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EXPERT COMMITTEE ON
BIOLOGICAL STANDARDIZATION

Eleventh Report

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EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION

Geneva, 16-21 September 1957

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CONTENTS

PHARMACOLOGICAL

Antibiotics

1. Streptomycin .................................................. 5
2. Tetracycline .................................................. 6
3. Erythromycin .................................................. 6
4. Neomycin ....................................................  6
5. Novobiocin ..................................................  6
6. Phenoxymethylpenicillin .................................  7
7. Procaine benzylpenicillin in oil with aluminium monostearate (PAM) ...........................................  7
8. Nystatin, oleandomycin, and other antibiotics .........  8

Hormones

9. Oxytocic, vasopressor, and antidiuretic substances ...  8
10. Corticotrophin ...............................................  8
11. Human menopausal gonadotrophin .......................  9
12. Prolactin ...................................................  9
13. Relaxin .....................................................  9
14. Insulin ......................................................  9

Miscellaneous

15. Dextran sulfate ............................................. 10
16. Heparin ..................................................... 10
17. Vitamin B₁₂ ................................................ 10
18. Pyrogens .................................................... 11

IMMUNOLOGICAL

Antigens

19. Pertussis vaccine ........................................... 11
20. Typhoid vaccines .......................................... 11
21. Cholera vaccine ........................................... 12
22. Rabies vaccine ............................................ 12
23. Smallpox vaccine ......................................... 13
24. Swine erysipelas vaccine .................................. 13
25. Poliomyelitis vaccine ..................................... 13
26. Japanese B encephalitis vaccine ......................... 14
27. Leptospirosis vaccines ................................... 14
28. Cardiolipin ............................................... 14
Antibodies

29. Gas gangrene antitoxin (vibrio septique) .................................................. 15
30. Anti-streptolysin O .................................................................................. 15
31. Blood-typing sera .................................................................................... 15
32. Poliomyelitis sera .................................................................................... 16
33. Typhoid and paratyphoid agglutinating sera ......................................... 16
34. Syphilitic human serum ........................................................................... 16
35. Leptospirosis sera .................................................................................... 17
36. Yellow fever immune serum ................................................................... 17

GENERAL

37. Recommended requirements for biological substances ....................... 18
38. Stability of biological standards ............................................................. 18
39. List of International Biological Standards ............................................. 18

ANNEX

1. International Biological Standards and Reference Preparations, 1958 19
2. Proposed International Biological Standards ......................................... 36
3. Author's Preparations ............................................................................... 37
4. Discontinued International Biological Standards ................................... 38
EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION

Eleventh Report *

The Expert Committee on Biological Standardization met in Geneva from 16 to 21 September 1957.

The Assistant Director-General, Central Technical Services, on behalf of the Director-General of the World Health Organization, welcomed the members of the Committee.

PHARMACOLOGICAL

ANTIBIOTICS

1. Streptomycin

The Committee noted that the National Institute for Medical Research, London, has completed the statistical analysis of the results of the collaborative assays,¹ and that as soon as agreement of the participants has been obtained² the second International Standard for Streptomycin will be established.

¹ The Executive Board, at its twenty-first session, adopted the following resolution: The Executive Board
1. NOTES the eleventh report of the Expert Committee on Biological Standardization;
2. THANKS the members of the Committee for their work; and
3. AUTHORIZES publication of the report

² Participants: Biologics Control Laboratory, Department of National Health and Welfare, Ottawa, Canada; Hindustan Antibiotics Ltd, Pimpri, near Poona, India; Istituto Superiore di Sanita, Rome, Italy; Department of Viral and Rickettsial Diseases, National Institute of Health, Tokyo, Japan; Distillers Company (Biochemicals) Ltd, Great Burgh, Epsom, United Kingdom; Glaxo Laboratories, Greenford, United Kingdom; National Institute for Medical Research, London, United Kingdom; Food and Drug Administration, Department of Health, Education, and Welfare, Washington, D.C., USA
2. Tetracycline

The Committee noted that, in accordance with the authorization given in its tenth report,¹ the International Standard for Tetracycline has been established² ² and that one International Unit is defined as the activity contained in 0.00101 milligram of the International Standard. The standard thus contains 990 units per milligram; one International Unit may be regarded as equivalent to one microgram of pure tetracycline hydrochloride.

3. Erythromycin

The Committee noted that, in accordance with the authorization given in its tenth report,¹ the International Standard for Erythromycin has been established⁴ ⁵ and that one International Unit is defined as the activity contained in 0.001053 milligram of the International Standard. The standard thus contains 950 units per milligram; one International Unit may be regarded as equivalent to one microgram of pure erythromycin base.

4. Neomycin

The Committee noted that the active material constituting the proposed international standard for neomycin is a mixture of approximately 80% of neomycin B and 20% of neomycin C.⁶ Since this composition is also characteristic of most commercial products and of the standard used by the Food and Drug Administration, Department of Health, Education, and Welfare, Washington, D.C., the Committee considered the material suitable and asked the National Institute for Medical Research, London, to proceed with the collaborative assay.

5. Novobiocin

The Committee decided that there was no need for an international standard for novobiocin at the present time. It noted that, in case such a

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² National Institute for Medical Research, London, unpublished working document WHO/BS/396
⁴ National Institute for Medical Research, London, unpublished working document WHO/BS/397
⁵ Humphrey, J. H., Lightbown, J. W. & Mussett, M. V., unpublished working document WHO/BS/397, Annex 1
⁶ National Institute for Medical Research, London, unpublished working document WHO/BS/398
need should arise, the quantity of novobiocin now held by the National Institute for Medical Research, London, would suffice for the establishment of an international standard.

6. Phenoxyethylpenicillin

The Committee endorsed the final report 2 on the collaborative assay 3 of the proposed international standard and established this material as the International Standard for Phenoxyethylpenicillin. The International Unit is defined as the activity contained in 0.00059 milligram of the International Standard. The International Standard thus contains 1695 International Units per milligram.

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

The Committee noted that preliminary studies of an assay method for PAM in terms of a reference preparation of PAM had been completed. The National Institute for Medical Research, London, had obtained several batches of PAM believed to possess different characteristics with respect to the production, after intramuscular injection, of persistent concentrations of penicillin in circulating blood, but only two of these were available in sufficient quantity to serve as international reference preparations. 4 In view of the continued use of this drug in mass campaigns against treponematoses, the Committee requested the National Institute for Medical Research to proceed with its plan for collaborative studies in man and in rabbits; the Committee emphasized that an adequate number of tests in man should be included.

