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WORLD HEALTH ORGANIZATION

TECHNICAL REPORT SERIES

No. 259

**EXPERT COMMITTEE ON
BIOLOGICAL STANDARDIZATION**

Fifteenth Report

WORLD HEALTH ORGANIZATION

GENEVA

1963

EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION

Geneva, 10-15 December 1962

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EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION

Fifteenth Report

The Expert Committee on Biological Standardization met in Geneva from 10 to 15 December 1962.

Dr O. V. Baroyan, Assistant Director-General, on behalf of the Director-General, welcomed the members of the Committee, as well as the representative of the Food and Agriculture Organization of the United Nations. He stated that with the co-operation and concurrence of that Organization and of the Ministry of Agriculture, Fisheries and Food of Great Britain, a third International Laboratory for Biological Standards had now been designated at the Central Veterinary Laboratory, Weybridge, England. This International Laboratory would co-operate in the work of the existing international laboratories for biological standards at Copenhagen and London, but would devote its particular attention to the development of international biological standards that are primarily of veterinary importance.

The Assistant Director-General recalled the origins and growth of the work of the World Health Organization in establishing the many international biological standards now available. This work had been supervised by the fourteen Expert Committees that had met so far and had entailed the collaboration of several hundred participating laboratories throughout the world. In reviewing the extensive agenda before the present meeting he expressed his confidence that the Expert Committee would continue to maintain the high standard of work that had been established over the years.

GENERAL

In view of the increasing rate at which new prophylactic, therapeutic, and diagnostic biological substances are introduced in human and veterinary medicine, the Committee reconsidered its traditional procedures for establishing and distributing International Standards and International Reference Preparations, and for designating International Units of potency.

The expansion of the work supervised by the Committee in the veterinary field has now led to the nomination by WHO and FAO of a third International Laboratory for Biological Standards at the Central Veterinary Laboratory, Weybridge, England. In spite of this, the existing three Inter-

national Laboratories are not able to cope unaided with the work involved in elaborating and distributing all the International Standards and Reference Preparations that are being established and held under the auspices of the Committee. Thus, for example, it had already been necessary to solicit the aid of well-known laboratories in special fields for conducting collaborative assays of new preparations, such as snake-antivenins. For arrangements preceding the establishment of many other preparations the Committee depended on collaboration with the WHO Secretariat and with networks of designated WHO Reference Laboratories, as, for example, in the case of type-specific Leptospiral and Viral Sera. It was understood that, whenever it is expedient to adopt arrangements of this sort, the existing International Laboratories for Biological Standards should continue to be involved, at least in the sense that small quantities of the reference materials should be in the custody of those laboratories to ensure continuity when replacement of preparations becomes necessary.

Another aspect of the increasing rate and volume of the work of the Committee is the necessity of making standards or reference preparations of many substances available as soon as possible after such substances have been introduced into widespread use. If the establishment of International Units had to await the outcome and analysis of extensive collaborative assays there was a risk that an international unit-notation for expressing potencies would not be used universally—for example, in the case of new antibiotics, anti-poliovirus and anti-measles sera. During the years required to bring such assays to a successful completion, extensive work might already have been undertaken in many laboratories of the world and a practice of potency designation which differed from the later international one might already have become firmly entrenched.

The Committee considered that in cases where a sufficient quantity of a representative preparation of a substance had been obtained, it would be reasonable and expedient to designate international units of potency forthwith, and that the assignment of such international units might precede an extensive collaborative assay of the material. This procedure could be adopted in all cases where the Committee had reason to feel confident that the material collected was satisfactory and where a delay in introducing an international unit notation should be avoided.

The Committee upheld the distinction, described in its twelfth report,¹ between International Standards and International Reference Preparations, with the new proviso, following from the above reasoning, that an international unit can be assigned not only to an International Standard, but also to an International Reference Preparation, in spite of the fact that a preparation in the latter category might not at the time of its establishment have been extensively studied.

¹ *Wld Hlth Org. techn. Rep. Ser.*, 1959, 172

PHARMACOLOGICAL

ANTIBIOTICS

1. Neomycins

The Committee noted that the National Institute for Medical Research, London,¹ had been unable to obtain pure material to serve as an international standard for neomycin B, since all the samples examined contained variable amounts of other neomycins. In view of the fact that preparations of neomycin used clinically are mixtures of different neomycins, and that the existing International Reference Preparation of Neomycin was a representative sample of such preparations, the Committee considered that there was no need for an international standard for neomycin B. Instead, the Committee defined the International Unit for Neomycin as the activity contained in 0.00147 milligrams of the present International Reference Preparation of Neomycin.

2. Novobiocin

The Committee noted that the participants in the collaborative study of the International Reference Preparation of Novobiocin had not agreed on its suitability to serve as an international standard because of the wide discrepancy in the results of the assay between laboratories,² and that the National Institute for Medical Research, London, had therefore obtained a sample of purer material, a collaborative study of which was being arranged.

3. Ristocetins

The Committee noted¹ that these antibiotics had only limited use, and that the preparations that are used clinically are mixtures of different ristocetins. An examination of the present International Reference Preparation of Ristocetin had shown that it consisted predominantly of ristocetin B. The Committee therefore asked the National Institute for Medical Research, London, to ascertain whether this international reference preparation was suitable to serve as an international standard for mixed ristocetin preparations and if not, to obtain a more representative sample for this purpose.

¹ Unpublished working document WHO/BS/592

² Unpublished working document WHO/BS/595

4. Nystatin

The Committee noted that the collaborative assay of the International Reference Preparation of Nystatin had been completed¹ and that this material would be established as the International Standard for Nystatin and the international unit defined by the National Institute for Medical Research, London, with the agreement of the participants in the assay, in accordance with the authorization in the fourteenth report of the Committee.²

5. Gramicidin S

The Committee noted³ that a sample of gramicidin S had been received by the National Institute for Medical Research, London, from the Institute of Antibiotics, Academy of Medical Sciences, Moscow. The Committee decided, on the basis of the information provided by the Russian workers, to establish this material as the International Reference Preparation of Gramicidin S.

6. Gramicidin B

The Committee was informed that in accordance with the request made in its thirteenth report⁴ the National Institute for Medical Research, London, was trying to acquire a sample of gramicidin B to serve as an international standard, but that so far it had not obtained sufficiently pure material.

7. Spiramycin

The Committee noted that the National Institute for Medical Research, London,⁵ had obtained a sample of Spiramycin which, on the basis of the information received, was considered suitable to serve as an international reference preparation. The Committee therefore established this material as the International Reference Preparation of Spiramycin.

8. Bacitracin

The Committee noted that in accordance with the request made in its thirteenth report,⁴ the National Institute for Medical Research, London,

¹ Unpublished working document WHO/BS/580

² *Wld Hlth Org. techn. Rep. Ser.*, 1961, 222

³ Unpublished working document WHO/BS/594

⁴ *Wld Hlth Org. techn. Rep. Ser.*, 1960, 187

⁵ Unpublished working document WHO/BS/596

had obtained suitable material to replace the International Standard for Bacitracin¹ and that a collaborative assay of the proposed second international standard was in progress. The Committee authorized the National Institute for Medical Research to establish this material as the second International Standard for Bacitracin on the basis of the results of the collaborative assay, and to define the international unit with the agreement of the participants in the collaborative assay.

9. Dihydrostreptomycin

The Committee noted² that stocks of the International Standard for Dihydrostreptomycin would soon be exhausted and that material suitable for its replacement had been obtained. The Committee requested the National Institute for Medical Research, London, to arrange a collaborative assay.

10. Griseofulvin

The Committee was informed that in response to a request made in its fourteenth report³ the National Institute for Medical Research, London, had ascertained that there is no need to establish an international reference preparation of griseofulvin, since this antibiotic is assayed by chemical methods.

11. Demethylchlortetracycline

The Committee decided that there is a need for an international reference preparation of demethylchlortetracycline and noted² that a suitable sample of this antibiotic had been obtained by the National Institute for Medical Research, London. The Committee established this material as the International Reference Preparation of Demethylchlortetracycline and defined the International Unit as the activity contained in 0.001 milligram of the material.

12. Colistin

The Committee was informed that in accordance with a request in its fourteenth report³ the National Institute for Medical Research, London, had ascertained that there is a need for an international reference preparation of colistin, and that attempts were being made to obtain a quantity of suitable material.

