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**EXPERT COMMITTEE ON
BIOLOGICAL STANDARDIZATION**

Sixth Report

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EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION

Sixth Session

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- * Attended during the discussion of subjects of special interest to FAO.

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EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION

Sixth Report ¹

The sixth session of the Expert Committee on Biological Standardization was held in Geneva from 20 to 25 October 1952.

The Deputy Director-General welcomed the experts and referred to the impressive and accelerating rate of increase in the number of international biological standards. This reflects an ever-increasing burden of responsibility, willingly shouldered by the committee and the other members of the expert panel. Without both their advisory and their technical activities it would be impossible for WHO to discharge its obligations to fullest effect in this vital field of work. WHO is therefore most grateful to them for their unremitting assistance.

An important development which the Deputy Director-General had noted was the increasing proportion of standards intended for diagnostic rather than for therapeutic purposes. Among these are several which are to be used in the diagnosis of zoonoses. This involves WHO in still closer co-operation with the Food and Agriculture Organization of the United Nations (FAO), a development which cannot fail to bring both organizations nearer to their common goal of increased human welfare. He wished therefore to express also to FAO the thanks of WHO for its continued co-operation in this work.

IMMUNOLOGICAL

ANTIGENS AND VACCINES

1. Tuberculins

Purified protein derivative (PPD) of mammalian tuberculin ²

The committee considered the unitage to be assigned to the International Standard for Purified Protein Derivative of Mammalian Tuberculin.

¹ The Executive Board, at its eleventh session, adopted the following resolution:
The Executive Board

1. NOTES the sixth report of the Expert Committee on Biological Standardization;
2. THANKS the members of the committee for their work; and
3. AUTHORIZES publication of the report
(Resolution EB11.R17, *Off. Rec. World Hlth Org.* 46, 6)

² Statens Seruminstitut, Department of Biological Standards, Copenhagen, unpublished working document WHO/BS/173; Green, H. H., unpublished working document WHO/BS/181

The desirability of equating the unit of this material to the International Unit of Old Tuberculin, as far as it is possible to do this, was confirmed. The standard established last year,³ prepared by Dr. Florence Seibert of the Henry Phipps Institute, Philadelphia, Pa., USA (by drying in ampoules a solution of PPD of mammalian tuberculin in phosphate buffer), includes a certain amount of non-specific material. In previously published work the unit of PPD of mammalian tuberculin has been regarded as 0.00002 mg of material which contains no buffer. Since the international standard does contain such buffer, the unit of the standard is somewhat larger and has been determined as 0.000028 mg. The committee decided that one International Unit is contained in 0.000028 mg of the International Standard for Purified Protein Derivative of Mammalian Tuberculin.

*PPD of avian tuberculin*⁴

The committee noted certain difficulties encountered in the preparation of the proposed International Standard for Purified Protein Derivative of Avian Tuberculin, and in the supply of stable cultures of strain D4 of *Mycobacterium tuberculosis* (avian). The Weybridge Laboratory, Surrey, United Kingdom, is continuing work on this problem and it is expected that these materials will be available for examination within the coming year.

2. Diphtheria Toxoids and Toxin

See below, under section 3, "Pertussis vaccine".

3. Pertussis Vaccine

The committee considered the recommendations made in a memorandum submitted by the Chairman (Dr. G. S. Wilson) of the WHO Conference of Heads of Laboratories producing Diphtheria and Pertussis Vaccines, held in Dubrovnik, Yugoslavia, from 13 to 18 October 1952 :⁵

(a) International Standard for Diphtheria Toxoid Adsorbed

The committee noted the recommendation that such a standard preparation should be set up at an early date, and reported that considerable progress had already been made, along the lines proposed at its fifth session.⁶

³ *World Hlth Org. techn. Rep. Ser.* 1952, 56, 6

⁴ Green, H. H., unpublished working document WHO/BS/181

⁵ *World Hlth Org. techn. Rep. Ser.* 1953, 61

⁶ *World Hlth Org. techn. Rep. Ser.* 1952, 56, 5

(b) *International reference preparation for opacity*

The committee noted that the conference recommended the establishment of an international reference preparation for opacity, and reported that such a standard was about to be established (see section 4, below).

(c) *Proposed reference preparation of Schick toxin*

The committee noted the recommendation of the conference that the provision of such a reference preparation should be considered, and authorized the Statens Seruminstitut, Copenhagen, to investigate the possibility of obtaining suitable stable material for this purpose.

(d) *Proposed standard for pertussis vaccine*

The committee noted that the conference recommended the setting up of a standard for pertussis vaccine, and authorized the Statens Seruminstitut to continue its investigations into the possibilities of doing so.

(e) *Proposed standard for anti-pertussis serum*

The committee noted the recommendation of the conference that it should consider the provision of a reference standard agglutinating anti-pertussis serum, and authorized the Statens Seruminstitut to investigate the possibility of providing such a standard.

(f) *Proposed reference strain of virulent Haemophilus pertussis*

The committee noted that the conference recommended that the provision of a reference strain of virulent *Haemophilus pertussis* should be considered. The committee was, however, not convinced of the usefulness of providing such a reference strain and was of the opinion that the provision of virulent strains could be undertaken by consultation and the exchange of strains between laboratories interested in this problem.