The Committee also noted the final report describing an assay method for the determination of small concentrations of penicillin in blood serum. 5

3 National Institute for Medical Research, London, unpublished working document WHO/BS/394

2 National Institute for Medical Research, London, unpublished working document WHO/BS/399

4 Participants: "Biochemie" G.m.b.H., Kundl, Tyrol, Austria; Laboratory of Hygiene, Department of National Health and Welfare, Ottawa, Canada; Statens Serum-institut, Copenhagen, Denmark; Institut Pasteur, Paris, France; Antibiotics Department, Institute of Hygiene, Warsaw, Poland; Distillers Company (Biochemicals) Ltd, Great Burgh, Epsom, United Kingdom; National Institute for Medical Research, London, United Kingdom; Food and Drug Administration, Department of Health, Education, and Welfare, Washington, D.C., USA

5 National Institute for Medical Research, London, unpublished working document WHO/BS/403

6 National Institute for Medical Research, London, unpublished working document WHO/BS/404
8. Nystatin, Oleandomycin, and Other Antibiotics

The Committee agreed that it may become necessary in the future to establish international standards for nystatin and oleandomycin, and it asked the National Institute for Medical Research, London, to obtain adequate quantities of these substances and to carry out preliminary studies of their suitability as international standards. The Committee also agreed that no steps should be taken at this time to set up international standards for other antibiotics.

HORMONES

9. Oxytocic, Vasopressor, and Antidiuretic Substances

The Committee noted that, in accordance with the authorization given in its tenth report, the International Standard for Oxytocic, Vasopressor, and Antidiuretic Substances has now been established and that one International Unit of each substance is defined as the activity contained in 0.5 milligram of the International Standard. The establishment of the third International Standard in place of the second has involved no change in the size of the International Units.

10. Corticotrophin

The Committee noted that the International Conference on Corticotrophin, which met in London in July 1957 under the auspices of the Medical Research Council, had recommended replacement of the International Standard for Corticotrophin with a preparation consisting of corticotrophin purified by adsorption on oxyzellulose. The Committee agreed with this proposal and asked the National Institute for Medical Research, London, to obtain material of pig origin and to proceed with its characterization in terms of the existing standard. The Committee recognized that the assay of the new standard in terms of the existing one would be complicated by the fact that the potency as determined by subcutaneous assay would probably be higher than the potency as determined by intravenous assay. Since most commercial preparations are administered subcutaneously, it was agreed that the definition of the unit should be based entirely

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² National Institute for Medical Research, London, unpublished working document WHO/BS/395
³ National Institute for Medical Research, London, unpublished working document WHO/BS/386
upon the results of subcutaneous assays, thereby ensuring clinical continuity of dosage.

The Committee noted that the Conference had recommended that the new international standard should be available for use as a working standard, but also recognized that there were great difficulties in handling an amount of material large enough to serve as a working standard for international use without running the risk of inhomogeneity. It recommended that the National Institute for Medical Research should try to obtain a large batch of material, part of which would be used as the international standard; the remainder could then be made available, in bulk, for the setting up of national working standards about which an a priori assumption of equivalence with the international standard could be made.

11. Human Menopausal Gonadotrophin

The Committee noted a request by the International Federation of Gynecology and Obstetrics for the establishment of an international standard for human menopausal gonadotrophin. A quantity of human menopausal gonadotrophin has been offered to the National Institute for Medical Research, London, and when received it will be examined for its suitability as an international reference preparation.

12. Prolactin

The Committee noted the progress made by the National Institute for Medical Research, London, with the preparation of the proposed second international standard for prolactin.

13. Relaxin

The Committee noted a suggestion that an international standard for relaxin be established. It asked the National Institute for Medical Research, London, to assess the need for such a standard and to investigate whether suitable material could be obtained.

14. Insulin

The Committee noted that the statistical analysis of the results of the international collaborative assay of the proposed fourth international

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1 National Institute for Medical Research, London, unpublished working document WHO/BS/387
2 National Institute for Medical Research, London, unpublished working document WHO/BS/392
3 National Institute for Medical Research, London, unpublished working document WHO/BS/405
standard for insulin is progressing,\textsuperscript{1} and recommended that high priority need not be given to the time-consuming calculations involved, since adequate supplies of the present International Standard are still available.

**MISCELLANEOUS**

15. Dextran Sulfate

The Committee noted that satisfactory progress\textsuperscript{2} is being made towards the establishment of an international standard for dextran sulfate.

16. Heparin

The Committee noted that satisfactory progress\textsuperscript{3} is being made towards the establishment of the second international standard for heparin.

17. Vitamin $\text{B}_{12}$

The Committee noted that the collaborative assay\textsuperscript{4} of the proposed international standard for vitamin $\text{B}_{12}$ is now complete,\textsuperscript{5} and that the standard will be established and the international unit defined as soon as agreement of the participants has been obtained.

The Committee recognized that, although vitamin $\text{B}_{12}$ can be fully characterized by chemical and physical means, the standard is needed for potency determinations in biological assays.

\textsuperscript{1} National Institute for Medical Research, London, unpublished working document WHO/BS/388

\textsuperscript{2} National Institute for Medical Research, London, unpublished working document WHO/BS/391

\textsuperscript{3} National Institute for Medical Research, London, unpublished working document WHO/BS/390

\textsuperscript{4} Participants: Biochemisches Laboratorium, Stockstadt am Main, Federal Republic of Germany; N.V. Organon, Oss, Netherlands; Statens Institut for Folkhalsan, Stockholm, Sverige; Glaxo Laboratories, Greenford, United Kingdom; National Institute for Medical Research, London, United Kingdom; National Institute for Research in Dairying, Shinfield, Reading, United Kingdom; Department of Scientific and Industrial Research, National Physical Laboratory, Teddington, United Kingdom; Lederle Laboratories, American Cyanamid Company, Pearl River, N.Y., USA; Merck & Co. (Analytical Department), Rahway, N.J., USA; Chas. Pfizer & Co., Inc., New York, N.Y., USA; E. R. Squibb & Sons (Product Specifications Department), New Brunswick, N.J., USA

\textsuperscript{5} National Institute for Medical Research, London, unpublished working document WHO/BS/389
18. Pyrogens

The Committee considered the report on the study carried out by the National Institute for Medical Research, London, on a highly purified preparation of the O somatic antigen of Shigella dysenteriae which produces threshold pyrogenic responses in rabbits after intravenous injection of about 0.003 microgram per kilogram of body-weight. The Committee noted that, in the opinion of the participants in the previous collaborative assay, any of a number of pyrogenic substances of bacterial origin would be suitable as a reference preparation; it therefore authorized the National Institute for Medical Research to establish the new material as the International Reference Preparation of Pyrogen, without further collaborative studies.

