i>Leptospira hyos</i> serum	---	
Anti- <i>Leptospira autumnalis</i> AB serum	---	
Anti- <i>Leptospira autumnalis</i> A serum	---	
Anti- <i>Leptospira pomona</i> serum	---	
Anti- <i>Leptospira bataviae</i> serum	---	
Anti- <i>Leptospira semaranga</i> serum	---	
Anti- <i>Leptospira hebdomadis</i> serum	---	
Anti- <i>Leptospira andamana</i> serum	---	
Anti- <i>Leptospira javanica</i> serum	---	
Anti- <i>Leptospira pyrogenes</i> serum	---	
MISCELLANEOUS		
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 (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., 1956, 113; WHO/BS 413, 437</i>
<i>1st Reference Preparation 1953</i>	<i>Bull. Wld Hlth Org., 1955, 12, 769; Wld Hlth Org. techn. Rep. Ser., 1954, 86, 14; WHO/BS 124, 172, 198, 256</i>

B. PHARMACOLOGICAL

Held by the International Laboratory for Biological Standards,

Substance	International Unit of present standard (mg)	Form in which dispensed
ANTIBIOTICS		
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)
Polymyxin B	0.000127	Ampoules containing 19 mg of purified polymyxin B sulfate (7874 I.U. per mg)

SUBSTANCES

National Institute for Medical Research, London, 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, 9, 15; <i>Bull. Hlth Org. L. o. N.</i> , 1945/46, 12, 181; <i>Pharmacopoea Internationalis</i> , 1955, Vol. II, 23, 277; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1960, 187, 7; WHO/BS 10, 15, 67, 94, 121, 170, 349 Rev.1, 404
1st Standard 1957	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1957, 127, 14; 1958, 147, 7; WHO/BS 399
1st Standard 1950 (0.001282 mg) 2nd Standard 1958	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1951, 36, 9; 1958, 147, 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, 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, 481
1st Standard 1957	<i>Bull. Wld Hlth Org.</i> , 1957, 17, 521; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1957, 127, 13; 1958, 147, 6; WHO/BS 323, 370, 396, 396 Annex 1
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 1957	<i>Bull. Wld Hlth Org.</i> , 1957, 17, 527; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1957, 127, 13; 1958, 147, 6; WHO/BS 322, 368, 397, 397 Annex 1
1st Standard 1955	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1956, 108, 14; WHO/BS 263, 326

Substance	International Unit of present standard (mg)	Form in which dispensed
Antibiotics (contd)		
Amphotericin B	—	Ampoules in preparation
Kanamycin	—	Ampoules in preparation
Vancomycin	—	Ampoules in preparation
Viomycin	—	Ampoules containing 35 mg of Viomycin
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 in preparation
Novobiocin	—	Ampoules in preparation
Oleandomycin	—	Ampoules in preparation
HORMONES		
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)
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)

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> 1959	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1960, 187 , 5; WHO/BS/450, 478
<i>1st Reference Preparation</i> 1959	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1960, 187 , 6; WHO/BS/450, 478
<i>1st Reference Preparation</i> 1959	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1960, 187 , 9; WHO/BS 450, 478
<i>1st Reference Preparation</i> 1959	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1960, 187 , 9; WHO/BS/493
<i>1st Reference Preparation</i> 1951	<i>Bull. Wld Hlth Org.</i> , 1954, 10 , 895; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1952, 56 , 11; WHO/BS 132
<i>1st Reference Preparation</i> 1958	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1958, 147 , 6; WHO/BS 347, 398, 428, 491
<i>1st Reference Preparation</i> 1958	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1958, 147 , 8; WHO/BS 347, 429, 476
<i>1st Reference Preparation</i> 1958	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1958, 147 , 6; WHO/BS/394, 431, 472
<i>1st Reference Preparation</i> 1958	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1958, 147 , 8; WHO/BS 430, 477
1st Standard 1925 (0.5 mg) 2nd Standard 1942 (0.5 mg) 3rd Standard 1957	<i>Bull. Wld Hlth Org.</i> , 1947/48, 1 , 9; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1957, 127 , 15; 1958, 147 , 8; <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; WHO/BS 351, 352, 395, 480
<i>1st Standard</i> 1939	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1957, 127 , 16; <i>Bull. Hlth Org. L. o. N.</i> , 1939, 8 , 901; 1942/43, 10 , 96; 1945/46, 12 , 62; WHO/BS 208, 310, 350, 405, 446, 492
1st Standard 1950 (1.00 mg) 2nd Standard 1955	<i>Bull. Wld Hlth Org.</i> , 1956, 14 , 543; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1951, 36 , 7; 1958, 147 , 8; WHO/BS 85, 156, 158, 249, 262, 308, 356, 386, 387, 432, 473