4. Opacity Standard for Bacterial Suspensions⁷

The committee noted that the Statens Seruminstitut, Copenhagen, had collected opinions on the standard for opacity used by the National Institutes of Health, Bethesda Md., USA. Opinions were unanimous that this material is suitable for the International Reference Preparation for Opacity. The committee, therefore, authorized the Statens Serum-

⁷ Statens Seruminstitut, Department of Biological Standards, Copenhagen, unpublished working document WHO/BS/172

institut, in consultation with the National Institutes of Health, Bethesda, to establish either the existing material or a new batch of equivalent material as the International Reference Preparation for Opacity, and to assign to it an opacity of 10 International Units per millilitre.

5. Smallpox Vaccines⁸

The committee noted a report by the Consultative Group on Laboratory Investigation of Dried Smallpox Vaccine, describing plans for the collaborative examination of a number of fluid and dried vaccines in order to determine the value of dried vaccines. As a first stage the work is now limited to observations in laboratory animals.

6. Cholera Vaccines and Antigens

Vaccines

The committee noted that examination of the proposed standard preparations for cholera vaccines is held up by the lack both of virulent cholera strains and of susceptible mice in the participating laboratories. The committee accepted the offer by the Pasteur Institute, Paris, and the Central Research Institute, Kasauli, India, to distribute virulent cholera vibrios, and the offer by the National Institutes of Health, Bethesda, to supply breeding colonies of susceptible mice to the participating laboratories.

Antigens for the preparation of diagnostic sera; diagnostic sera⁹

The committee noted that (a) dried preparations of cholera vibrios (Ogawa and Inaba respectively) prepared by the late Dr. P. B. Bruce White, National Institute for Medical Research, London, to be used for the production of diagnostic sera, and (b) monospecific Ogawa and Inaba agglutinating sera, prepared by Lieutenant-Colonel M. L. Ahuja, Central Research Institute, Kasauli, were now available at the Statens Seruminstitut, Copenhagen. The committee decided that these preparations should be accepted as international reference preparations, subject to an examination as to their suitability. The committee asked the Statens Seruminstitut and the Haffkine Institute, Bombay, to undertake this investigation in collaboration with other interested laboratories.

⁸ Consultative Group on Laboratory Investigation of Dried Smallpox Vaccine, unpublished working document WHO/Smallpox/3

⁹ Statens Seruminstitut, Department of Biological Standards, Copenhagen, unpublished working document WHO/BS/167

7. Cardiolipin and Lecithins

The committee authorized the Statens Seruminstitut, in consultation with the New York State Department of Health, Albany N.Y., USA, to proceed with the collection and characterization of batches of cardiolipin and of beef-heart lecithin and egg lecithin suitable for replacing the provisional international reference preparations of these materials. The committee recommended that a collaborative study of the reactivity of the preparations be instituted and that the stability tests already in progress¹⁰ be continued.

SERA

8. Anti-Brucella abortus Serum¹¹

The committee noted that the Weybridge Veterinary Laboratory had obtained, for the proposed international standard, a batch of bovine serum equivalent in potency to the standard which they have already held for many years on behalf of the Office International des Epizooties (OIE). This batch of serum has now been examined by a number of interested medical workers, all of whom are agreed that it is suitable for adoption as the international standard. The committee therefore established the batch as the International Standard for *Anti-Brucella abortus* Serum. The committee discussed the question of assigning a unitage to this serum, and it was agreed that, although there are some advantages in a unit notation for diagnostic sera in general, there was as yet insufficient information for the committee to assign unitages to all sera of this kind. The committee further decided to reconsider this question at the earliest opportunity.

It was also decided that a portion of the international standard should be held by the Weybridge Veterinary Laboratory acting as co-custodian with the Statens Seruminstitut. This arrangement is especially appropriate in view of the fact that the OIE standard, on which this new international standard is based, was in use as long ago as 1933 and has been distributed from Weybridge since 1937.¹²

9. Q Fever Serum¹³

At its fifth session the committee decided to establish an International Standard for Q Fever Serum, and agreed that it should consist of pooled

¹⁰ Unpublished working document WHO/VD/SERO/14

¹¹ Stableforth, A. W., unpublished working document WHO/BS/162

¹² Stableforth, A. W., unpublished working document WHO/BS/128

¹³ Kaplan, M. M., unpublished working document WHO/BS/177

human sera. It has since been suggested that bovine serum should be used instead, since such material will be easier to obtain and to replace in the amounts required. The committee agreed that this would be desirable. It was noted that the material had now been freeze-dried and that a collaborative investigation of its suitability is in progress. It was agreed that the question of assigning a unitage should be considered at a later session of the committee.

The committee recommended that, as in the case of anti-*Brucella abortus* serum, a portion of the International Standard for Q Fever Serum should be held at the Veterinary Laboratory, Weybridge, acting as co-custodian with the Statens Seruminstitut.

10. Cholera Sera

See page 8 under "Antigens for the preparation of diagnostic sera ; diagnostic sera".