IMMUNOLOGICAL

ANTIGENS

19. Pertussis Vaccine

The Committee noted that, in accordance with the authorization given in its tenth report, the International Standard for Pertussis Vaccine has been established, and it defined the International Unit as the activity contained in 1.5 milligrams of the International Standard, this activity being equivalent to the protective unit used by the National Institutes of Health, Bethesda, Md., USA. The Committee emphasized that, in view of the fact that current assay methods yield inexact estimates, great care should be taken to avoid giving a false impression of accuracy when stating the immunizing potency of a vaccine.

20. Typhoid Vaccines

The Committee noted the progress made towards obtaining two stable typhoid vaccines in quantities sufficient for one or two future field trials, for extensive laboratory studies, and for the possible establishment of an

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1 National Institute for Medical Research, London, unpublished working document WHO/BS/400
2 WHO/BS/401
3 WHO/BS/408
4 WHO/BS/401
5 WHO Secretariat, unpublished working document WHO/BS/409
6 WHO/BS/409
international standard for typhoid vaccine. The two lots will be prepared from the same strain of *Salmonella typhosa*; one will be acetone-dried, the other heat-killed and freeze-dried. The Committee, recognizing that it may be some time before a field trial is possible and considering that it is essential that the materials used in the field and for laboratory study be identical, recommended that the bulk of these preparations, intended for field trials, should not be handled differently from the portions set aside for use as standard preparations. The Committee asked the Statens Serum-institut, Copenhagen, to initiate laboratory studies of a variety of assay methods¹ as soon as the dried vaccines become available.

21. Cholera Vaccine

The Committee considered the problem of standardizing cholera vaccine.²

Most studies so far undertaken have indicated that vaccination against cholera confers a degree of protection in man; assay methods are in use which appear to give consistent results in some, but not in all, laboratories. Despite these facts, there is still no evidence that a vaccine which would be considered good on the basis of laboratory results would also be a good vaccine for prophylactic use in man. Such evidence can be obtained only by concurrent field and laboratory studies in which the potency of a number of available cholera vaccines, as evaluated by laboratory methods, is compared with their prophylactic efficacy in man.

The Committee therefore recommended that a careful and detailed survey be made in an endemic area in order to determine whether a combined field and laboratory investigation can be carried out on a sufficiently large scale.

For several years to come, the control of cholera vaccines will continue to depend on determination of the bacteriological and immunological characteristics of the seed cultures and on animal tests of the antigenic properties of the vaccine. The Committee noted that the Study Group on Recommended Requirements for Biological Substances might consider this aspect of the problem.³

22. Rabies Vaccine

The Committee noted that the proposed international standard for rabies vaccine is available in insufficient quantity and that its stability is

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¹ Prigg, R. & Günther, O., unpublished working document WHO/BS/378
² Maaloe, O., unpublished working document WHO/BS/410
³ The report of this study group, which met in Geneva from 7 to 12 October 1957, has been issued as mimeographed document WHO/BS/IR/27.
questionable. It recommended that a larger quantity of dried rabies vaccine be provided as soon as possible and that it be studied for stability and for suitability in assay.

23. Smallpox Vaccine

The Committee noted that arrangements had been made for a collaborative study of the behaviour, in various assay methods, of different freeze-dried smallpox vaccines, including the proposed international reference preparation. It stressed the need for concurrent studies on the efficiency of the vaccines in producing specific skin lesions in man.

The Committee noted reports on an improved design for assay of the potency of smallpox vaccine by intracutaneous injection into rabbits, and on the use of tissue-culture methods for the determination of the virus content of such vaccines.

24. Swine Erysipelas Vaccine

The Committee noted that the type B swine erysipelas vaccine which has been examined by the Paul-Ehrlich-Institut, Frankfurt-on-Main, and the Central Veterinary Laboratory, Weybridge, while possessing the qualities required of an international standard, is not available in sufficient quantity for this purpose. The Committee therefore asked the Paul-Ehrlich-Institut to make available a larger quantity of similar material, with a view to establishing it as the International Standard for Swine Erysipelas Vaccine.

Preliminary studies in mice inoculated with type B vaccine have shown that satisfactory assays can be performed, provided Erysipelothrix rhusiopathiae, type B or N, is used for challenge. It is not known whether the proposed standard would be suitable in the assay of type A vaccines.

25. Poliomyelitis Vaccine

The Committee noted that efforts were being made in several countries to obtain a stable dried vaccine for use as a reference preparation. The determination of stability is complicated by the fact that existing tests cannot demonstrate small changes in potency unless large numbers of animals are employed. The Committee considered that this was a proper

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1 WHO Secretariat, unpublished working document WHO/BS/411
2 Statens Seruminstitut, Copenhagen, unpublished working document WHO/BS/383
3 Fisek, N. H., unpublished working document WHO/BS/381
4 Catchins, F. & Warren, J., unpublished working document WHO/BS/417
5 Prigge, R. & Eisner, G., unpublished working document WHO/BS/377
field for international collaboration since national resources might be inadequate for proper evaluation of the stability of dried vaccines.

It was understood that preliminary studies had suggested that certain dried preparations of poliomyelitis vaccine might be stable. The Statens Seruminstitut, Copenhagen, was asked to try to obtain supplies of such preparations and to compile a list of laboratories willing to take part in collaborative stability studies. It was agreed that at present the aim must be to obtain a trivalent standard vaccine in order to minimize the number of animals required in the determination of potency.

The Committee recommended that the stability study be regarded as a matter of urgency and not postponed until better assay methods for potency became available, since the development of improved methods of potency testing might be greatly facilitated by the provision of a stable standard.¹

26. Japanese B Encephalitis Vaccine

The Committee noted that the WHO Secretariat had investigated the need for an international reference preparation of Japanese B encephalitis vaccine,² and decided that it would be premature to attempt to standardize this vaccine.

27. Leptospirosis Vaccines

The Committee noted that the WHO Secretariat had investigated the need for international reference preparations of leptospirosis vaccines,³ and decided that there would be little advantage in setting up international reference preparations, in view of the fact that the antigenic composition of the vaccines used in different parts of the world varied according to the prevalent strains of Leptospira.

28. Cardiolipin

The Committee considered a report ⁴ on the collaborative study ⁵ of the material intended for replacement of the present International Reference Preparation of Cardiolipin, and noted that this material would be established as the third International Reference Preparation of Cardiolipin when the agreement of participants had been obtained.

¹ Prigge, R. & Bonin, O., unpublished working document WHO/BS/376, Annex 1
² WHO Secretariat, unpublished working document WHO/BS/412
³ WHO Secretariat, unpublished working document WHO/BS/413
⁴ Weis Bontzon, M. & Krag, P., unpublished working document WHO/BS/414
⁵ Participants: Serodiagnostic Department, Statens Seruminstitut, Copenhagen, Denmark; Laboratoire de Sérologie, Faculté de Médecine et de Pharmacie de l'Université de Bordeaux, Bordeaux, France; Venereal Disease Research Laboratory, Communicable Disease Center, Chamblee, Ga., USA; Division of Laboratories and Research, New York State Department of Health, Albany, N.Y., USA
ANTIBODIES

29. Gas Gangrene Antitoxin (Vibrio Septique)

The Committee noted that, in accordance with the authorization given in its tenth report, 1 the third International Standard for Gas Gangrene Antitoxin (vibrio septique) has been established 2 and that one International Unit is defined as the activity contained in 0.118 milligram of the International Standard.