Substance	International Unit of present standard (mg)	Form in which dispensed
Hormones (contd)		
Thyrotrophin	13.5	Ampoules 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 in preparation
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)
MISCELLANEOUS		
Vitamin D ₃	0.000025	Bottles containing 10 g of a solution of vitamin D ₃ in vegetable oil (1000 I.U. per g)
Vitamin B ₁₂	—	Ampoules containing ten 20-mg tablets of cyanocobalamin

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> 1954	<i>Bull. Wld Hlthg. Or.</i> , 1955, 13 , 917; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1955, 96 , 14; 1956, 108 , 16; WHO/BS 1955, 158, 210, 284, 309
<i>1st Standard</i> 1955	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1956, 108 , 16; WHO/BS 140, 158, 250, 320
<i>1st Reference Preparation</i> 1959	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1959, 172 , 9; 1960, 187 , 9; WHO/BS/329, 434, 474
<i>1st Standard</i> 1939	<i>Bull. Hlth Org. L. o. N.</i> , 1939, 8 , 887, 898; 1945/46, 12 , 60; <i>Pharmacopoea Internationalis</i> , 1955, Vol. II, 98, 263
<i>1st Standard</i> 1939	<i>Bull. Hlth Org. L. o. N.</i> , 1939, 8 , 862, 884; 1945/46, 12 , 60; <i>Pharmacopoea Internationalis</i> , 1955, Vol. II, 98, 261; WHO/BS 93, 141
1st Standard 1925 (0.12500 mg) 2nd Standard 1935 (0.04550 mg) 3rd Standard 1952 (0.04082 mg) 4th Standard 1958	<i>Bull. Wld Hlth Org.</i> , 1952, 7 , 445; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1958, 147 , 9; <i>Bull. Hlth Org. L. o. N.</i> , 1935, 4 , 525; 1936, 5 , 575, 584; 1945/46, 12 , 44; <i>Pharmacopoea Internationalis</i> , 1955, Vol. II, 130, 264; WHO/BS 89, 116, 119, 137, 138, 204, 205, 267, 311, 357, 388, 427
1st Standard 1942 (0.0077 mg) 2nd Standard 1958	<i>Bull. Wld Hlth Org.</i> , 1947/48, 1 , 9; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1958, 147 , 10; <i>Bull. Hlth Org. L. o. N.</i> , 1942/43, 10 , 144, 151; 1945/46, 12 , 46; <i>Pharmacopoea Internationalis</i> , 1951, Vol. I, 104, 341; 1955, Vol. II, 126 WHO/BS 353, 390, 424
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
<i>1st Reference Preparation</i> 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

Substance	International Unit of present standard (mg)	Form in which dispensed
Miscellaneous (contd)		
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
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)
<i>1st Standard</i> 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) <i>3rd Standard</i> 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 <i>3rd Reference Preparation</i> 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 <i>3rd Reference Preparation</i> 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
<i>1st Reference Preparation</i> 1951	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1952, 56 , 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, 96 , 16; WHO/BS 134, 148, 202, 273
<i>1st Reference Preparation</i> 1954	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1955, 96 , 16; WHO/BS 134, 148, 202, 273
<i>1st Reference Preparation</i> 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
<i>1st Reference Preparation</i> 1954	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1955, 96 , 14; WHO/BS 261
<i>1st Reference Preparation</i> 1958	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1958, 147 , 11; WHO/BS 90, 147, 206, 264, 312, 365, 400, 425

**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)
BCG-vaccine	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1960, 187 , 12; WHO/BS/455
Newcastle disease vaccine	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1960, 187 , 20
Poliomyelitis vaccine	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1959, 178 , 5, 18; WHO/BS/235, 260, 321, 376, 376 Annex 1, 449, 459, 460, 466, 466 Add.1
Rabies vaccine	WHO/BS/372, 411, 411 Annex 1, 490
Smallpox vaccine	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1959, 180 , 4, 11; WHO/BS/14, 73, 105, 371, 381, 383, 417, 442, 461, 467
Tetanus toxoid, adsorbed	WHO/BS/452, 468, 468 Add.1, 469
Typhoid vaccine	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1958, 147 , 11; 1960, 187 , 15; WHO/BS 217, 291, 301, 340, 378, 409, 441
<i>Clostridium botulinum</i> Type A anti-toxin	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1960, 187 , 18; WHO/BS/485
<i>Clostridium botulinum</i> Type B anti-toxin	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1960, 187 , 18; WHO/BS/485
<i>Clostridium botulinum</i> Type C anti-toxin	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1960, 187 , 18; WHO/BS/485
<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	WHO/BS/316, 317, 333, 334, 364, 373
<i>Naja</i> antivenin	WHO/BS 316, 317, 333, 334, 364, 373, 471
Anti-Rh ₀ (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