11. Typhoid and Paratyphoid Sera¹⁴

The committee noted that Dr. A. Felix of the Central Enteric Reference Laboratory and Bureau, Public Health Laboratory Service (Medical Research Council), London, has now almost completed the preparation of the sera for the specification of agglutinable suspensions for use in the serodiagnosis of typhoid and paratyphoid infections, and that the National Institute for Medical Research, London, is preparing these materials in a form suitable for issue as prospective international standards. When the preparations are completed, the Statens Seruminstitut will arrange for a collaborative examination of their suitability.

The committee further noted that the provisional standard anti-typhoid serum,¹⁵ prepared also by Dr. Felix, has been available for general distribution since December 1950.

12. Pertussis Serum

See page 6 under "Pertussis vaccine".

¹⁴ *World Hlth Org. techn. Rep. Ser.* 1950, 2, 6; Felix, A. (1950) *Bull. World Hlth Org.* 2, 643

¹⁵ National Institute for Medical Research, Department of Biological Standards, London, unpublished working document WHO/BS/182

13. Scarlet Fever Streptococcus Antitoxin¹⁶

The committee established the material already available as the International Standard for Scarlet Fever Streptococcus Antitoxin. The difference in magnitude between the national unit already in existence was discussed and it was agreed that the International Unit should be made equivalent as far as possible to the unit used by the National Institutes of Health, Bethesda. One International Unit is therefore contained in 0.049 mg of the International Standard for Scarlet Fever Streptococcus Antitoxin.

14. Staphylococcus β Antitoxin¹⁷

Since the demand for Staphylococcus β antitoxin has been steady for a number of years and since the material seems to be satisfactory in all respects the committee decided that the standard should no longer be regarded as provisional and therefore established it as the International Standard for Staphylococcus β Antitoxin. One International Unit is contained in 2.623 mg of the standard.

15. Gas-Gangrene Antitoxin (Oedematiens)

The committee noted that the present International Standard for Gas-Gangrene Antitoxin (Oedematiens) is nearly exhausted and authorized the Statens Seruminstitut to establish the material which had been used as a temporary standard during the Second World War as the Second International Standard for Gas-Gangrene Antitoxin (Oedematiens). The proposed new standard has already been tested and found suitable in comparison with the existing international standard. The international unit will be contained in 0.1135 mg of the new standard.¹⁸

16. Rh Blood-Typing Sera¹⁹

The committee noted the progress made by the Lister Institute of Preventive Medicine, London, in collecting Rh blood-grouping sera suitable for establishment as international standards. Sufficient of the

¹⁶ Miles, A. A., unpublished working document WHO/BS/150

¹⁷ Ipsen, J. & Rostock, O. (1946) *Bull. Hlth Org. L.o.N.* **12**, 390; Statens Seruminstitut, Copenhagen, Department of Biological Standards, unpublished working document WHO/BS/166

¹⁸ Hartley, P. & Evans, D. G. (1943) *Bull. Hlth Org. L.o.N.* **10**, 97

¹⁹ National Institute for Medical Research, Department of Biological Standards, London, unpublished working document WHO/BS/165

anti-D serum had already been obtained and was being distributed into ampoules. It was agreed that this material should be subjected to a collaborative examination of its suitability as an international standard.

The collection of anti-C and anti-E sera is proceeding.

17. Syphilitic Sera ²⁰

The committee noted that considerable progress has been made in obtaining freeze-dried sera from syphilitic and non-syphilitic donors for the collection held at the Statens Seruminstitut, to be used in the evaluation of serological methods in the diagnosis of syphilis.

PHARMACOLOGICAL

HORMONES

18. Insulin and Insulin Preparations ^{21, 22}

The committee noted that the Third International Standard for Insulin (1952) has been established and that one International Unit is contained in 0.04082 mg of the new standard. This material is now available for distribution from the National Institute for Medical Research, London.

The committee discussed the need for international standards for globin-zinc insulin and protamine-zinc insulin and authorized the National Institute for Medical Research to investigate whether standard preparations of globin and protamine uncombined with insulin, to be used in combination with the existing International Standard for Insulin, would be preferable. The committee recommended that the National Institute for Medical Research should try to obtain suitable batches of both globin and protamine, and to obtain information about the stability of globin-zinc insulin and protamine-zinc insulin preparations.

There is likely to be a considerable increase in the demand for the International Standard for Insulin and the committee accepted the offer made by the United States Pharmacopoeia Revision Committee to collect a large quantity of insulin for the Fourth International Standard and possibly, in combination with globin and protamine, as international standards

²⁰ Unpublished working documents WHO/VD/SERO/15, WHO/VD/SERO/16

²¹ Miles, A. A., Mussett, M. V. & Perry, W. L. M. (1952) *Bull. World Hlth Org.* 7, 445

²² Miles, A. A. & Perry, W. L. M., unpublished working document WHO/BS/138

for these preparations of insulin. The committee therefore authorized the National Institute for Medical Research, in consultation with the Insulin Committee of the University of Toronto, Canada and the United States Pharmacopoeia Revision Committee to proceed with the collection and examination of suitable material.

As a result of inquiries made by the Department of National Health and Welfare, Ottawa,²³ the committee decided that no tests need be recommended for the presence of glycogenolytic factors in manufactured batches of insulin.