30. Anti-Streptolysin O

The Committee noted that a quantity of human anti-streptolysin O of satisfactory stability had been obtained, 3 and authorized the Statens Seruminstitut, Copenhagen, to establish this material as the International Standard for Anti-Streptolysin O when the collaborative study had been completed and agreement obtained from the participants. It decided that the International Unit should be equated to the unit used by the Statens Seruminstitut.

31. Blood-Typing Sera

The Committee noted that a collaborative study of albumin-potentiated anti-Rh₀ (anti-D) blood-typing serum has been completed. 4 It authorized the Statens Seruminstitut, Copenhagen, in consultation with the International Blood Group Reference Laboratory, London, to establish this material as the International Standard for Albumin-Potentiated Anti-Rh₀ (anti-D) Blood-Typing Serum and to define the International Unit when agreement had been obtained from participants in the collaborative study. 5

The Committee noted that there is a need for establishing international standards for agglutinating ("saline-agglutinating") anti-Rh₀ (anti-D)

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2 Statens Seruminstitut, Copenhagen, unpublished working document WHO/BS/384
3 Statens Seruminstitut, Copenhagen, unpublished working document WHO/BS/402
5 Participants: Dr V. Friedenreich, Statens Seruminstitut, Copenhagen, Denmark; Dr J. Moulec, Centre national de Transfusion sanguine, Paris, France; Dr J. Gurevitch, Hadassah Medical School, The Hebrew University, Jerusalem, Israel; Dr J. J. van Loghem, Blood Transfusion Service, Amsterdam, Netherlands; Dr O. Hartmann, States Institut for Folkehelse, Oslo, Norway; Professor B. Broman, Statens Rattskemiska Laboratorium, Stockholm, Sweden; Dr A. Hägg, Blood Donor Service, Berne, Switzerland; Dr F. Stratton, Regional Transfusion Centre, Manchester, United Kingdom; Dr J. Wallace, Blood Transfusion Service, Law Hospital, Carluke, United Kingdom
blood-typing serum, as well as for anti-rh' (anti-C) and anti-rh" (anti-E) blood-typing sera, but that continuing difficulties in obtaining adequate quantities of these sera to serve as standards have not been overcome.

32. Poliomyelitis Sera

The Committee noted that the Statens Seruminstitut, Copenhagen, had obtained supplies, sufficient for a collaborative laboratory study, of freeze-dried preparations of human, monkey, guinea-pig, and horse immune sera.\(^1\) Comparative titrations of these sera in terms of the proposed international reference preparations will be made in order to determine whether the international reference preparations are suitable for use in tests of the virus-neutralizing potency of sera from different animals. The Committee authorized the Statens Seruminstitut, with the agreement of the participants in the collaborative study, to establish the International Reference Preparations of Poliomyelitis Sera of Types 1, 2, and 3, and to assign unitages to them. The Committee emphasized the urgent need for these reference sera.

33. Typhoid and Paratyphoid Agglutinating Sera

The Committee noted that the opinions expressed by the participants in the collaborative assay of the proposed international reference sera for the Widal test were divergent as to the value of this test as well as to the usefulness of the sera.\(^2\) It was therefore decided that these sera would be held by the Statens Seruminstitut, Copenhagen, as Author's Preparations.

34. Syphilitic Human Serum

The Committee considered the final report \(^3\) from the WHO Serological Reference Centre, Copenhagen, on the results of the collaborative investigation of the proposed international reference preparation of syphilitic human serum, and noted that this serum, which is a pool of reactive human sera, was of satisfactory stability and had proved useful for the detection of differences in sensitivity between assay methods.

While this investigation was in progress, a national reference preparation of syphilitic human serum and a national unit were established by the Paul-Ehrlich-Institut, Frankfurt-on-Main.\(^4\) Comparative studies had

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\(^1\) Statens Seruminstitut, Copenhagen, unpublished working document WHO/BS/385
\(^2\) WHO Secretariat, unpublished working document WHO/BS/415
\(^3\) Krag, P. & Weis Bentzon, M., unpublished working document WHO/BS/380 Rev.1
\(^4\) Prigge, R. & Heymann, G., unpublished working document WHO/BS/379
revealed that the potency of the German reference serum in terms of the proposed international reference serum was higher when assayed by complement-fixation methods than when assayed by flocculation methods. It was decided that the equation of the international unit to the existing German unit should be based on the results of complement-fixation tests, such as had been carried out in the Paul-Ehrlich-Institut. The Committee authorized the Statens Seruminstitut, Copenhagen, to establish the International Reference Preparation of Syphilitic Human Serum and to define its unitage when agreement had been obtained from the participants in the international collaborative study.¹

35. Leptospirosis Sera

The Committee considered that leptospirosis reference sera are required mainly for typing purposes, and noted that such sera are now being prepared by WHO/FAO Leptospirosis Reference Laboratories.² The Committee considered that there is no need at the present time for international standard sera for assay purposes.

36. Yellow Fever Immune Serum

The Committee noted that the Expert Committee on Yellow Fever Vaccine has recommended the establishment of international reference preparations of yellow fever immune serum and of serum non-immune to yellow fever virus.³ It noted that steps have been taken to produce sufficient quantities of immune serum for the establishment of an international reference preparation,⁴ and asked the Statens Seruminstitut, Copenhagen, in consultation with the West African Council for Medical Research, Lagos, Nigeria, to arrange a collaborative examination of this material for its suitability in mouse protection assays.

The Committee considered that it would not be appropriate to establish an international reference preparation of non-immune (normal human) serum. It noted that, since normal human serum is used as a reagent in

¹ Participants: Laboratory of Hygiene, Department of National Health and Welfare, Ottawa, Canada; Serodiagnostic Department, Statens Seruminstitut, Copenhagen, Denmark; Laboratoire de Sérologie, Faculté de Médecine et de Pharmacie de l'Université de Bordeaux, Bordeaux, France; School of Tropical Medicine, Calcutta, India; Gades Institut, University of Bergen, Bergen, Norway; Venereal Disease Research Laboratory, Communicable Disease Center, Chamblee, Ga., USA; Division of Laboratories and Research, New York State Department of Health, Albany, N.Y., USA; Bellevue Medical Center, New York University, New York, N.Y., USA

² WHO Secretariat, unpublished working document WHO/BS/413

³ WHO Public Health Series, No. 136, 1957

⁴ WHO Secretariat, unpublished working document WHO/BS/416
the assay of yellow fever immune serum, the Statens Serum Institute would hold and distribute such normal serum.