¹ Unpublished working document WHO/BS/593

² Unpublished working document WHO/BS/592

³ *Wld Hlth Org. techn. Rep. Ser.*, 1961, 222

13. Triacetyloandomycin

The Committee was informed in response to a request made in its fourteenth report,¹ that there is a need for an international reference preparation of triacetyloandomycin, and it noted² that a suitable quantity of this antibiotic had been obtained by the National Institute for Medical Research, London. The Committee established this material as the International Reference Preparation of Triacetyloandomycin and defined the International Unit as the activity contained in 0.0012 milligram of the material.

14. Viomycin, Vancomycin, Kanamycin, Amphotericin B

The Committee noted² that there is a need to establish international standards for viomycin, vancomycin, kanamycin and amphotericin B, for which international reference preparations already exist. Until this could be done, the Committee assigned International Units for these substances as follows:

The International Unit for Viomycin is the activity contained in 0.00137 mg of the International Reference Preparation of Viomycin.

The International Unit for Vancomycin is the activity contained in 0.000993 mg of the International Reference Preparation of Vancomycin.

The International Unit for Kanamycin is the activity contained in 0.001232 mg of the International Reference Preparation of Kanamycin.

The International Unit for Amphotericin B is the activity contained in 0.001064 mg of the International Reference Preparation of Amphotericin B.

15. Semisynthetic Penicillins

The Committee noted that many of the semisynthetic penicillins that are in widespread clinical use are prepared in a highly pure state, and can be precisely assayed by chemical methods (e.g., methicillin, oxacillin,

¹ *Wld Hlth Org. techn. Rep. Ser.*, 1961, 222

² Unpublished working document WHO/BS/592

cloxacillin).¹ In view of this, international standards for these substances are not required. The Committee also noted that some of the semisynthetic penicillins exist in optically isomeric forms of differing biological activity (e.g., phenbenicillin, propicillin, phenethicillin).¹ The Committee was of the opinion that whereas international standards were not necessary for this group of semisynthetic penicillins, preparations of the pure substances and the pure optical isomers should be made internationally available by the WHO Centre for Authentic Chemical Substances, Stockholm. Such preparations would serve as a basis for the assessment of identity and purity of this group of penicillins.

The Committee also noted that in some preparations of semisynthetic penicillins used clinically, a high degree of purity is not normally achieved and estimation by biological assay is more reliable than by physical and chemical means (e.g., ampicillin).¹ The Committee considered that the provision of reference preparations for these substances was limited to the countries of manufacture and would be best served by the national control authorities in each case. International reference preparations were, therefore, not necessary.

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

The Committee considered the progress reports² of the National Institute for Medical Research, London, on studies relating to long-acting procaine benzylpenicillin in oil with aluminium monostearate (PAM). It observed that a sample of PAM, suitable for use as an international reference preparation was now available and established this material as the International Reference Preparation of Procaine Benzylpenicillin in Oil with Aluminium Monostearate (PAM).

The Committee noted that in accordance with the request made in its eighth report³ a laboratory assay method, including a suitable blood level duration test in rabbits permitting proper statistical assessment, had now been developed⁴ and that this test produced results comparable with those obtained in man. These methods may therefore form the basis of requirements for PAM preparations.

¹ Unpublished working document WHO/BS/610

² Unpublished working document WHO/BS/607; unpublished mimeographed report, WHO/VDT/304

³ *Wld Hlth Org. techn. Rep. Ser.*, 1955, 96

⁴ Unpublished working document WHO/BS/608

HORMONES AND ENZYMES**17. Prolactin**

The Committee noted that the analysis of the results of the collaborative assay had been completed¹ and that in accordance with the authorization given in its tenth report² the National Institute for Medical Research, London, had established the second International Standard for Prolactin and with the agreement of participants in the collaborative assay had defined the International Unit as the activity contained in 0.04545 mg of the material.

18. Chorionic Gonadotrophin

The Committee noted that in accordance with the request made in its fourteenth report³ the National Institute for Medical Research, London, had obtained material suitable for the proposed replacement of the International Standard for Chorionic Gonadotrophin⁴ and that a collaborative assay had been arranged. It authorized the National Institute for Medical Research, London, to establish the second International Standard for Chorionic Gonadotrophin and to define the international unit with the agreement of the participants in the collaborative assay.

19. Serum Gonadotrophin

The Committee noted that in accordance with the request made in its fourteenth report³ the National Institute for Medical Research, London, had obtained material suitable to serve as a proposed replacement for the International Standard for Serum Gonadotrophin⁵ and that a collaborative assay had been arranged.

20. Human Menopausal Gonadotrophin

The Committee was informed that the collaborative assay of the proposed International Standard for Human Menopausal Gonadotrophin³ had been completed, and that the analysis of results was in progress.

¹ Unpublished working document WHO/BS/577

² *Wld Hlth Org. techn. Rep. Ser.*, 1957, 127

³ *Wld Hlth Org. techn. Rep. Ser.*, 1961, 222

⁴ Unpublished working document WHO/BS/612

⁵ Unpublished working document WHO/BS/600

21. Corticotrophin

The Committee noted that in accordance with the authorization given in its twelfth report¹ the National Institute for Medical Research, London, had established the third International Standard for Corticotrophin² and with the agreement of the participants in the collaborative assay had defined the International Unit as the activity contained in 1 mg of this material.

22. Lysine Vasopressin

The Committee noted that there was a need for an international standard for lysine vasopressin for the assay of vasopressin in preparations of the posterior pituitary gland of the pig,³ and that the existing International Standard for Oxytocic, Vasopressor, and Antidiuretic Substances was unsuitable for use for this purpose, since this standard was prepared from the posterior pituitary gland of the ox and therefore contained arginine vasopressin. The Committee noted that the National Institute for Medical Research, London,³ had obtained a quantity of an acetone-dried powder of the posterior pituitary gland of the pig and had distributed it into ampoules. Preliminary studies had shown that this material was suitable to serve as an international standard. The Committee asked the National Institute for Medical Research, to arrange a collaborative study of this material with a view to establishing it as an international standard.

23. Human Growth Hormone

The Committee was informed that a preparation of growth hormone of human origin was available and it therefore asked the National Institute for Medical Research, London, to assess the need for an international standard for human growth hormone.

24. Streptokinase-Streptodornase

The Committee noted that in accordance with the request made in its fourteenth report⁴ the National Institute for Medical Research, London, had selected a preparation of streptokinase-streptodornase which on the basis of the information supplied was considered suitable for serving as

¹ *Wld Hlth Org. techn. Rep. Ser.*, 1959, 172

² Unpublished working document WHO/BS/548; *Bull. Wld Hlth Org.*, 27, 395

³ Unpublished working document WHO/BS/598

⁴ *Wld Hlth Org. techn. Rep. Ser.*, 1961, 222

an international standard.¹ The Committee asked the National Institute for Medical Research to arrange a collaborative assay of this material with a view to establishing it as an international standard.

IMMUNOLOGICAL

ANTIGENS

25. Anthrax Vaccine

The Committee noted that the material referred to in its fourteenth report² had been investigated for its suitability to serve as an international standard for anthrax vaccine.³ The preparation had been shown to give protection in laboratory animals but difficulties had arisen in the assay. The Committee asked the Central Veterinary Laboratory, Weybridge, to continue its studies with a view to devising a satisfactory assay method.

26. BCG Vaccine

The Committee noted the progress⁴ made towards the acquisition of a preparation of BCG vaccine suitable to serve as an international reference preparation. Several preparations obtained by the Secretariat from different countries had been examined for thermostability. These studies were being continued,⁵ and attempts would be made to correlate the allergenic properties of the preparations in man with the results obtained in animal tests.

27. Newcastle Disease Vaccine (Inactivated)

The Committee noted that the collaborative assay of the proposed international standard for Newcastle disease vaccine (inactivated) had been completed⁶ and authorized the Central Veterinary Laboratory, Weybridge, to establish this material as the International Standard for Newcastle Disease Vaccine (Inactivated) and, with the agreement of the participants in the collaborative assay, to define as the International Unit the amount of this material that is equivalent to the existing German unit.

¹ Unpublished working document WHO/BS/599

² *Wld Hlth Org. techn. Rep. Ser.*, 1961, 222

³ Unpublished working document WHO/BS/570

⁴ Unpublished working document WHO/BS/588

⁵ Unpublished working document WHO/BS/590

⁶ Unpublished working document WHO/BS/571 & Addendum. 1

28. Influenza Virus Vaccine

The Committee considered that an international reference preparation of influenza virus vaccine was impracticable because the strain composition of influenza virus vaccines designed to provide protection against influenza virus strains prevalent at any particular time could not be predicted.

The Committee was informed, however, that an international reference preparation of influenza virus vaccine might be useful in the haemagglutination test. The Committee asked the National Institute for Medical Research, London, to collect information regarding the possible value of such a preparation.