19. Adrenocorticotrophic Hormone²⁴

The committee decided that the proposed Second International Standard for Adrenocorticotrophic Hormone should be a preparation similar to the existing standard. It was considered that there is still insufficient information about the nature of oxycellulose purified preparations to justify the use of such a preparation for the new standard. It was accordingly decided that the four contributions to the new standard should be blended and that the form of the standard should be decided by consultation between the National Institute for Medical Research, and the United States Pharmacopoeia Revision Committee. The proposed new standard is then to be subjected to a collaborative assay in comparison with the existing standard in various laboratories throughout the world.

The committee further decided that a quantity of adrenocorticotrophic hormone should be purified by the oxycellulose method and distributed for concurrent examination with the proposed new standard, with a view to determining whether such purified material can be assayed in terms of a crude standard or will require the establishment of a new and separate standard. The committee authorized the National Institute for Medical Research, in consultation with the United States Pharmacopoeia Revision Committee, to proceed with the collection of such a quantity of purified material, possibly using a part of the blend of the four batches already received.

20. Thyrotrophin²⁵

The committee noted that difficulties had arisen in setting up the proposed International Standard for Thyrotrophin. The committee decided

²³ Morrell, C. A., unpublished working document WHO/BS/139

²⁴ National Institute for Medical Research, Department of Biological Standards, London, unpublished working document WHO/BS/156; Nichols, A. B., unpublished working document WHO/BS/158

²⁵ Miles, A. A., unpublished working document WHO/BS/155; Nichols, A. B., unpublished working document WHO/BS/158

that the two contributions of beef thyrotrophin already received should be blended, without the addition of material from any other animal source. The blend should be diluted with an inert substance and put up in tablet form. It was recommended that the National Institute for Medical Research, in consultation with the United States Pharmacopoeia Revision Committee, should proceed with this as soon as possible. The committee further recommended that the standard in its final form should be distributed to laboratories in various parts of the world for assay in comparison with the existing reference substance of the United States Pharmacopoeia.

21. Growth Hormone ²⁶

The committee recommended that the National Institute for Medical Research should continue its attempts to obtain a sufficient supply of suitable material for the proposed international standard. It also decided that this material, when obtained should be subjected to a collaborative assay against reference material supplied by Dr. C. H. Li, University of California. The committee discussed the form in which the standard should be distributed and the methods of assay suitable for use in the collaborative study, and authorized the National Institute for Medical Research to proceed with the necessary consultations and investigations.

22. Chorionic Gonadotrophin ²⁷

The committee noted that four batches of chorionic gonadotrophin had been collected by the National Institute for Medical Research, and were to be distributed to a number of interested laboratories for assay by different methods with a view to comparing the precision and accuracy of these methods, and recommended that the investigation should be continued.

VITAMINS AND ENZYMES

23. Vitamin A ²⁸

The committee discussed the use of the present International Standard for Vitamin A (pure vitamin A acetate). The distribution of this standard is very widespread but it is now used almost entirely for the calibration of

²⁶ National Institute for Medical Research, Department of Biological Standards, London, unpublished working document WHO/BS/140; Nichols, A. B., unpublished working document WHO/BS/158

²⁷ Jacques, R. & Perry, W. L. M., unpublished working document WHO/BS/141

²⁸ Miles, A. A., unpublished working document WHO/BS/154

spectrophotometric instruments and not as a standard in biological assays. Supplies of the current standard are almost exhausted but the committee decided not to replace it (see section 44, page 20).

24. Vitamin B₁₂²⁹

The committee noted the progress made in the collection of suitable material for the proposed International Standard for Vitamin B₁₂ and asked the National Institute for Medical Research, to proceed with the collaborative examination of the material. The committee reaffirmed that the International Unit should be contained in one microgram of crystalline Vitamin B₁₂.

25. Hyaluronidase³⁰

The committee discussed the progress made towards setting up an International Standard for Hyaluronidase and noted that the United States Pharmacopoeia Revision Committee was proceeding with a pilot trial of bovine testicular hyaluronidase in order to study the method of assay. The committee authorized the National Institute for Medical Research, in consultation with the United States Pharmacopoeia Revision Committee, and subject to a satisfactory result of the pilot experiments, to proceed with the collection of a number of batches of bovine testicular hyaluronidase for blending to form the proposed international standard.

26. Thrombin³¹

The committee noted that, owing to the danger of homologous serum hepatitis, the use of human thrombin is becoming restricted, and agreed that the standard preparation of thrombin should be made from bovine material. It authorized the National Institute for Medical Research, London, in consultation with the National Institutes of Health, Bethesda, to proceed with the collection of bovine thrombin for the proposed international standard and to arrange for a collaborative examination of its suitability for this purpose.

²⁹ National Institute for Medical Research, Department of Biological Standards, London, unpublished working document WHO/BS/142; Nichols, A. B., unpublished working document WHO/BS/164

³⁰ National Institute for Medical Research, Department of Biological Standards, London, unpublished working document WHO/BS/160; Nichols, A. B., unpublished working document WHO/BS/163

³¹ National Institute for Medical Research, Department of Biological Standards, London, unpublished working document WHO/BS/161

ANTIBIOTICS

27. Penicillin³²

The committee noted that the proposed Second International Standard for Penicillin had been assayed by a number of laboratories in different parts of the world against the existing international standard, and agreed to establish it as the Second International Standard for Penicillin. One International Unit is contained in 0.0005988 mg of the international standard.