**GENERAL**

**37. Recommended Requirements for Biological Substances**

The Committee noted that WHO will convene a study group this year which will consider the problem of making recommendations on assay methods and on requirements for biological substances.¹ The Committee welcomed the fact that an attempt is now being made to deal with these complex matters and agreed that the Expert Committee on Biological Standardization could offer assistance or comments at a later stage, when the study group has drafted definitive proposals.

**38. Stability of Biological Standards**

The Committee noted a report ² on the stability of preparations of cardiolipin and lecithins. It also noted ³ that the International Standard for Tetanus Toxoid is stable after reconstitution if held at about 5°C.

**39. List of International Biological Standards**

The Committee was of the opinion that the list of International Biological Standards and Reference Preparations, included as an annex to the tenth report of the Committee,⁴ had enhanced the value of this report. The bibliographical information contained in the list facilitates access to available information about international standards. The Committee asked the WHO Secretariat to prepare an up-to-date list as an annex to the present report (see Annex, page 19).

The Committee recognized that the names of several international standards no longer conform to accepted international nomenclature and asked the WHO Secretariat to review the present names and to propose changes which would bring them into agreement with modern usage.

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¹ The report of this study group, which met in Geneva from 7 to 12 October 1957, has been issued as mimeographed document WHO/BS/IR/27.
² Fisk, N. H., unpublished working document WHO/BS/382
³ WHO Serological Reference Centre & Statistical Department, Statens Serum-institut, Copenhagen, unpublished working document WHO/VDT/Sero/65
Annex

I. INTERNATIONAL BIOLOGICAL STANDARDS AND REFERENCE PREPARATIONS

1958

The primary purpose underlying the establishment of International Biological Standards and Reference Preparations is to provide a means of ensuring uniformity throughout the world in the designation of potency of preparations which are used in the prophylaxis, therapy, or diagnosis of human and animal disease, and which cannot be characterized adequately by chemical and physical means. A secondary purpose in the provision of International Biological Standards is the facilitation of research work out of which clinical application may arise.

The 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 Reference Preparations, and distribute samples of these preparations, free of charge, to national laboratories for biological standards in all countries.
## A. IMMUNOLOGICAL

*Held by the International Laboratory for Biological Standards,*

<table>
<thead>
<tr>
<th>Substances</th>
<th>International Unit of present standard (mg)</th>
<th>Form in which dispensed</th>
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<tbody>
<tr>
<td><strong>ANTIGENS</strong></td>
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<td></td>
</tr>
<tr>
<td>Old tuberculin</td>
<td>0.0100</td>
<td>Ampoules containing 2 ml of Old tuberculin (100,000 International Units (I.U.) per ml)</td>
</tr>
<tr>
<td>Purified protein derivative of mammalian tuberculin</td>
<td>0.0000280</td>
<td>Ampoules containing 10 mg of PPD plus 4 mg of salts (500,000 I.U. per ampoule)</td>
</tr>
<tr>
<td>Purified protein derivative of avian tuberculin</td>
<td>0.0000726</td>
<td>Ampoules containing 10 mg of PPD plus 25.3 mg of salts (500,000 I.U. per ampoule)</td>
</tr>
<tr>
<td>Tetanus toxoid</td>
<td>0.03</td>
<td>Ampoules containing 25 mg (420 LF) of alcohol purified tetanus toxoid plus glycine (833 I.U. per ampoule)</td>
</tr>
<tr>
<td>Diphtheria toxoid, plain</td>
<td>0.50</td>
<td>Ampoules containing 50 mg (1730 LF) of alcohol purified diphtheria toxoid plus glycine (100 I.U. per ampoule)</td>
</tr>
<tr>
<td>Diphtheria toxoid, adsorbed</td>
<td>0.75</td>
<td>Ampoules containing 80 mg (50 LF) of diphtheria toxoid adsorbed to aluminium hydroxide, dried, plus lactose (107 I.U. per ampoule)</td>
</tr>
<tr>
<td>Schick test toxin (diphtheria)</td>
<td>0.0042</td>
<td>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)</td>
</tr>
<tr>
<td>Pertussis vaccine</td>
<td>1.5</td>
<td>Ampoules containing 52 mg of dried vaccine (34.7 I.U. per ampoule)</td>
</tr>
<tr>
<td>Cholera antigen (Inaba)</td>
<td></td>
<td>Ampoules containing approximately 100 mg of dried antigen</td>
</tr>
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</table>
### Substances