29. Poliomyelitis Vaccine (Inactivated)

The Committee noted that the collaborative assay of inactivated poliomyelitis vaccines was completed, and that the study had shown that the variability of estimations of potency between laboratories could be considerably reduced by using a reference preparation.¹ The Committee therefore established as the International Reference Preparation of Poliomyelitis Vaccine (Inactivated) the proposed fluid reference vaccine referred to in its fourteenth report.² The Committee stressed that this international reference preparation was intended only for the determination of the relative potencies of preparations of poliomyelitis vaccines (inactivated) and not for the assessment of other aspects of their quality.

The Committee noted that a quantity of highly purified trivalent vaccine had been obtained and that the Institute for Poliomyelitis Prophylactics, Moscow, and the Rijks Instituut voor de Volksgezondheid, Utrecht, had carried out studies³ of the effect of freeze-drying on the antigenic properties of this vaccine as well as of other trivalent vaccines. The former laboratory had been successful in freeze-drying the vaccines with satisfactory retention of the antigenic activity of the type 2 and type 3 components, whereas the latter laboratory had been successful in this respect with the type 1 and type 2 components.

The Committee asked the Statens Seruminstitut, Copenhagen, in collaboration with the Rijks Instituut voor de Volksgezondheid and the Institute for Poliomyelitis Prophylactics, to arrange for a continuation of this work with a view to obtaining a satisfactory freeze-dried preparation of trivalent poliomyelitis vaccine.

¹ Unpublished working document WHO/BS/565

² *Wld Hlth Org. techn. Rep. Ser.*, 1961, 222

³ Unpublished working documents WHO/BS/563, WHO/BS/583 & WHO/BS/613

30. Poliomyelitis Vaccine (Oral)

The Committee noted that Requirements for Poliomyelitis Vaccine (Oral)¹ had been published by the World Health Organization, but in view of the rapid developments in this field it stressed the need for early revision of these requirements.

The Committee considered that the establishment of international reference preparations of poliomyelitis vaccine (oral)² is at present impracticable.

31. Tuberculins

The Committee noted that investigations on the adsorption of tuberculins at interfaces had been continued³ and that the results obtained so far did not warrant a change of the decisions contained in its fourteenth report.⁴

The Committee was informed that the stock of the second International Standard for Old Tuberculin was running low and therefore asked the Statens Seruminstitut, Copenhagen, to obtain material suitable for the replacement of this standard. The Committee noted,³ with regard to the suggestion referred to in its fourteenth report,⁴ that there was no evidence at present for the instability of this standard.

In view of the present state of knowledge of tuberculins and their widespread use in the diagnosis of human and animal tuberculosis and in the assessment of results of BCG vaccination, the Committee requested the WHO Secretariat to make arrangements for the formulation of requirements for tuberculins.

In view of the fact that the assays for the definition of the International Unit of Purified Protein Derivative of Avian Tuberculin had been made under conditions that did not allow significant interface adsorption,⁵ the Committee decided not to change the definition of the international unit.

32. Rabies Vaccine

The Committee noted⁶ that the International Reference Preparation of Rabies Vaccine, established in 1960, had shown a loss of potency, that the issue of this preparation had been suspended, and that laboratories to which it had been distributed had been informed. The Committee

¹ *Wld Hlth Org. techn. Rep. Ser.*, 1962, 237

² Unpublished working document WHO/BS/605

³ Unpublished working documents WHO/BS/581, WHO/BS/591 & WHO/BS/597

⁴ *Wld Hlth Org. techn. Rep. Ser.*, 1961, 222

⁵ Unpublished working document WHO/BS/576

⁶ Unpublished working document WHO/BS/602

accordingly discontinued the International Reference Preparation of Rabies Vaccine.

The Committee further noted¹ that two new large quantities of freeze-dried material, one a rabbit brain suspension inactivated by ultraviolet light and the other a sheep brain suspension inactivated by phenol, had been obtained by the WHO Secretariat from the Division of Biologics Standards, National Institutes of Health, Bethesda, and the Antirabies Laboratory, Institute for Viral Prophylactics, Moscow, respectively. Collaborative studies had been initiated to select material suitable to serve as an international reference preparation.

33. Smallpox Vaccine

The Committee noted that the analysis of the results of the collaborative assay of the proposed international reference preparation of smallpox vaccine had been completed² and that in accordance with the authorization in the fourteenth report³ the Statens Seruminstitut, Copenhagen, had established the International Reference Preparation of Smallpox Vaccine with the agreement of the participants in the collaborative assay.

34. Typhoid Vaccine

The Committee was informed of the results of the field trials with the acetone-killed and the heat-phenol-killed typhoid vaccines.³ Both vaccines were effective in protecting against typhoid in man, but the acetone-killed vaccine had been found to be more effective than the heat-phenol-killed vaccine.

The Committee noted that the extensive collaborative laboratory studies of these and other vaccines used in the field trials had been completed⁴ but that none of the potency tests in animals showed a satisfactory quantitative correlation with the protective effectiveness against typhoid in man.

The Committee established the remaining quantities of these two materials as the International Reference Preparation of Typhoid Vaccine (Acetone-inactivated) and the International Reference Preparation of Typhoid Vaccine (Heat-phenol-inactivated).

¹ Unpublished working document WHO/BS/602

² Unpublished working document WHO/BS/546; *Bull. Wld Hlth Org.*, to be published

³ *Wld Hlth Org. techn. Rep. Ser.*, 1961, 222

⁴ Unpublished working documents WHO/BS/549-560 & WHO/BS/578; unpublished mimeographed report WHO/BD/TY/17

The Committee decided, however, that these two vaccines of proven efficacy in man were too valuable to be freely distributed and that they should be used for the purpose of developing a reliable assay method that would directly reflect the protective value of typhoid vaccine in man.

The Committee was also informed that a number of ampoules of the freeze-dried seed strain used in preparing both these vaccines were now in the custody of the Statens Seruminstitut, Copenhagen, and would be retained together with the international reference preparations.

35. Paratyphoid Vaccines

The Committee noted that field studies of paratyphoid vaccines were under consideration¹ and it was of the opinion that if such trials were made they should be along the lines of those undertaken with typhoid vaccines.

36. Tetanus Toxoid (Adsorbed)

The Committee noted that thermostability studies and potency tests on a pilot batch of tetanus toxoid (adsorbed) had been completed² and that such material would be suitable for determining the relative potency of other tetanus toxoid (adsorbed) preparations. The Committee was informed that the Paul Ehrlich Institut, Frankfurt, had provided a further quantity of material prepared in the same way as the pilot batch, and that in accordance with the request made in the fourteenth report³ collaborative studies would be arranged by the Rijks Instituut voor de Volksgezondheid, Utrecht, in collaboration with the Paul Ehrlich Institut and the Statens Seruminstitut, Copenhagen.

37. Cholera Vaccine

The Committee was informed of plans for WHO participation in proposed field trials of cholera vaccine in India to be conducted along lines similar to those undertaken for typhoid vaccine in other parts of the world.⁴ It is the intention that the trials should be linked with laboratory studies of the vaccines used in the field in order to select or to develop a laboratory assay that reflects the protective value of cholera vaccine in man.

¹ Unpublished working document WHO/BS/566

² Unpublished working document WHO/BS/586

³ *Wld Hlth Org. techn. Rep. Ser.*, 1961, 222

⁴ Unpublished mimeographed report WHO/BD/Ch./2

The Committee welcomed these proposals, as they might lead to the establishment of an international reference preparation of cholera vaccine of proven efficacy in man.

The Committee strongly urged that all preparations used in the planned trials should be prepared in a form and stored under conditions that ensured their stability, and that sufficient quantities be set aside to serve as international reference preparations if the trials prove to be successful. A sufficient number of ampoules containing, in the freeze-dried form, the seed strains from which the vaccines included in the trials are to be made, should likewise be stored on behalf of WHO.

The Committee emphasized that it would be possible to obtain maximum benefit from a successful trial in man only if these provisions were made for ensuring continuity and reproducibility of the vaccines under test.

Regarding problems of international standardization of other biological reagents relating to cholera, the Committee refers to its remarks under the section covering biological diagnostic reagents (page 27).

38. *Clostridium Oedematiens* (Alpha) Toxoid

The Committee noted that the Central Veterinary Laboratory, Weybridge, had been unable to obtain the quantity of material originally offered to serve as a proposed international standard for *Clostridium oedematiens* (alpha) toxoid.¹ The Committee was informed, however, that a quantity of material had been obtained from the Wellcome Research Laboratories, Beckenham, England, and that collaborative studies of this material would be carried out.