28. Aureomycin³³

The committee noted that the proposed International Standard for Aureomycin had been subjected to a collaborative assay and that the results were being analysed. It authorized the National Institute for Medical Research to establish this material as the International Standard for Aureomycin and to assign a unitage to it on the basis of the results of the collaborative examination.

29. Bacitracin³⁴

The committee noted that the proposed International Standard for Bacitracin had been subjected to a collaborative assay and that the results were being analysed. It authorized the National Institute for Medical Research to establish this material as the International Standard for Bacitracin and to assign a unitage to it on the basis of the results of the collaborative examination.

30. Oxytetracycline^{35, 36}

The committee noted that the proposed International Standard had been subjected to a collaborative examination for its suitability and that

³² Humphrey, J. H., Mussett, M. V. & Perry, W. L. M. (1953) *Bull. World Hlth Org.* **8** (*in press*).

³³ National Institute for Medical Research, Department of Biological Standards, London, unpublished working document WHO/BS/143

³⁴ National Institute for Medical Research, Department of Biological Standards, London, unpublished working document WHO/BS/144

³⁵ Oxytetracycline is the international non-proprietary name for "Terramycin" (see *Chron. World Hlth Org.* 1953, 7, 41).

³⁶ National Institute for Medical Research, Department of Biological Standards, London, unpublished working document WHO/BS/145

variations had been found in the activity of the material in different ampoules. The committee recommended that the National Institute for Medical Research should continue its investigation of this heterogeneity and, if necessary, should endeavour to obtain a more suitable batch of material to serve as the international standard.

31. Dihydrostreptomycin³⁷

The committee noted that the proposed International Standard for Dihydrostreptomycin had been subjected to a collaborative assay and that the results were being analysed. It authorized the National Institute for Medical Research to establish this material as the international standard and to assign a unitage to it on the basis of the results of the collaborative examination.

32. Pristimerin³⁸

The committee noted that a sample of Pristimerin had been received as an author's preparation (see section 43, page 20) at the National Institute for Medical Research, and was available to interested workers.

MISCELLANEOUS

33. Melaminyl Trypanocides³⁹

The committee noted that the National Institute for Medical Research had obtained materials for the proposed reference preparations of Melarsen, Mel B and MSb. It was agreed that although Melarsen could be characterized completely by chemical tests, a collaborative examination of all three preparations should be carried out, and the committee authorized the National Institute for Medical Research to distribute these materials for collaborative examination.

³⁷ National Institute for Medical Research, Department of Biological Standards, London, unpublished working document WHO/BS/146

³⁸ National Institute for Medical Research, Department of Biological Standards, London, unpublished working document WHO/BS/151; Bhātnagar, S. S. & Divekar, P. V. (1951) *J. sci. industr. res.* **10B**, 56

³⁹ National Institute for Medical Research, Department of Biological Standards, London, unpublished working document WHO/BS/148

34. Dimercaprol⁴⁰

The committee established the existing British standard as the International Standard for Dimercaprol. It authorized the National Institute for Medical Research to proceed with the collection of a suitable quantity of material to replace this standard when necessary.

35. Dextran Sulfate⁴¹

The committee noted that a sample of dextran sulfate had been received as an author's preparation (see section 43, page 20) at the National Institute for Medical Research. The committee recommended that samples of this material should be distributed to interested workers throughout the world for examination and consultation with a view to establishing, if necessary, an international standard.

36. Male Fern⁴²

The committee noted that samples of male fern had been received by the National Institute for Medical Research. It had not yet proved possible to have these materials assayed, and the committee recommended that attempts to interest workers in this problem should be continued.

37. Pyrogens⁴³

The committee noted that the National Institute for Medical Research had arranged to collect two different preparations of pyrogens, one a crude polysaccharide and the other a highly purified polysaccharide. It recommended that both these preparations should be freeze-dried in ampoules and that samples should then be sent to interested workers throughout the world for examination. All participants in this study should be asked to examine both materials for their suitability as international standards for the potency of pyrogens and also for determining the sensitivity of rabbits. It was further recommended that the two preparations should be assayed against one another by as wide a variety of methods as possible in order to obtain information about the precision and accuracy of assay methods.

⁴⁰ National Institute for Medical Research, Department of Biological Standards, London, unpublished working document WHO/BS/159

⁴¹ National Institute for Medical Research, Department of Biological Standards, London, unpublished working document WHO/BS/151

⁴² National Institute for Medical Research, Department of Biological Standards, London, unpublished working document WHO/BS/149

⁴³ Perry, W. L. M., unpublished working document WHO/BS/147

38. Tubocurarine

The committee decided that the International Standard for D-Tubocurarine should in future be known as the International Standard for Tubocurarine.

GENERAL

39. Distribution of Standards from the International Centres, and their Depletion-Rates

The committee noted the reports submitted by the Statens Serum-institut, Copenhagen,⁴⁴ and the National Institute for Medical Research, London,⁴⁵ on the distribution of international standards. These reports also quote the existing stocks and depletion-rates of all the current standards. The information appears in tabular form as Annexes 1 and 2 to the present report (see pages 23 and 24).