*Statens Serum Institut, Copenhagen, Denmark*

<table>
<thead>
<tr>
<th>Years of establishment of standards (in brackets, unitage of previous standards)</th>
<th>References (WHO/BS refers to unpublished working documents of the WHO Expert Committees on Biological Standardization)</th>
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<td><strong>Antigens (cont.)</strong></td>
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<tr>
<td>Cholera antigen (Ogawa)</td>
<td>—</td>
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<tr>
<td>Cholera vaccine (Inaba)</td>
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<tr>
<td>Cholera vaccine (Ogawa)</td>
<td>—</td>
</tr>
<tr>
<td>Cardiolipin</td>
<td>—</td>
</tr>
<tr>
<td>Lecithin (beef heart)</td>
<td>—</td>
</tr>
<tr>
<td>Lecithin (egg)</td>
<td>—</td>
</tr>
<tr>
<td><strong>ANTIBODIES</strong></td>
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</tr>
<tr>
<td>Tetanus antitoxin</td>
<td>0.3094</td>
</tr>
<tr>
<td>Diphtheria antitoxin</td>
<td>0.0628</td>
</tr>
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<td>Years of establishment of standards (in brackets, unitage of previous standards)</td>
<td>References (WHO/BS refers to unpublished working documents of the WHO Expert Committees on Biological Standardization)</td>
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<tr>
<td>1st Reference Preparation 1951</td>
<td>Bull. Wild Hlth Org., 1951, 4, 151; Wild Hlth Org. techn. Rep. Ser., 1952, <strong>56</strong>, 8; Cardiolipin antigens, 1955 (WHO Monograph No. 6); WHO/BS 72, 117, 238, 278, 278 Add.1, 305, 414</td>
</tr>
<tr>
<td>1st Reference Preparation 1951</td>
<td>Bull. Wild Hlth Org., 1951, 4, 151; 1955, <strong>13</strong>, 323; 1956, <strong>14</strong>, 567, 577; Wild Hlth Org. techn. Rep. Ser., 1952, <strong>56</strong>, 8; Cardiolipin antigens, 1955 (WHO Monograph No. 6); WHO/BS 72, 238, 278, 278 Add.1, 305</td>
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<tr>
<td>1st Reference Preparation 1951</td>
<td>Bull. Wild Hlth Org., 1951, 4, 151; 1955, <strong>13</strong>, 323; 1956, <strong>14</strong>, 567, 577; Wild Hlth Org. techn. Rep. Ser., 1952, <strong>56</strong>, 8; Cardiolipin antigens, 1955 (WHO Monograph No. 6); WHO/BS 72, 238, 278, 278 Add.1, 305</td>
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<tr>
<td>Antibodies (cont.)</td>
<td></td>
</tr>
<tr>
<td>Diphtheria antitoxin for flocculation test</td>
<td></td>
</tr>
<tr>
<td>Antidysentery serum (Shiga)</td>
<td>0.05</td>
</tr>
<tr>
<td>Gas gangrene antitoxin (perfringens) (Clostridium welchii type A antitoxin)</td>
<td>0.1132</td>
</tr>
<tr>
<td>Clostridium welchii (perfringens) type B antitoxin</td>
<td>0.0137</td>
</tr>
<tr>
<td>Clostridium welchii (perfringens) type D antitoxin</td>
<td>0.0657</td>
</tr>
<tr>
<td>Gas-gangrene antitoxin (vibrio septique)</td>
<td>0.118</td>
</tr>
<tr>
<td>Gas-gangrene antitoxin (oedematios)</td>
<td>0.1135</td>
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<tr>
<td>Gas-gangrene antitoxin (histolyticus)</td>
<td>0.2</td>
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<tr>
<td>Gas-gangrene antitoxin (Sordelli)</td>
<td>0.1334</td>
</tr>
<tr>
<td>Years of establishment of standards (in brackets, usage of previous standards)</td>
<td>References (WHO/BS refers to unpublished working documents of the WHO Expert Committees on Biological Standardization)</td>
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<tr>
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<tr>
<td>1st Standard 1935 (0.3575 mg)</td>
<td>Bull. Hith Org. L. o. N., 1938, 7, 698, 807; 1939, 8, 856; 1945/46, 12, 21</td>
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<tr>
<td>2nd Standard 1951</td>
<td>Bull. Hith Org. L. o. N., 1938, 7, 698, 807; 1939, 8, 856; 1945/46, 12, 21</td>
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<td>Substances</td>
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<tr>
<td>Antibodies (cont.)</td>
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</tr>
<tr>
<td>Staphylococcus α antitoxin</td>
<td>0.2376</td>
</tr>
<tr>
<td>Scarlet fever streptococcus anti- toxin</td>
<td>0.049</td>
</tr>
<tr>
<td>Swine erysipelas serum (anti-N)</td>
<td>0.14</td>
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<tr>
<td>Antipneumococcus serum (type 1)</td>
<td>0.0886</td>
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<tr>
<td>Antipneumococcus serum (type 2)</td>
<td>0.0894</td>
</tr>
<tr>
<td>Anti-Brucella abortus serum</td>
<td>0.091</td>
</tr>
<tr>
<td>Anti-Q-fever serum</td>
<td>0.1017</td>
</tr>
<tr>
<td>Antirabies serum</td>
<td>1.0</td>
</tr>
<tr>
<td>Anti-A blood-typing serum</td>
<td>0.3465</td>
</tr>
<tr>
<td>Anti-B blood-typing serum</td>
<td>0.3520</td>
</tr>
<tr>
<td>Antityphoid serum (provisional)</td>
<td>—</td>
</tr>
<tr>
<td>Years of establishment of standards (in brackets, unitage of previous standards)</td>
<td>References (WHO/BS refers to unpublished working documents of the WHO Expert Committees on Biological Standardization)</td>
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<tr>
<td>---</td>
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</tr>
<tr>
<td><strong>1st Standard 1934 (0.5000 mg)</strong>&lt;br&gt;2nd Standard 1938</td>
<td><em>Bull. Hlth Org. L. o. N.</em>, 1935, 4, 6, 68, 514; 1938, 7, 702, 845; 1945, 46, 12, 32</td>
</tr>
</tbody>
</table>
### B. PHARMACOLOGICAL

*Held by the International Laboratory for Biological Standards,*

<table>
<thead>
<tr>
<th>Substances</th>
<th>International Unit of present standard (mg)</th>
<th>Form in which dispensed</th>
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</thead>
<tbody>
<tr>
<td><strong>ANTIBIOTICS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillin</td>
<td>0.0005988</td>
<td>Ampoules containing 30 mg of sodium benzylpenicillin (1670 I.U. per mg)</td>
</tr>
<tr>
<td>Penicillin K</td>
<td></td>
<td>Ampoules containing 20 mg of 89.9% pure sodium η-heptylpenicillin, with 9.6% penicillin dihydro F and 0.5% penicillin F</td>
</tr>
<tr>
<td>Phenoxyethylpenicillin</td>
<td>0.00059</td>
<td>Ampoules containing 75 mg of phenoxyethylpenicillin (1695 I.U. per mg)</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>0.001282</td>
<td>Ampoules containing 25 mg of streptomycin sulfate (780 I.U. per mg)</td>
</tr>
</tbody>
</table>
### ELEVENTH REPORT

#### SUBSTANCES

**National Institute for Medical Research, London, England**

<table>
<thead>
<tr>
<th>Years of establishment of standards (in brackets, unitage of previous standards)</th>
<th>References (WHO/BS refers to unpublished working documents of the WHO Expert Committees on Biological Standardization)</th>
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<tbody>
<tr>
<td>Substances (cont.)</td>
<td>International Unit of present standard (mg)</td>
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<tr>
<td>--------------------</td>
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<tr>
<td>Dihydrostreptomycin</td>
<td>0.001316</td>
</tr>
<tr>
<td>Bacitracin</td>
<td>0.0182</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>0.00101</td>
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<tr>
<td>Chlortetracycline</td>
<td>0.001</td>
</tr>
<tr>
<td>Oxytetracycline</td>
<td>0.00111</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>0.001053</td>
</tr>
<tr>
<td>Polymyxin B</td>
<td>0.000127</td>
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**HORMONES**