39. Pertussis Vaccine

The Committee noted that recent studies of the International Standard for Pertussis Vaccine had provided some results that might possibly be interpreted as showing that a loss of potency had occurred in this standard or that there was heterogeneity between ampoules.² The Committee considered that on the basis of all the information now available there was no proof of a change in this Standard, and asked the Statens Serum-institut, Copenhagen, to collect further information from laboratories investigating this problem.

40. *Schistosoma* Antigen for Skin-test

The Committee noted a suggestion of a Scientific Group³ for the provision of an international reference preparation of an antigen prepared

¹ Unpublished working document WHO/BS/569

² Unpublished working documents WHO/BS/606 & WHO/BS/611

³ Unpublished mimeographed report MHO/PA/66.61

from *Schistosoma* species for use in a diagnostic skin test. A quantity of freeze-dried material was available for this purpose and a collaborative study of this and a number of other preparations would be arranged by the WHO Secretariat. The Committee decided to assess the need for establishing an international reference preparation of this antigen when the results of these studies were available.

ANTIBODIES

41. Anti-*Leptospira* Sera

The Committee noted that a quantity of anti-*Leptospira semaranga* serum suitable for replacement of the first international reference preparation had been obtained and had been found satisfactory by the WHO Scientific Group on Research on Leptospirosis.¹ The Committee established this material as the second International Reference Preparation of Anti-*Leptospira semaranga* Serum.

The Committee noted that the stability of the International Reference Preparations of Anti-*Leptospira canicola* Serum, Anti-*Leptospira grippityphosa* Serum, and Anti-*Leptospira australis A* Serum was in doubt. The issue of these preparations had been suspended and further studies were in progress.¹

The Committee noted that the WHO/FAO Leptospirosis Laboratories had prepared a further number of type-specific anti-leptospira sera which had been subjected to collaborative studies and which were considered suitable by the WHO Scientific Group on Research on Leptospirosis to serve as international reference preparations.¹

The Committee therefore established the following international reference preparations of type-specific anti-leptospira sera:

International Reference Preparation of Anti-*Leptospira naam* Serum
International Reference Preparation of Anti-*Leptospira mankarso*
Serum

International Reference Preparation of Anti-*Leptospira sarmin* Serum
International Reference Preparation of Anti-*Leptospira poi* Serum
International Reference Preparation of Anti-*Leptospira schueffneri*
Serum

International Reference Preparation of Anti-*Leptospira muenchen* Serum
International Reference Preparation of Anti-*Leptospira cynopteri* Serum

¹ Unpublished working document WHO/BS/601; unpublished mimeographed report MHO/PA/44.62

International Reference Preparation of Anti-*Leptospira bangkinang* Serum

International Reference Preparation of Anti-*Leptospira wolffii* Serum

International Reference Preparation of Anti-*Leptospira hardjo* Serum

International Reference Preparation of Anti-*Leptospira kremastos* Serum

International Reference Preparation of Anti-*Leptospira benjamin* Serum

International Reference Preparation of Anti-*Leptospira zanoni* Serum

International Reference Preparation of Anti-*Leptospira medanensis* Serum

International Reference Preparation of Anti-*Leptospira paidjan* Serum

The Committee noted that a further collection of type-specific anti-leptospira sera had been prepared and would be studied.¹

42. Anti-Trichinella Human Serum

The Committee was informed that a collection of material had been made by the Communicable Disease Center, Atlanta, USA, and that the WHO Secretariat was making arrangements for a collaborative assay with a view to establishing the proposed international standard for anti-trichinella human serum.

43. Anti-Toxoplasma Serum

The Committee noted that the Statens Seruminstitut, Copenhagen, had obtained quantities of human serum and bovine serum to be studied with a view to selecting suitable material to serve as an international standard for anti-toxoplasma serum.²

44. Anti-Measles Serum³

The Committee was of the opinion that there is an urgent need for the provision of an international standard for anti-measles serum which would serve a useful purpose in evaluating the potency of anti-measles gamma globulin and in assessing measles vaccines. The Committee was informed that the Division of Biologics Standards, National Institutes of Health,

¹ Unpublished working document WHO/BS/601; unpublished mimeographed report MHO/PA/44.62

² Unpublished working document WHO/BS/609

³ Unpublished working document WHO/BS/561

Bethesda, had offered a sufficient quantity of monkey serum which might serve as an international standard. The Committee therefore authorized the Statens Seruminstitut, Copenhagen, to obtain this material, and in collaboration with the Division of Biologics Standards, National Institutes of Health, to investigate the suitability of this material to serve as an international standard.

45. Anti-Poliovirus sera

The Committee noted that in accordance with the authorization given in its fourteenth report¹ the Statens Seruminstitut, Copenhagen, with the agreement of the participants in the collaborative assay, had established the International Standards for Anti-Poliovirus Sera of Types 1, 2 and 3, which replace the existing International Reference Preparations.² The Committee defined the International Units as the activity contained in 10.78 mg of the International Standard for Anti-Poliovirus Serum, Type 1; 10.46 mg of the International Standard for Anti-Poliovirus Serum, Type 2, and 10.48 mg of the International Standard for Anti-Poliovirus Serum, Type 3.

46. Anti-Swine-Fever Serum

The Committee noted that the collaborative assay of the proposed international standard for anti-swine-fever serum had been completed,³ and it authorized the Central Veterinary Laboratory, Weybridge, to establish this material as the International Standard for Anti-Swine-Fever Serum and to define the international unit with the agreement of the participants in the collaborative assay.

The Committee asked the Central Veterinary Laboratory to carry out thermostability studies of this material.

47. Anti-Tick-Borne Encephalitis Serum

The Committee noted that the Statens Seruminstitut, Copenhagen, had obtained quantities of three serum preparations for the purpose of selecting the material most suitable to serve as an international reference preparation for the identification of the group of tick-borne encephalitis viruses.⁴ The Committee also noted that collaborative studies of these materials were in progress.

¹ *Wld Hlth Org. techn. Rep. Ser.*, 1961, 222

² Unpublished working document WHO/BS/564; *Bull. Wld Hlth Org.*, 26, 341

³ Unpublished working document WHO/BS/573

⁴ Unpublished working document WHO/BS/562

48. Anti-Yellow-Fever Serum

The Committee noted that the collaborative assay of the proposed international reference preparation of anti-yellow-fever serum had been completed.¹

The Expert Committee on Yellow Fever Vaccine² and the Study Group on Requirements for Yellow Fever Vaccine³ had recommended that an international reference preparation be made available to serve as a reference serum in the mouse protection test used in the control of yellow-fever vaccines. The participants in the collaborative assay had agreed that the serum studied is suitable for this purpose. The Committee established this material as the International Reference Preparation of Anti-Yellow-Fever Serum.

Since this international reference preparation can also be used to determine the relative potencies of other anti-yellow-fever sera,⁴ the Committee designated the activity contained in 0.5 mg of this material as the International Unit of Anti-Yellow-Fever Serum.

49. *Naja* Antivenin

The Committee noted that the South African Institute for Medical Research, Johannesburg, had conducted extensive studies on the neutralizing potency of the proposed international standard for *Naja* antivenin in comparison with other *Naja* antivenins prepared in a number of laboratories, using samples of venom from various *Naja* species obtained from different parts of the world.⁵

The Committee agreed that, in spite of some discrepancies resulting from the inclusion of a diversity of test venoms, the proposed international standard had served well in the assays, but considered that it would be of value to carry out a few more limited studies if these could be arranged with the collaboration of workers in South-East Asia. The Committee authorized the Statens Seruminstitut, Copenhagen, in consultation with the South African Institute for Medical Research, to establish the material as the International Standard for *Naja* Antivenin, and to define the international unit with the agreement of the participants in the further studies.

The Committee requested the WHO Secretariat to determine which genus of snake should now be chosen for continuing the project of international antivenin standardization.

¹ Unpublished working document WHO/BS/545 & Corrigendum 1

² *Wld Hlth Org. techn. Rep. Ser.*, 1957, 136

³ *Wld Hlth Org. techn. Rep. Ser.*, 1959, 179

⁴ Unpublished working document WHO/BS/587

⁵ Unpublished working document WHO/BS/604

The Committee was informed that the Queen Saovabha Memorial Institute, Bangkok, had provided a quantity of freeze-dried snake anti-venins for three species of snakes, namely the banded krait (*Bungarus fasciatus*), the Russell's viper (*Viper russellii*) and a pit viper (*Ancistrodon rhodostoma*).

50. Anti-Streptococcus Hyaluronidase Serum

The Committee considered the question of a possible need for an international reference preparation of anti-Streptococcus hyaluronidase serum,¹ and was of the opinion that such a preparation was unlikely to be much used and that there was no need for providing one at present.