40. Stability of Some Serum Standards⁴⁶

The committee discussed a report submitted by the Statens Serum-institut on stability tests carried out on the International Standards for Tetanus Antitoxin and Antidysentery Serum (Shiga). These tests have been carried out both on the dried standards themselves and on the solutions in glycerol as dispensed to the national control centres. The results indicate that the stability of the dried standard preparations is very high, but the committee recommended that the Statens Seruminstitut continue these investigations. It was further suggested that experiments should be carried out to determine the moisture content of the dried serum standards and its effect on their stability. The glycerol solutions of the sera are considerably less stable but the committee agreed that the currency period of six months is safe. The Statens Seruminstitut was asked to continue work on this problem especially at temperatures intermediate between those already investigated.

⁴⁴ Statens Seruminstitut, Department of Biological Standards, Copenhagen, unpublished working document WHO/BS/168

⁴⁵ National Institute for Medical Research, Department of Biological Standards, London, unpublished working document WHO/BS/153

⁴⁶ Statens Seruminstitut, Department of Biological Standards, Copenhagen, unpublished working document WHO/BS/169

41. Postal Transmission of Biological Materials⁴⁷

The committee noted that WHO had been in consultation with the Universal Postal Union, with a view to facilitating rapid transport of biological materials. Arrangements have been made for continued collaboration with the Union in this connexion, and the committee felt that it would be unnecessary to consult any other official body for further help in the matter at the present stage.

42. National Control Centres

The committee discussed the functions and activities of national control centres and reaffirmed its recommendation made at the fifth session⁴⁸ that personal contacts with the centres should be extended by visits of technical experts on biological standards, preferably attached to WHO. The committee was strongly of the opinion that such visits are essential for maximal efficiency in the distribution and use of the international standards throughout the world.

43. Author's Preparations⁴⁹

The committee discussed the collection of author's preparations initiated at its last session. It decided that the collection should not be restricted to antibiotics but should be extended to include other biological active materials. It was further agreed that no material should be received as an author's preparation without the approval of the committee (see sections 32 and 35, pages 17 and 18).

44. Proposed Collection of Authentic Chemical Substances⁵⁰

The committee noted that the Expert Committee on the International Pharmacopoeia had approved the principle of the establishment of a collection of authentic chemical substances.⁵¹ It was decided to forward the specific recommendations contained in Annex 3 (page 25) of this report to the Expert Committee on the International Pharmacopoeia.

⁴⁷ Unpublished working document WHO/BS/176

⁴⁸ *World Hlth Org. techn. Rep. Ser.* 1952, 56, 16

⁴⁹ National Institute for Medical Research, Department of Biological Standards, London, unpublished working document WHO/BS/151

⁵⁰ Miles, A. A. & Perry, W. L. M., unpublished working document WHO/BS/152

⁵¹ WHO Expert Committee on the International Pharmacopoeia, Report on tenth session, unpublished working document WHO/Pharm/220, p. 12

The committee accepted as a general principle that standard preparations which are authentic chemicals should, whether or not they are used in biological tests, be the responsibility of the Expert Committee on the International Pharmacopoeia.

45. Recommended Diagnostic Methods⁵²

The committee reviewed the information collected by WHO on the need for a compilation of recommended diagnostic methods, but considered that this committee was probably not the most suitable body to advise on the details of a compilation of routine clinical pathological procedures. The committee nevertheless requested WHO to make further inquiries about the general need for such a publication.

The committee agreed that a useful purpose might be served by a compilation of suggested methods for the use (including the preparation of substandards) of some international standards, particularly those used for diagnostic purposes, and agreed that it could properly accept responsibility for advising on such a collection.

46. Questions Referred by the Expert Committee on the International Pharmacopoeia

(a) The committee approved draft monographs on insulin preparations for Volume II of the *Pharmacopoea Internationalis*.⁵³

(b) Members will send their comments before 1 December 1952 on various other draft monographs and appendices for inclusion in Volume II of the *Pharmacopoea Internationalis*. The National Institute for Medical Research, will, if possible, establish the International Standard for Aureomycin in time for the inclusion of a monograph on aureomycin in Volume II of the *Pharmacopoea Internationalis*.

47. Reports on BCG Vaccine Production-Centres

(a) The committee approved the reports of Dr. W. Aeg. Timmerman on BCG production-laboratories at Karachi, Athens and Ankara.⁵⁴

⁵² Unpublished working document WHO/BS/175

⁵³ Unpublished working documents WHO/Pharm/182 Rev.1, WHO/Pharm/184 Rev.1

⁵⁴ Timmerman, W. Aeg., unpublished working documents WHO/BS/178, WHO/BS/179, WHO/BS/180

(b) The committee decided that the requirements for laboratories engaged in the preparation of BCG vaccine should be amended by the inclusion of a clause making it necessary for such laboratories to provide a means of excluding daylight from those rooms in which BCG strains and vaccines are handled.

(c) The committee recommended that WHO should study the requirements for laboratories engaged in the preparation of BCG vaccine, with a view to modifying them in the light of present knowledge.