Substance	References (WHO BS refers to unpublished working documents of the WHO Expert Committees on Biological Standardization)
Anti-toxoplasma human serum Anti-tick-borne encephalitis serum Anti-yellow-fever serum	WHO BS 447, 496 WHO BS 463 <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1957, 136, 9; 1959, 179, 12; WHO/BS/416, 438, 464, 464 Add.1
Anti-trichinosis serum	WHO/BS/470
Anti-echinococcosis serum	WHO/BS/470
Anti- <i>Leptospira mankarso</i> serum	WHO/BS 437, 489
Anti- <i>Leptospira muenchen</i> serum	WHO/BS 437, 489
Anti- <i>Leptospira naam</i> serum	WHO/BS 437, 489
Anti- <i>Leptospira poi</i> serum	WHO/BS 437, 489
Anti- <i>Leptospira sarmin</i> serum	WHO/BS 437, 489
Anti- <i>Leptospira schüffneri</i> serum	WHO/BS 437, 489
Anti- <i>Leptospira bangkinang</i> serum	WHO/BS 437, 489
Anti- <i>Leptospira celledoni</i> serum	WHO/BS 437, 489
Anti- <i>Leptospira cynopteri</i> serum	WHO/BS 437, 489
Anti- <i>Leptospira hardjo</i> serum	WHO/BS 437, 489
Anti- <i>Leptospira kremastos</i> serum	WHO/BS 437, 489
Anti- <i>Leptospira wolffii</i> serum	WHO/BS 437, 489
Anti- <i>Leptospira zanoni (australis B)</i> serum	WHO/BS 437, 489
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

B. PHARMACOLOGICAL SUBSTANCES

Substance	References (WHO/BS refers to unpublished working documents of the WHO Expert Committees on Biological Standardization)
Gramicidin	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1960, 187, 6; WHO/BS/450, 478
Leucomycin	WHO/BS/450, 478
Ristocetin	WHO/BS/450, 478
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
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 remaining stock of Staphylococcus β Antitoxin may be obtained on request from the International Laboratory for Biological Standards, Statens Seruminstitut, Copenhagen, Denmark, by laboratories desiring to establish their own working standard for research purposes.

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

Although there is no longer an International Standard for Vitamin A, the International Unit for Vitamin A is still used extensively. This Unit has therefore been redefined by the Expert Committee on Biological Standardization as the activity of 0.000344 mg of pure all-*trans* vitamin A acetate.¹

Substance	International Unit (mg)	Adopted	Discontinued
Arsphenamine	—	1925	1935
Ouabain	—	1928	1954
Provitamin A (β -carotene)	0.0006	1931	1956
Vitamin B (synthetic vitamin B ₁)	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 (α -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 β antitoxin	2.623	1952	1956
*Chloramphenicol	—	1953	1956

¹ *Wld Hlth Org. techn. Rep. Ser.*, 1960, **187**, 10

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Amphotericin	40	Ouabain	48
Androsterone	48	Oxophenarsine	44
Antidiuretic hormone	40	Oxytocic hormone	40
Arsphenamine	48	Penicillins	38, 40, 47
Bacitracin	38	Pertussis vaccine	26
BCG vaccine	46	Pneumococcus sera	32
Blood typing sera	32, 46	Poliomyelitis sera	34
Bruella serum	32	Poliomyelitis vaccine	46
Cardiolipin	28	Polymyxin	38
Chloramphenicol	48	Progesterone	48
Cholera antigen	26, 28	Prolactin	40
Cholera serum	32, 34	Protamine	44
Cholera vaccine	28	Pyrogen	44
Clostridium antitoxins	30, 46	Q-fever serum	32
Corticotrophin	40	Rabies serum	32
Digitalis	44	Rabies vaccine	46
Dimercaprol	44	Ristocetin	47
Diphtheria antitoxin	28, 34	Smallpox vaccine	46
Diphtheria toxin	26	Snake antivenins	46
Diphtheria toxoid	26	Staphylococcus antitoxins	30, 48
Dysentery antitoxin	30	Streptococcus antitoxins	32
Echinococcosis serum	47	Streptodornase	47
Erythromycin	38	Streptokinase	47
Gas-gangrene antitoxins	30	Streptomycins	38
Gonadotrophins	42	Sulfarsphenamine	44
Growth hormone	42	Swine erysipelas serum	32
Gramicidin	47	Swine erysipelas vaccine	28
Heparin	42	Syphilitic serum	32
Hyaluronidase	44	Tetanus antitoxin	28
Insulin	42	Tetanus toxoid	26, 46
Kanamycin	40	Tetracyclines	38
Lecithins	28	Thyrotrophin	42
Leptospira sera	34, 36, 47	Tick-borne encephalitis serum	47
Leucomycin	47	Toxoplasma serum	47
Melaminyl trypanocides	44	Trichinosis serum	47
Nearsphenamine	44	Tuberculins	26
Neomycin	40	Tubocurarine	48
Newcastle disease vaccine	46	Typhoid serum	34
Novobiocin	40	Typhoid vaccine	46
Nystatin	40	Vaccinia gamma globulin	46
Oestradiol	48	Vancomycin	40
Oestrone	48	Vasopressor hormone	40
Oleandomycin	40	Viomycin	40
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