51. Other Streptococcal Reagents

The Committee noted¹ that a diversity of reagents had been developed for tests used in the serological investigation of streptococcal diseases. These tests included the sensitized sheep cell reaction, latex fixation reaction, streptococcus agglutination and antistreptokinase determination.

The Committee also noted a suggestion for the establishment of an international reference preparation of rheumatoid arthritis serum for use in research.² In view of the uncertainty as to which particular antibodies would be of value as international reference preparations, the Committee felt that further information was necessary to clarify this problem and therefore asked the WHO Secretariat to collect such information.

52. Gas-gangrene Antitoxin (Perfringens) (*Clostridium welchii* Type A antitoxin)

The Committee noted that the collaborative assay of the proposed fifth international standard for gas-gangrene antitoxin (perfringens) had now been completed³ and that the results permitted a satisfactory definition of the international unit. The Committee authorized the National Institute for Medical Research, London, to establish the material as the fifth International Standard for Gas Gangrene Antitoxin (Perfringens) (*Clostridium welchii* Type A Antitoxin) and to define the international unit with the agreement of the participants in the collaborative assay.

¹ Unpublished working document WHO/BS/567

² Unpublished working document WHO/BS/574

³ Unpublished working document WHO/BS/547, Revision 1

53. *Clostridium Botulinum* (Types A, B, C, D, E) Antitoxins

The Committee noted that British standards for *Clostridium botulinum* types A, B, C, D and E antitoxins had been established and that British units for each of these antitoxins had been defined by the National Institute for Medical Research, London.¹ The Committee also noted¹ that it was proposed that these antitoxins might serve as international standards and that a sufficient quantity had been offered for this purpose.

The Committee was informed that the only other national standards existing for these substances were those held by the State Control Institution of Medical Biological Preparations, Moscow. This Institute had examined the five proposed international standards and had found that only negligible differences existed between the Russian and British units for types A, B, C and D, but that there was a forty-fold difference between the units for type E. In view of this the Russian and British workers had agreed on a common unit for type E antitoxin that would be one-tenth of the existing British unit.

The Committee agreed to adopt this solution and authorized the National Institute for Medical Research to establish the International Standards for *Clostridium botulinum* Types A, B, C, D and E Antitoxins and to define the international units.

54. Anti-Vaccinia Gamma Globulin

The Committee was informed that in accordance with a request made in its thirteenth report² the National Institute for Medical Research, London, had obtained a preparation of sheep anti-vaccinia gamma globulin and that a collaborative study was in progress in order to determine the suitability of this material for use in assays of anti-vaccinia gamma globulin intended for the prophylaxis and treatment of smallpox and post-vaccination complications.

The Committee was of the opinion that a sample of human anti-vaccinia gamma globulin should also be included in these studies.

55. Staphylococcal Products

The Committee noted that there was evidence for the clinical effectiveness of several staphylococcus vaccine preparations,³ but that it was not

¹ Unpublished working document WHO/BS/582; *Bull. Wld Hlth Org.*, to be published

² *Wld Hlth Org. techn. Rep. Ser.*, 1960, 187

³ Unpublished working documents WHO/BS/568, WHO/BS/572, WHO/BS/575 & WHO/BS/589

possible with the information available to establish an international reference preparation which could be used in the potency determination of the various types of staphylococcal vaccines in clinical use.¹

The Committee considered that the establishment of an international reference serum against the F and S components of staphylococcal P-V leucocidin would be of value in immunological research.¹ The Committee therefore asked the National Institute for Medical Research, London, to arrange for the examination of anti-leucocidin sera with a view to establishing an international reference preparation.

MISCELLANEOUS

56. Opacity Reference Preparation

The Committee noted that material had been obtained for the replacement of the International Opacity Reference Preparation and the collaborative study had been completed.² The Committee established this material as the second International Opacity Reference Preparation and assigned a value of 10 International Units of Opacity per ml of this preparation.

The Committee emphasized that the International Opacity Reference Preparation is intended for use in comparison with bacterial suspensions by direct visual inspection only.

57. Diagnostic Reagents

In recent years the Expert Committee on Biological Standardization has been asked to establish a number of microbiological diagnostic reagents as international reference preparations on the basis of information supplied to the Committee after completion of collaborative studies that had been initiated and supervised by specialized groups other than the Expert Committee.

Examples are the international reference preparations of type-specific leptospira sera.

The need exists for an increasing number of specific antisera for the identification of the ever-expanding group of viruses isolated from human and animal sources. The international provision of specific reagents would be of great value to many diagnostic and research laboratories throughout the world, in order to enable them to verify the specificity of

¹ Unpublished working document WHO/BS/603

² Unpublished working documents WHO/BS/584 & WHO/BS/585; *Bull. Wld Hlth Org.*, 26, 213, 219

the reagents used by them routinely. Also, such international reference preparations of specific reagents would assist in preserving continuity in viral taxonomy.

The Committee was informed of an offer made to WHO by the National Institutes of Health, Bethesda, of quantities of carefully tested specific viral diagnostic sera which as international reference preparations could serve the purposes outlined above.

The Committee accepted the responsibility for establishing the sera offered as international reference preparations subject to agreement on the arrangements necessary for ascertaining the suitability of these sera and on the way they should be held and distributed under the auspices of WHO.

The Committee noted the recommendation of a WHO Scientific Group on Cholera Research¹ for replacing the existing International Reference Preparations of Cholera Antigens (Inaba and Ogawa) with preparations of specific antigens offered by the Institut Pasteur, Paris. In view of the many problems still to be resolved in the field of cholera serology the Committee was of the opinion that further studies of the type-specific sera prepared from these antigens should be undertaken and that such studies might well be carried out in the framework of the WHO cholera programme, so as to provide data on which the Committee could base a decision at a later date.

58. International Requirements for Biological Substances

The Committee noted that requirements for oral poliomyelitis vaccine formulated by a WHO study group² had been published and it agreed that these international requirements made a substantial contribution to the effective control of oral poliomyelitis vaccine. In view of the rapid increase of knowledge in applied virology, and of the many advances in methods of production and testing, the Committee stressed the need for early revision of the existing international requirements.

The Committee was informed that work was in progress on the formulation of international requirements for BCG vaccine and pertussis vaccine.

The Committee was of the opinion that the positive evidence of protection against typhoid in man found in the field trials of typhoid vaccines might contribute towards the formulation of international requirements for these vaccines.

¹ Unpublished mimeographed report MHO/PA/62.62

² *Wld Hlth Org. techn. Rep. Ser.*, 1962, 237

Annex 1

REQUIREMENTS FOR BIOLOGICAL SUBSTANCES

The specification of requirements to be fulfilled by preparations of biological substances is necessary in order to ensure that these products are safe, reliable and potent prophylactic or therapeutic agents. International recommendations on requirements are intended to facilitate the exchange of biological substances between different countries and to provide guidance to workers responsible for the production of these substances and to others who may have to decide upon appropriate methods of assay and control.

Recommended requirements for biological substances formulated by international groups of experts and published in the Technical Report Series of the World Health Organization are listed hereunder :

No. Year

- 178** 1959 Requirements for Biological Substances :
1. General Requirements for Manufacturing Establishments and Control Laboratories
 2. Requirements for Poliomyelitis Vaccine (Inactivated)
- 179** 1959 Requirements for Biological Substances :
3. Requirements for Yellow Fever Vaccine
 4. Requirements for Cholera Vaccine
- 180** 1959 Requirements for Biological Substances :
5. Requirements for Smallpox Vaccine
- 200** 1960 Requirements for Biological Substances :
6. General Requirements for the Sterility of Biological Substances
- 237** 1962 Requirements for Biological Substances :
7. Requirements for Poliomyelitis Vaccine (Oral)

Should individual countries wish to adopt these requirements, or any part of them, as the basis of their national regulations for biological substances, it is recommended that they insert a clause permitting modifications to the regulations, on the condition that the modified requirements have been demonstrated, to the satisfaction of the national control authority, to ensure for each product a degree of safety and a potency at least equal to those provided by the requirements contained in the above publications. In any such cases, the World Health Organization should be informed of the action taken.