48. List of International Standards and Reference Preparations

In the fifth report a definitive list of international standards and reference preparations was published.⁵⁵ The following should be added to that list:

- (1) "International Preparation" of Anterior Pituitary Gland.⁵⁶
- (2) Provisional International Standard Anti-Typhoid Serum (see section 11, page 10).
- (3) International Standard for Anti-*Brucella abortus* Serum (see section 8, page 9).
- (4) International Standard for Scarlet Fever Streptococcus Antitoxin (see section 13, page 11).
- (5) International Standard for Staphylococcus β Antitoxin (see section 14, page 11).
- (6) International Standard for Dimercaprol (see section 34, page 18).

⁵⁵ *World Hlth Org. techn. Rep. Ser.* 1952, 56, 18

⁵⁶ National Institute for Medical Research, Department of Biological Standards, London (1943) *Bull. Hlth Org. L.o.N.* 10, 94

**Annex 1. — DISTRIBUTION OF INTERNATIONAL STANDARDS
FROM THE STATENS SERUMINSTITUT, COPENHAGEN**

Standard	Approximate number of units per ampoule	Number of ampoules distributed per annum				Average per annum since 1945	Number of ampoules prepared from each stock ampoule	Stock of ampoules at 1 September 1952	Estimated life (years)
		1939	1945	1948	1951				
<i>Antitoxins and antibacterial sera</i>									
Diphtheria	100	130	101	134	138	135	95	195	96
Diphtheria, for flocculation test	5,000	94	47	112	118	115	—	Bulk	8
Tetanus	50	139	107	140	156	155	30	98	16
Gas-gangrene (perfringens)	100	122	100	122	124	125	25	60	10
Gas-gangrene (vibrio septique)	250	109	46	126	120	125	16	32	4
Gas-gangrene (oedematiens)	100	118	58	124	116	120	16 * (35 **)	9 * (60 **)	1 * (15 **)
Gas-gangrene (histolyticus)	100	59	38	96	92	95	16	282	35
Staphylococcus α	100	122	65	112	100	105	20	359	60
Staphylococcus β	200	9	1	10	16	15	2	92	9
Antidysentery (Shiga)	1,600	113	84	108	102	105	12	415	41
Antipneumococcus (type I)	2,000	21	0	0	0	0	2.5	8	†
Antipneumococcus (type II)	2,000	13	0	0	0	0	2.5	23	†
<i>Blood-typing sera</i>									
Anti-A	260	—	—	—	3	—	1	313	?
Anti-B	260	—	—	—	3	—	1	513	?
<i>Antigens</i>									
Old Tuberculin	200,000	15	0	14	10	12	1	Bulk	> 100
PPD, mammalian	500,000	—	—	—	—	—	1	18.5 g	?
Diphtheria toxoid, plain	50 mg	—	—	—	—	—	1	50 g	?
Tetanus toxoid	25 mg	—	—	—	—	—	1	54 g	?
PROVISIONAL INTERNATIONAL REFERENCE PREPARATIONS									
Cardiolipin	72 mg	—	—	—	—	—	1	30	?
Beef-heart lecithin	900 mg	—	—	—	—	—	1	33	?
Egg lecithin	900 mg	—	—	—	—	—	1	37	?
Cholera O-antigen (Ogawa)	100 mg	—	—	—	—	—	1	500	?
Cholera O-antigen (Inaba)	100 mg	—	—	—	—	—	1	400	?