<table>
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<th>Substances</th>
<th>International Unit of present standard (mg)</th>
<th>Form in which dispensed</th>
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</thead>
<tbody>
<tr>
<td>Oxytocic, vasopressor and antidiuretic substances (previously named: posterior pituitary lobe)</td>
<td>0.5</td>
<td>Ampoules containing 30 mg of acetone dried powder of whole posterior ox pituitary gland (2 oxytocic, 2 vasopressor, and 2 antidiuretic I.U. per mg)</td>
</tr>
<tr>
<td>Prolactin</td>
<td>0.1</td>
<td>Ampoules containing ten 10-mg tablets of dried active principle from anterior ox pituitary gland (approximately 100 I.U. per tablet)</td>
</tr>
<tr>
<td>Corticotrophin (previously named: adrenocorticotropic hormone)</td>
<td>0.88</td>
<td>Ampoules containing 28 mg of crude corticotrophin from anterior pig pituitary gland (1.14 I.U. per mg)</td>
</tr>
<tr>
<td>Years of establishment of standards (in brackets, unitage of previous standards)</td>
<td>References (WHO/BS refers to unpublished working documents of the WHO Expert Committees on Biological Standardization)</td>
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<tr>
<td><strong>2nd Standard 1942 (0.5 mg)</strong></td>
<td>Bull. WHO L. o. N., 1939, 8, 901; 1942/43, 10, 96; 1945/46, 12, 62; WHO/BS 208, 310, 350, 405</td>
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</tr>
<tr>
<td><strong>1st Standard 1950 (1.00 mg)</strong></td>
<td>Bull. WHO, 1956, 14, 543; <em>WHO</em> WHO techn. Rep. Ser., 1951, 16, 7; WHO/BS 85, 156, 158, 249, 262, 308, 356, 386, 387</td>
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<tr>
<td>Substances</td>
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<td>Form in which dispensed</td>
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<tr>
<td><strong>Hormones (cont.)</strong></td>
<td></td>
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</tr>
<tr>
<td>Thyrotrophin</td>
<td>13.5</td>
<td>Ampoules containing ten 20-mg tablets of a blend of 1 part purified thyrotrophin from anterior ox pituitary gland and 19 parts lactose (approximately 1.48 I.U. per tablet)</td>
</tr>
<tr>
<td>Growth hormone</td>
<td>1.0</td>
<td>Ampoules containing 30 mg of dried active principle from anterior pituitary gland (1 I.U. per mg)</td>
</tr>
<tr>
<td>Serum gonadotrophin</td>
<td>0.25</td>
<td>Ampoules containing twenty-five 10-mg tablets of dried active principle from serum of pregnant mares, diluted with lactose (approximately 100 I.U. per tablet)</td>
</tr>
<tr>
<td>Chorionic gonadotrophin</td>
<td>0.1</td>
<td>Ampoules containing 20 mg of purified insulin, largely from the ox (24.5 I.U. per mg)</td>
</tr>
<tr>
<td>Insulin</td>
<td>0.04082</td>
<td>Ampoules containing 50 mg of sodium salt of purified active principle from bovine tissue (130 I.U. per mg)</td>
</tr>
<tr>
<td><strong>VITAMINS, ENZYMES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D₃</td>
<td>0.000025</td>
<td>Bottles containing 10 g of a solution of vitamin D₃ in vegetable oil (1000 I.U. per g)</td>
</tr>
<tr>
<td>Hyaluronidase</td>
<td>0.1</td>
<td>Ampoules containing ten 20-mg tablets of dried bovine testicular hyaluronidase diluted with lactose (approximately 200 I.U. per tablet)</td>
</tr>
<tr>
<td><strong>MISCELLANEOUS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digitalis</td>
<td>76.0</td>
<td>Ampoules containing 2500 mg of dry powdered leaves of Digitalis purpurea (0.01316 I.U. per mg)</td>
</tr>
<tr>
<td>Years of establishment of standards (in brackets, unification of previous standards)</td>
<td>References (WHO/BS refers to unpublished working documents of the WHO Expert Committees on Biological Standardization)</td>
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<tr>
<td>Substances</td>
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<td>---------------------</td>
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<td>-------------------------------------------------------------</td>
</tr>
<tr>
<td>Miscellaneous (cont.)</td>
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<td></td>
</tr>
<tr>
<td>Neoarsphenamine</td>
<td></td>
<td>Ampoules containing 300 mg of neoarsphenamine</td>
</tr>
<tr>
<td>Sulfarsphenamine</td>
<td></td>
<td>Ampoules containing 300 mg of sulfarsphenamine</td>
</tr>
<tr>
<td>Oxophenarsine</td>
<td></td>
<td>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</td>
</tr>
<tr>
<td>Mel B</td>
<td></td>
<td>Ampoules containing 100 mg of melaminyl-4-phenylarsenodithioglycerol</td>
</tr>
<tr>
<td>MSb</td>
<td></td>
<td>Ampoules containing 500 mg of sodium ( p )-melaminylphenylstibonate polymer</td>
</tr>
<tr>
<td>Dimercaprol</td>
<td></td>
<td>Ampoules containing 2 ml of 2,3-dimercaptopropanol</td>
</tr>
<tr>
<td>Protamine</td>
<td></td>
<td>Ampoules containing 60 mg of protamine</td>
</tr>
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<td>Years of establishment of standards (in brackets, existence of previous standards)</td>
<td>References (WHO/BS refers to unpublished working documents of the WHO Expert Committees on Biological Standardization)</td>
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<td>3rd Standard 1951</td>
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<td>1st Standard 1952</td>
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<td>1st Reference Preparation 1954</td>
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<tr>
<td>1st Reference Preparation 1954</td>
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</table>
II. PROPOSED INTERNATIONAL BIOLOGICAL STANDARDS

International Standards or Reference Preparations have been proposed for the following substances. The international collaborative studies of those listed under C and L are now so far advanced that the International Laboratories for Biological Standards at the Statens Seruminstitut, Copenhagen, and at the National Institute for Medical Research, London, respectively, have been authorized to establish these standards and to define the international units. Preparations of those listed under S are at present being studied for their stability and suitability to serve as international standards or reference preparations, whereas preliminary efforts are being made for obtaining and examining suitable quantities of the substances listed under P for international standardization purposes.