Annex 2

**INTERNATIONAL BIOLOGICAL STANDARDS
AND
INTERNATIONAL BIOLOGICAL REFERENCE PREPARATIONS
1963**

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. Most of the substances listed to which an International Unit has been assigned are International Biological Standards. Most of 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
ANTIGENS		
Old tuberculin (OT)	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
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)
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

SUBSTANCES

Statens Seruminstitut, Artager 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, 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. 1 , 257, 354; WHO/BS 3, 16, 28, 64, 120
1st Standard 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; 1961, 222 , 14; WHO/BS 3, 16, 28, 64, 106, 120, 127, 173, 181, 488, 581, 591, 597
1st Standard 1954	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1955, 96 , 11; 1960, 187 , 13; 1961, 222 , 15; WHO/BS 126, 181, 227, 293, 293 Add. 1 and 2, 504, 504 Add. 1, 576
1st Standard 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
1st Standard 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
1st Standard 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
1st Standard 1954	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1955, 96 , 7; WHO/BS 229, 247, 274, 275, 275 Add. 1 and 2
1st Standard 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, 606, 611
1st Standard 1959	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1960, 187 , 20; 1961, 222 , 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
Antigens (contd)		
Newcastle disease vaccine (inactivated)	1.0	Ampoules containing 500 mg of freeze-dried vaccine derived from formalin-treated allantoic fluid of eggs infected with strains of Newcastle disease virus adsorbed to aluminium hydroxide (500 I.U. per ampoule)
Cholera antigen (Inaba)	—	Ampoules containing approximately 100 mg of dried antigen
Cholera antigen (Ogawa)	—	Ampoules containing approximately 100 mg of dried antigen
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 (6.4 mg of 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 ultraviolet irradiation
Smallpox vaccine	—	Ampoules containing 14 mg of freeze-dried purified smallpox vaccine

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> 1962	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1960, 187 , 20; 1961, 222 , 13; 1963, 259 , 14; WHO/BS/528, 528 Add. 1, 571, 571 Add. 1
<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> , 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; 1961, 24 , 265; <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 Reference Preparation</i> 1960 (discontinued 1962)	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1960, 201 ; 1961, 222 , 15; WHO/BS/372, 411, 411 Annex 1, 490, 507, 507 Corr. 1, 602; WHO/Rabies/111, 123, 146
<i>1st Reference Preparation</i> 1962	<i>Bull. Wld Hlth Org.</i> , 1963, in press; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1961, 222 , 16; 1963, 259 , 17; WHO/BS/14, 73, 105, 371, 381, 383, 417, 442, 461, 467, 500, 536, 546

Substance	International Unit of present standard (mg)	Form in which dispensed
Antigens (contd)		
Typhoid vaccine (acetone-inactivated)	—	Ampoules containing 11 mg of dried vaccine
Typhoid vaccine (heat-phenol-inactivated)	—	Ampoules containing 34 mg of freeze-dried vaccine
Poliomyelitis vaccine (inactivated)	—	Ampoules containing 10 ml of trivalent inactivated poliomyelitis vaccine, frozen
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)
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)	0.3346	Bottles containing 90.35 mg of dried hyperimmune horse serum (270 I.U. per ampoule)
<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)

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> 1962	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1958, 147 , 11; 1960, 187 , 15; 1961, 222 , 17; 1963, 259 , 17; WHO/BS/217, 291, 301, 340, 378, 409, 441, 505, 515, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 578
<i>1st Reference Preparation</i> 1962	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1958, 147 , 11; 1960, 187 , 15; 1961, 222 , 17; 1963, 259 , 17; WHO/BS/217, 291, 301, 340, 378, 409, 441, 505, 515, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 578
<i>1st Reference Preparation</i> 1962	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1959, 178 , 5, 18; 1961, 222 , 13; 1963, 259 , 15; WHO/BS/235, 260, 321, 376, 376 Annex 1, 449, 459, 460, 466, 466 Add. 1, 537, 563, 565, 583, 613
<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
<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) 4th Standard 1953 (0.1132 mg) 5th Standard 1963	<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, 547 Rev. 1
<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; 1956, 108 , 7; 1957, 127 , 8; 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; 1956, 108 , 7; 1957, 127 , 8; WHO/BS 281, 283, 298, 303, 343

Substance	International Unit of present standard (mg)	Form in which dispensed
Antibodies (contd)		
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)
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)

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 1934 (0.2377 mg) 2nd Standard 1947 (0.0974 mg) 3rd Standard 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>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) 2nd Standard 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) 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
1st Standard 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
1st Standard 1952	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1953, 68, 11; WHO/BS 38, 60, 84, 150, 225
1st Standard 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
1st Standard 1954	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1955, 96, 10; 1956, 108, 12; WHO/BS 246, 297, 300
1st Standard 1934	<i>Bull. Hlth Org. L. o. N.</i> , 1935, 4, 4, 48, 512
1st Standard 1934	<i>Bull. Hlth Org. L. o. N.</i> , 1935, 4, 5, 65, 512
1st Standard 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

Substance	International Unit of present standard (mg)	Form in which dispensed
Antibodies (contd)		
Anti-Q-fever serum	0.1017	Ampoules containing 101.7 mg of dried bovine serum (1000 I.U. per ampoule)
Antirabies serum	1.0	Ampoules containing 86.6 mg of dried hyperimmune horse serum (86.6 I.U. per ampoule)
Anti-A blood-typing serum	0.3465	Ampoules containing 88.7 mg of dried human serum (256 I.U. per ampoule)
Anti-B blood-typing serum	0.3520	Ampoules containing 90.1 mg of dried human serum (256 I.U. per ampoule)
Syphilitic human serum	3.617	Ampoules containing 177.4 mg of dried human serum (49 I.U. per ampoule)
Antipoliomyelitis serum (type 1)	10.78	Ampoules containing 107.8 mg of dried hyperimmune monkey serum (10 I.U. per ampoule)
Antipoliomyelitis serum (type 2)	10.46	Ampoules containing 104.6 mg of dried hyperimmune monkey serum (10 I.U. per ampoule)
Antipoliomyelitis serum (type 3)	10.48	Ampoules containing 104.8 mg of dried hyperimmune monkey serum (10 I.U. per ampoule)
<i>Clostridium botulinum</i> Type A antitoxin	0.1360	Ampoules containing 68.0 mg of dried hyperimmune horse serum (500 I.U. per ampoule)
<i>Clostridium botulinum</i> Type B antitoxin	0.1740	Ampoules containing 87.0 mg of dried hyperimmune horse serum (500 I.U. per ampoule)
<i>Clostridium botulinum</i> Type C antitoxin	0.0800	Ampoules containing 80.0 mg of dried hyperimmune horse serum (1000 I.U. per ampoule)
<i>Clostridium botulinum</i> Type D antitoxin	0.0121	Ampoules containing 12.1 mg of dried hyperimmune horse 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)
<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>Bull. Wld Hlth Org.</i> , 1961, 24, 271; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1958, 147, 16; 1961, 222, 21; WHO/BS 239, 289 Rev. 1, 304, 341, 379, 380 Rev. 1, 439, 465, 509
<i>1st Standard</i> 1962	<i>Bull. Wld Hlth Org.</i> , 1962, 26, 341; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1959, 172, 15; 1959, 178, 18; 1963, 259, 22; WHO/BS 313, 361, 363, 385, 433, 444, 475, 483, 516, 564
<i>1st Standard</i> 1962	<i>Bull. Wld Hlth Org.</i> , 1962, 26, 341; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1959, 172, 15; 1959, 178, 18; 1963, 259, 22; WHO/BS 313, 361, 363, 385, 433, 444, 475, 483, 516, 564
<i>1st Standard</i> 1962	<i>Bull. Wld Hlth Org.</i> , 1962, 26, 341; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1959, 172, 15; 1959, 178, 18; 1963, 259, 22; WHO/BS 313, 361, 363, 385, 433, 444, 475, 483, 516, 564
<i>1st Standard</i> 1963	<i>Bull. Wld Hlth Org.</i> , to be published; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1960, 187, 18; 1963, 259, 25; WHO/BS 485, 582
<i>1st Standard</i> 1963	<i>Bull. Wld Hlth Org.</i> , to be published; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1960, 187, 18; 1963, 259, 25; WHO/BS 485, 582
<i>1st Standard</i> 1963	<i>Bull. Wld Hlth Org.</i> , to be published; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1960, 187, 18; 1963, 259, 25; WHO/BS 485, 582
<i>1st Standard</i> 1963	<i>Bull. Wld Hlth Org.</i> , to be published; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1960, 187, 18; 1963, 259, 25; WHO/BS 485, 582