* First International Standard

** Second International Standard

† No longer issued

**Annex 2. — DISTRIBUTION OF INTERNATIONAL STANDARDS
FROM THE NATIONAL INSTITUTE FOR MEDICAL RESEARCH, LONDON**

Standard	Number of ampoules distributed per annum												Total		Average per annum per annum since 1945	Stock at 1 January 1952	Estimated life (years)	
	1939	1940	1941	1942	1943	1944	1945	1946	1947	1948	1949	1950	1951	National control centres				Other laboratories
<i>Vitamins</i>																		
Provitamin A	354	230	8	20	26	42	44	38	56	187	271	109	135	1,382	138	120	Bulk	50
Vitamin A	—	—	—	—	—	—	—	—	—	—	—	—	—	1,382	460	2,964	5,232	1½
Vitamin B ₁	154	26	13	43	18	6	44	97	42	79	50	66	55	506	187	62	685	11
Vitamin C	57	19	17	33	68	14	28	13	31	31	20	23	19	310	63	24	539	22
Vitamin D ₂ *	196	118	19	55	36	72	77	132	110	251	169	25	—	1,103	157	127	Bulk	*
Vitamin D ₃	—	—	—	—	—	—	—	—	—	—	—	—	—	887	57	467	Bulk	50
Vitamin E	—	—	2	131	23	23	30	29	20	17	42	30	35	305	67	29	218	7
<i>Hormones, etc.</i>																		
Insulin	160	63	15	28	63	2	59	47	69	56	97	63	126	675	183	74	1,040	14
Pituitary (posterior)	56	90	15	40	68	6	70	31	69	95	75	83	134	681	151	80	602	7
Pituitary (crude anterior)	—	—	—	1	—	—	15	4	27	5	33	5	9	88	11	14	110	8
ACTH	—	—	—	—	—	—	—	—	—	—	—	—	—	207	16	178	1,111	6**
Gonadotrophin (serum)	379	17	8	16	11	7	46	39	126	85	72	89	52	767	180	73	1,026	14
Gonadotrophin (chorionic)	295	21	8	140	11	2	30	41	141	124	124	78	31	867	137	75	1,477	18
Prolactin	372	16	11	29	11	5	25	19	20	24	32	36	43	487	187	28	122	4
Progesterone	25	21	5	14	65	2	42	28	32	31	32	18	14	280	49	28	371	13
Oestradiol *	33	29	10	36	11	2	35	31	26	22	43	19	3	256	44	26	—	*
Oestrone *	45	21	15	40	14	2	74	36	75	31	49	26	34	404	58	46	560	*
Androsterone *	22	8	3	81	68	9	33	95	28	74	69	59	57	538	68	59	47	*
Heparin	—	—	—	—	—	—	68	30	32	43	50	70	32	271	54	46	528	11
<i>Glycosides and alkaloids</i>																		
Digitalis	318	119	68	82	105	39	58	68	108	342	58	231	164	1,464	296	147	4,700	32
Ouabain	11	4	9	21	110	8	55	21	31	9	18	19	29	200	45	26	64	2
Tubocurarine	—	—	—	—	—	—	—	—	—	11	17	29	30	87	0	22	141	6
<i>Arsenicals</i>																		
Neosarsphenamine	152	78	80	102	170	36	116	105	207	41	89	62	60	1,053	245	97	931	10
Sulfarsphenamine	145	50	80	84	30	84	110	68	144	29	54	26	138	838	204	81	6,500	80
Oxophensarsine	—	—	—	—	—	—	—	—	—	—	2	0	10	12	0	4	596	150
<i>Antibiotics</i>																		
Penicillin	—	—	—	—	—	—	5	77	20	20	32	13	80	200	47	41	1,242	30
Streptomycin	—	—	—	—	—	—	—	—	—	—	—	—	41	33	8	41	335	8

* No longer issued

** Estimates based on restricted issues

Annex 3

COLLECTION OF AUTHENTIC CHEMICAL SUBSTANCES *

**Recommendations of the Expert Committee on Biological Standardization
to the Expert Committee on the International Pharmacopoeia**

The Expert Committee on Biological Standardization notes that the Expert Committee on the International Pharmacopoeia has agreed¹ with their recommendation of the fifth session that a collection of authentic chemical substances should be instituted.² The Expert Committee on Biological Standardization therefore makes the following specific proposals :

(1) The maintenance of the collection should be the responsibility of the Expert Committee on the International Pharmacopoeia, since many of the substances concerned are required by monographs of the *Pharmacopoea Internationalis*. The Expert Committee on Biological Standardization will be glad to advise the Expert Committee on the International Pharmacopoeia on such problems as storage and distribution, whenever this should prove necessary ; and the Expert Committee on Biological Standardization would welcome, in the initial stages, the formation of a subcommittee of both expert committees to discuss such matters.

(2) The collection should include :

(a) standards for substances which can be characterized completely by chemical and physical tests, but which are in demand as authentic chemicals or as convenient standards for biological assay (e.g. androsterone);

(b) standards for chemicals required for some of the assays described in the *Pharmacopoea Internationalis* (e.g. histamine) ;

(c) authentic chemicals required for purposes of biological research (e.g., cortical steroids).

(3) The collection should be held by an institute engaged in active chemical research. The Expert Committee on Biological Standardization recommends that a suitable laboratory in the USA should, if possible, be asked to carry out this work. The institute should be responsible to

* See section 44, page 20.

¹ WHO Expert Committee on the International Pharmacopoeia, Report on the tenth session, unpublished working document WHO/Pharm/220

² *World Hlth Org. Techn. Rep. Ser.* 1952, **56**, 14

the Expert Committee on the International Pharmacopoeia for the proper holding of the materials.

(4) The distribution of the materials should be carried out by a system similar to that used for the distribution of the biological standards in Copenhagen and London, i.e., the distribution should be done through national centres, responsible, among other things, for ensuring that what may well be scarce and valuable materials are supplied only to bona fide workers.

(5) The Expert Committee on Biological Standardization has now decided not to replace the International Standard for Vitamin A,³ and, in view of the continuing demand for a reference preparation for the calibration of instruments, the Expert Committee on the International Pharmacopoeia should consider the inclusion of such a substance as one of the first in its collection of authentic chemicals. The Expert Committee on Biological Standardization wishes to point out that the supply of the present international standard will last, at present rates of issue, only for another year.

(6) The Expert Committee on the International Pharmacopoeia should also consider in the very near future the provision of authentic chemical reference preparations for ouabain and oxophenarsine, since the Expert Committee on Biological Standardization later intends to discontinue the provision of international standards for these materials.

(7) The following substances among others should be considered for inclusion in the collection :

Androsterone	Vitamin B ₁
Oestradiol monobenzoate	Vitamin C
Oestriol	Chloramphenicol
Oestrone	Adrenocortical steroids
Progesterone	Amino acids
Provitamin A	

(8) This question should be regarded as one of considerable urgency and WHO should be requested to study the problem as soon as possible

³ See section 23, page 14.

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