<table>
<thead>
<tr>
<th>Substances</th>
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<tbody>
<tr>
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<tr>
<td>Syphilitic human serum</td>
<td>WHO/BS 239, 289 Rev.1, 304, 341, 379, 380 Rev.1</td>
</tr>
<tr>
<td>Anti-polioyelitis serum (type 1)</td>
<td>WHO/BS 313, 361, 363, 385</td>
</tr>
<tr>
<td>Anti-polioyelitis serum (type 2)</td>
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</tr>
<tr>
<td>Anti-polioyelitis serum (type 3)</td>
<td><em>Wld Hlth Org. techn. Rep. Ser.</em>, 1950, 2, 12; WHO/BS 46, 165, 213, 328,</td>
</tr>
<tr>
<td>Anti-Rh&lt;sub&gt;6&lt;/sub&gt; (anti-D) albumin-potentiaged blood-typing serum</td>
<td>366, 407</td>
</tr>
<tr>
<td>Antistreptolysin O</td>
<td>WHO/BS 402</td>
</tr>
<tr>
<td>Cardiolipin (3rd Int. Ref. Prep.)</td>
<td>WHO/BS 360, 414</td>
</tr>
<tr>
<td><strong>L</strong></td>
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</tr>
<tr>
<td>Vitamin B&lt;sub&gt;12&lt;/sub&gt;</td>
<td>WHO/BS 151, 207, 220, 270, 354, 391</td>
</tr>
<tr>
<td>Pyrogen</td>
<td>WHO/BS 34, 58, 61, 118, 142, 164, 209, 268, 355, 389</td>
</tr>
<tr>
<td>Prolactin (2nd Int. Standard)</td>
<td>WHO/BS 90, 147, 206, 264, 312, 365, 400</td>
</tr>
<tr>
<td>Insulin (4th Int. Standard)</td>
<td>WHO/BS 350, 405</td>
</tr>
<tr>
<td>Heparin (2nd Int. Standard)</td>
<td>WHO/BS 357, 388</td>
</tr>
<tr>
<td>Streptomycin (2nd Int. Standard)</td>
<td>WHO/BS 353, 390</td>
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<td>WHO/BS 369, 393</td>
</tr>
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<td>Substances</td>
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<td>----------------------------------------------------------------------------</td>
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<td>S</td>
<td>WHO BS 14, 73, 105, 371, 381, 383, 417</td>
</tr>
<tr>
<td>Smallpox vaccine</td>
<td>WHO BS 344, 377</td>
</tr>
<tr>
<td>Swine erysipelas vaccine</td>
<td>WHO BS 360</td>
</tr>
<tr>
<td>Egg lecithin (3rd Int. Ref. Prep.)</td>
<td>WHO BS 398</td>
</tr>
<tr>
<td>Neomycin</td>
<td>WHO BS 324, 349 Rev.1, 358 Rev.1, 403, 404</td>
</tr>
<tr>
<td>Procaine benzylpenicillin in oil with aluminium monostearate</td>
<td>WHO BS 392</td>
</tr>
<tr>
<td>Human menopausal gonadotrophin</td>
<td></td>
</tr>
</tbody>
</table>

| P                                                                          |                                                                                                                    |
| Rabies vaccine                                                             | WHO/BS 372, 411, 411 Annex 1                                                                                       |
| Typhoid vaccine                                                           | WHO/BS 217, 291, 301, 340, 378, 409                                                                                 |
| Poliomyelitis vaccine                                                     | WHO/BS 235, 260, 321, 376, 376 Annex 1                                                                           |
| Anti-yellow-fever serum                                                    | WHO/BS 416                                                                                                         |
| *Bohrops* antivenin                                                        | WHO/BS 316, 317, 333, 334, 364, 373                                                                               |
| *Naja* antivenin                                                           | WHO/BS 46, 165, 366, 407                                                                                            |
| Anti-rh⁺ (anti-C) blood-typing serum                                       | WHO/BS 356, 386, 387                                                                                               |
| Anti-rh⁻ (anti-E) blood-typing serum                                       |                                                                                                                    |
| Corticotrophin (3rd Int. Standard)                                        |                                                                                                                    |
| Nystatin                                                                  |                                                                                                                    |
| Oleandomycin                                                              |                                                                                                                    |

### III. AUTHOR’S PREPARATIONS

This class of substances was introduced in order to meet situations in which the pressure of more urgent work may make it impossible to create international standards without considerable delay, but in which further research work may be facilitated by the provision of common points of reference. The Expert Committees on Biological Standardization can take no responsibility for the authenticity or stability of any Author’s Preparations, but the storage and distribution of these preparations will be undertaken under the same conditions as for the International Standards, as a service to research workers. *(Wld Hlth Org. techn. Rep. Ser., 1955, 96, 18)*

The following hyperimmune horse sera were prepared by the late Dr A. Felix to serve as reference preparations for use in the serodiagnosis of typhoid and paratyphoid infections. Samples of these Author’s Preparations are available on request from the International Laboratory for

Anti-Salmonella typhi H serum
Anti-Salmonella typhi O serum
Anti-Salmonella typhi Vi serum
Anti-Salmonella paratyphi A H serum
Anti-Salmonella paratyphi B H serum
Anti-Salmonella paratyphi B non-specific H serum
Anti-Salmonella paratyphi B O serum

IV. 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: Wild Hth Org. techn. Rep. Ser., 1952, 56, 14; 1953, 68, 25; 1957, 127, 9, 19)

Samples of the remaining stock of Staphylococcus β Antitoxin may be obtained on request from the International Laboratory for Biological Standards, Statens Serum Institut, Copenhagen, Denmark, by laboratories desiring to establish their own working standards for research purposes.

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

<table>
<thead>
<tr>
<th>Substances</th>
<th>International Unit (mg)</th>
<th>Adopted</th>
<th>Discontinued</th>
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<tr>
<td>Arsphenamine</td>
<td>—</td>
<td>1925</td>
<td>1935</td>
</tr>
<tr>
<td>Ouabain</td>
<td>—</td>
<td>1928</td>
<td>1954</td>
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<tr>
<td>Provitamin A (β-carotene)</td>
<td>0.0006</td>
<td>1931</td>
<td>1956</td>
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<tr>
<td>Vitamin B (synthetic vitamin B₁)</td>
<td>0.003</td>
<td>1931</td>
<td>1956</td>
</tr>
<tr>
<td>*Oestrone</td>
<td>0.0001</td>
<td>1932</td>
<td>1949</td>
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<tr>
<td>Vitamin C</td>
<td>0.05</td>
<td>1934</td>
<td>1956</td>
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<td>Oestradiol monobenzoate</td>
<td>0.0001</td>
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<td>Androsterone</td>
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<td>1935</td>
<td>1950</td>
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<td>*Progestosterone</td>
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<td>1935</td>
<td>1955</td>
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<td>Vitamin E (α-tocopheryl acetate)</td>
<td>1.0</td>
<td>1941</td>
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<td>*Vitamin A (vitamin A acetate)</td>
<td>0.000344</td>
<td>1949</td>
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<td>*Tubocurarine (d-tubocurarine chlo-ride)</td>
<td>1.0</td>
<td>1951</td>
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<td>Staphylococcus β antitoxin</td>
<td>2.623</td>
<td>1952</td>
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<td>*Chloramphenicol</td>
<td>—</td>
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<td>The Agreement of Brussels, 1924, respecting Facilities to be given to</td>
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<td>Merchant Seamen for the Treatment of Venereal Diseases</td>
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THERAPEUTIC AND
DIAGNOSTIC SUBSTANCES

Introduction


The assay of diphtheria toxin—Julia Gerwing, D.A. Long & Marjorie V. Mussett

The assay of penicillin in blood-serum using Sarcina lutea—J. W. Lightbown & D. Sulitzeanu


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