Substance	International Unit of present standard (mg)	Form in which dispensed
Antibodies (contd)		
<i>Clostridium botulinum</i> Type E antitoxin	0.0691	Ampoules containing 69.1 mg of dried hyperimmune horse serum (1000 I.U. per ampoule)
Anti-swine-fever serum	0.89	Ampoules containing 889.5 mg of freeze-dried pig serum (1000 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	—	Ampoules containing 5 ml of hyperimmune horse serum, dried
Anti-yellow-fever serum	0.5	Ampoules containing 71.5 mg of dried monkey serum (143 I.U. per ampoule)
Anti- <i>Leptospira saxkoebing</i> serum ¹	—	Ampoules containing 0.5 ml or 1.0 ml of hyperimmune rabbit serum, dried
Anti- <i>Leptospira ballum</i> AB serum ¹	—	
Anti- <i>Leptospira canicola</i> serum ¹	—	
Anti- <i>Leptospira sejroe</i> serum ¹	—	
Anti- <i>Leptospira mini</i> AB serum ¹	—	
Anti- <i>Leptospira grippotyphosa</i> serum ¹	—	
Anti- <i>Leptospira australis</i> A serum ¹	—	
Anti- <i>Leptospira icterohaemorrhagiae</i> AB serum ¹	—	

¹ 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)
<i>1st Standard 1963</i>	<i>Bull. Wld Hlth Org.</i> , to be published; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1960, 187 , 18; 1963, 259 , 25; WHO/BS 485, 582
<i>1st Standard 1963</i>	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1961, 222 , 19; 1963, 259 , 22; WHO/BS 573
<i>1st Reference Preparation 1953</i>	<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
<i>1st Reference Preparation 1953</i>	<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 1952</i>	<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 1962</i>	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1957, 136 , 9; 1959, 179 , 12; 1961, 222 , 20; 1963, 259 , 23; WHO/BS 416, 438, 464, 464 Add. 1, 506, 514, 545, 545 Corr. 1, 587
<i>1st Reference Preparation 1958</i>	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1956, 113 ; 1959, 172 , 17; WHO/BS 413, 437, 508

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
Antibodies (contd)		
Anti- <i>Leptospira icterohaemorrhagiae</i> A serum ¹	—	Ampoules containing 0.5 ml or 1.0 ml of hyperimmune rabbit serum, dried
Anti- <i>Leptospira hyos</i> serum ¹	—	
Anti- <i>Leptospira autumnalis</i> AB serum ¹	—	
Anti- <i>Leptospira autumnalis</i> A serum ¹	—	
Anti- <i>Leptospira pomona</i> serum ¹	—	Ampoules containing 1.0 ml of hyperimmune rabbit serum, dried
Anti- <i>Leptospira bataviae</i> serum ¹	—	
Anti- <i>Leptospira semaranga</i> serum ¹	—	
Anti- <i>Leptospira hebdomadis</i> serum ¹	—	Ampoules containing 0.5 ml or 1.0 ml of hyperimmune rabbit serum, dried
Anti- <i>Leptospira andamana</i> serum ¹	—	
Anti- <i>Leptospira javanica</i> serum ¹	—	
Anti- <i>Leptospira pyrogenes</i> serum ¹	—	
Anti- <i>Leptospira naam</i> serum ¹	—	
Anti- <i>Leptospira mankarso</i> serum ¹	—	
Anti- <i>Leptospira sarmin</i> serum ¹	—	
Anti- <i>Leptospira poi</i> serum ¹	—	
Anti- <i>Leptospira schueffneri</i> serum ¹	—	
Anti- <i>Leptospira muenchen</i> serum ¹	—	
Anti- <i>Leptospira cynopteri</i> serum ¹	—	Ampoules containing 0.5 ml or 1.0 ml of hyperimmune rabbit serum, dried
Anti- <i>Leptospira bangkinang</i> serum ¹	—	
Anti- <i>Leptospira wolffii</i> serum ¹	—	
Anti- <i>Leptospira hardjo</i> serum ¹	—	

¹ 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)
1st Reference Preparation 1958	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1956, 113; 1959, 172, 17; WHO/BS 413, 437, 508
1st Reference Preparation 1958 2nd Reference Preparation 1962	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1956, 113; 1959, 172, 17; 1963, 259, 20; WHO/BS 413, 437, 508, 601
1st Reference Preparation 1958	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1956, 113; 1959, 172, 17; WHO/BS 413, 437, 508
1st Reference Preparation 1962	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1956, 113; 1961, 222, 18; 1963, 259, 20; WHO/BS 437, 489, 543, 601

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
Antibodies (contd) Anti- <i>Leptospira kremastos</i> serum ¹ Anti- <i>Leptospira benjamin</i> serum ¹ Anti- <i>Leptospira zanoni</i> serum ¹ Anti- <i>Leptospira medanensis</i> serum ¹ Anti- <i>Leptospira paidjan</i> serum ¹	— — — — —	Ampoules containing 0.5 ml or 1.0 ml of hyperimmune rabbit serum, dried
MISCELLANEOUS		
Opacity reference preparation	—	Ampoules containing 15 ml of a suspension of Pyrex-glass particles in water (10 I.U. of opacity per ml)

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

B. PHARMACOLOGICAL

Held and distributed 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)
Nystatin	0.000333	Ampoules containing 75 mg of nystatin (3000 I.U. per mg)
Amphotericin B	0.001064	Ampoules containing 100 mg of amphotericin B (940 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, 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, 529
1st Standard 1957	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1957, 127, 14; 1958, 147, 7; WHO/BS 399
1st Standard 1950 (0.001282mg) 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, 592
1st Standard 1953	<i>Bull. Wld Hlth Org.</i> , 1953, 9, 861; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1954, 86, 15; 1960, 187, 6; 1963, 259, 8; WHO/BS 122, 144, 236, 481, 593
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
1st Standard 1963	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1958, 147, 8; 1963, 259, 8; WHO/BS 347, 429, 476, 524, 580
1st Reference Preparation 1959	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1960, 187, 5; 1963, 259, 10; WHO/BS 450, 478, 592

Substance	International Unit of present standard (mg)	Form in which dispensed
Antibiotics (contd)		
Kanamycin	0.001232	Ampoules containing 50 mg of kanamycin sulfate (812 I.U. per mg)
Vancomycin	0.000993	Ampoules containing 50 mg of vancomycin sulfate (1007 I.U. per mg)
Viomycin	0.00137	Ampoules containing 35 mg of viomycin sulfate (730 I.U. per mg)
Penicillin K	—	Ampoules containing 20 mg of 89.9% pure sodium <i>n</i> -heptylpenicillin, with 9.6% penicillin dihydro F and 0.5% penicillin F
Neomycin	0.00147	Ampoules containing 100 mg of neomycin sulfate (680 I.U. per mg)
Novobiocin	—	Ampoules containing 150 mg of sodium novobiocin
Oleandomycin	—	Ampoules containing 75 mg of oleandomycin chloroform adduct
Ristocetin	—	Ampoules containing 45 mg of ristocetin
Gramicidin S	—	Ampoules containing 50 mg of gramicidin S
Spiramycin	—	Ampoules containing 50 mg of spiramycin base
Demethylchlortetracycline	0.001	Ampoules containing 80 mg of demethylchlortetracycline (1000 I.U. per mg)
Triacetyloleandomycin	0.0012	Ampoules containing 100 mg of triacetyloleandomycin (833 I.U. per mg)
Procaine benzylpenicillin in oil with aluminium monostearate (PAM)	—	Vials containing 10 ml of procaine benzylpenicillin for injection in oil with aluminium monostearate
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)

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 1959</i>	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1960, 187 , 6; 1963, 259 , 10; WHO/BS 450, 478, 592
<i>1st Reference Preparation 1959</i>	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1960, 187 , 9; 1963, 259 , 10; WHO/BS 450, 478, 592
<i>1st Reference Preparation 1959</i>	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1960, 187 , 9; 1963, 259 , 10; WHO/BS 493, 592
<i>1st Reference Preparation 1951</i>	<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 1958</i>	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1958, 147 , 6; 1963, 259 , 7; WHO/BS 347, 398, 428, 491, 592
<i>1st Reference Preparation 1958</i>	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1958, 147 , 6; 1963, 259 , 7; WHO/BS 394, 431, 472, 595
<i>1st Reference Preparation 1958</i>	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1958, 147 , 8; WHO/BS 430, 477
<i>1st Reference Preparation 1960</i>	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1961, 222 , 8; 1963, 259 , 7; WHO/BS 450, 478, 518, 592
<i>1st Reference Preparation 1962</i>	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1961, 222 , 9; 1963, 259 , 8; WHO/BS 530, 594
<i>1st Reference Preparation 1962</i>	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1961, 222 , 9; 1963, 259 , 8; WHO/BS 530, 596
<i>1st Reference Preparation 1962</i>	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1961, 222 , 8; 1963, 259 , 9; WHO/BS 592
<i>1st Reference Preparation 1962</i>	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1961, 222 , 8; 1963, 259 , 10; WHO/BS 592
<i>1st Reference Preparation 1962</i>	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1953, 63 , 55; 1955, 96 , 13; 1963, 259 , 11; WHO/BS 324, 349 Rev. 1, 358 Rev. 1, 403, 404, 484, 607, 608
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

Substance	International Unit of present standard (mg)	Form in which dispensed
Hormones (contd)		
Prolactin	0.04545	Ampoules containing 10 mg of dried active principle from anterior pituitary gland of the sheep (22 I.U. per mg)
Corticotrophin (previously named : adrenocorticotrophic hormone)	1.0	Ampoules containing 50 µg. of purified corticotrophin from anterior pituitary gland of the pig in 5 mg of lactose (1 I.U. per mg)
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 of the ox (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)
1st Standard 1939 (0.1 mg) 2nd Standard 1962	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1957, 127, 16; 1963, 259, 12; <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, 523, 577
1st Standard 1950 (1.00 mg) 2nd Standard 1955 (0.88 mg) 3rd Standard 1962	<i>Bull. Wld Hlth Org.</i> , 1956, 14, 543; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1951, 36, 7; 1958, 147, 8; 1959, 172, 8; 1963, 259, 13; WHO/BS 85, 156, 158, 249, 262, 308, 356, 386, 387, 432, 473, 526, 548
1st Standard 1954	<i>Bull. Wld Hlth Org.</i> , 1955, 13, 917; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1955, 96, 14; 1956, 108, 16; WHO/BS 155, 158, 210, 284, 309
1st Standard 1955	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1956, 108, 16; WHO/BS 140, 158, 250, 320
1st Reference Preparation 1959	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1959, 172, 9; 1960, 187, 9; 1961, 222, 9; 1963, 259, 12; WHO/BS 392, 434, 474, 532, 533
1st Standard 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>Wld Hlth Org. techn. Rep. Ser.</i> , 1961, 222, 9; 1963, 259, 12; WHO/BS 519, 600
1st Standard 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; <i>Wld Hlth Org. techn. Rep. Ser.</i> , 1963, 259, 12; WHO/BS 93, 141, 519, 612
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

Substance	International Unit of present standard (mg)	Form in which dispensed
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
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)
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
Miscellaneous (contd)		
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>Ist Reference Preparation 1954</i>	<i>Wld Hlth Org. techn. Rep. Ser., 1955, 96, 14; WHO/ BS 261</i>
<i>Ist 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>

Annex 3

**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, 222 , 11; WHO/BS 527, 570
BCG-vaccine	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1960, 187 , 12; 1961, 222 , 12; WHO/BS 455, 513, 588, 590, 590 Corr. 1
Clostridium oedematiens (alpha) toxoid	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1961, 222 , 12; WHO/BS 569
Newcastle disease vaccine (live)	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1961, 222 , 13; WHO/BS 528, 528 Add. 1
Tetanus toxoid, adsorbed	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1961, 222 , 16; WHO/BS 452, 468, 468 Add. 1, 469, 510, 586
<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; 1963, 259 , 23; WHO/BS 316, 317, 333, 334, 364, 373, 471, 501, 502, 502 Add. 1, 503, 541, 604
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; 1963, 259 , 25; WHO/BS 454
Anti-measles serum	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1961, 222 , 19; 1963, 259 , 21; WHO/BS 539, 544, 561
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

Substance	References (WHO/BS refers to unpublished working documents of the WHO Expert Committees on Biological Standardization)
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-staphylococcal leucocidin	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1963, 259 , 26; WHO/BS 603
Anti- <i>Leptospira celledoni</i> serum	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1956, 113 ; 1961, 222 , 18; WHO/BS 437, 489, 543, 601
Anti- <i>Leptospira djasiman</i> serum	WHO/BS 437, 489
Anti- <i>Leptospira sentot</i> serum	WHO/BS 437, 489
Anti- <i>Leptospira fugis</i> serum	
Anti- <i>Leptospira worsfoldi</i> serum	
Anti- <i>Leptospira malaya</i> serum	
Anti- <i>Leptospira atlantae</i> serum	
Anti- <i>Leptospira mini georgia</i> serum	
Anti- <i>Leptospira bratislava</i> serum	WHO/BS 601
Anti- <i>Leptospira erinacei-auriti</i> serum	
Anti- <i>Leptospira coxus</i> serum	
Anti- <i>Leptospira biggis</i> serum	
Anti- <i>Leptospira butembo</i> serum	
Anti- <i>Leptospira hamptoni</i> serum	

B. PHARMACOLOGICAL SUBSTANCES

Substance	References (WHO/BS refers to unpublished working documents of the WHO Expert Committees on Biological Standardization)
Colistin	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1963, 259 , 9
Human urinary menopausal gonadotrophins	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1961, 222 , 9; WHO/BS 532, 533
Streptokinase-streptodornase	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1961, 222 , 11; 1963, 259 , 13; WHO/BS 479, 599
Lysine vasopressin	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1963, 259 , 13; WHO/BS 598
Human growth hormone	<i>Wld Hlth Org. techn. Rep. Ser.</i> , 1963, 259 , 13

Annex 4

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,¹ and the International Unit for Provitamin A as the activity of 0.0006 mg of pure all-*trans* beta carotene.²

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

² *Wld Hlth Org. techn. Rep. Ser.*, 1961, 222, 10

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Amphotericin	10, 46	Kanamycin	10, 48
Androsterone	58	Lecithins	32
Anthrax vaccine	14, 56	Leptospira sera	20, 40, 42, 44, 57
Antidiuretic hormone	48	Measles serum	21, 56
Arsphenamine	58	Melaminyl trypanocides	52
Bacitracin	8, 46	Neoarsphenamine	52
BCG vaccine	14, 56	Neomycins	7, 48
Blood typing sera	38, 56	Newcastle disease vaccine	14, 32, 56
Brucella serum	36	Novobiocin	7, 48
Cardiolipin	32	Nystatin	8, 46
Chloramphenicol	58	Oestradiol	58
Cholera antigen	32	Oestrone	58
Cholera serum	40	Oleandomycin	48
Cholera vaccine	18, 32	Opacity	26, 44
Clostridium antitoxins	24, 25, 34	Ouabain	58
Clostridium toxoids	19, 56	Oxophenarsine	52
Colistin	9, 57	Oxytocic hormone	48
Corticotrophin	14, 50	Paratyphoid vaccines	18
Demethylchlortetracycline	9, 48	Penicillins	10, 11, 46, 48
Diagnostic reagents	26	Pertussis vaccine	19, 30
Dihydrostreptomycin	9, 46	Pneumococcus sera	36
Digitalis	52	Poliomyelitis sera	22, 38
Dimercaprol	52	Poliomyelitis vaccine	15, 16, 34
Diphtheria antitoxin	34, 40	Polymyxin	46
Diphtheria toxin	30	Progesterone	58
Diphtheria toxoid	30	Prolactin	12, 50
Dysentery antitoxin	34	Protamine	54
Echinococcus serum	57	Pyrogen	54
Erythromycin	46	Q-fever serum	38
Gas-gangrene antitoxins	24, 34, 36	Rabies serum	38
Gonadotrophins	12, 50, 57	Rabies vaccine	16, 32
Growth hormones	13, 50, 57	Requirements for biological sub- stances	27, 28
Gramicidins	8, 48	Ristocetins	7, 48
Griseofulvin	9	Schistoma antigen	19
Heparin	50	Smallpox vaccine	17, 32
Hyaluronidase	52	Snake antivenins	23, 56
Influenza vaccine	15	Spiramycin	8, 48
Insulin	50	Staphylococcus antitoxins	25, 36, 57, 58
International laboratories for biolog- ical standards	5, 6	Streptococcus antitoxins	24, 36
International units of potency	5, 6		

Streptokinase-streptodornase	57	Triacetyloleandomycin	10, 48
Streptomycins	9, 46	Trichinella serum	21, 57
Sulfarsphenamine	52	Tuberculins.	16, 30
Swine erysipelas serum	36	Tubocurarine	58
Swine erysipelas vaccine	30	Typhoid serum	40
Swine-fever serum	22, 40	Typhoid vaccine	17, 34
Syphilitic serum	38		
		Vaccinia gamma globulin	25, 56
Tetanus antitoxin	34	Vancomycin	10, 48
Tetanus toxoid	18, 30, 56	Vasopressor hormones	13, 48, 57
Tetracyclines	46	Viomycin	10, 48
Thyrotrophin	50	Vitamins	52, 58
Tick-borne encephalitis serum	22, 56		
Toxoplasma serum	21, 56	Yellow-fever serum	23, 40