

This report contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the World Health Organization.

**WORLD HEALTH ORGANIZATION
TECHNICAL REPORT SERIES**

No. 56

**EXPERT COMMITTEE ON
BIOLOGICAL STANDARDIZATION**

Fifth Report

	Page
1. Cholera	4
2. Pertussis vaccine	4
3. Diphtheria toxoid	4
4. Tetanus toxoid	5
5. Streptococcus antitoxin	6
6. Enteric and rickettsial diagnostic antisera	6
7. Tuberculin	6
8. Organic arsenical substances	7
9. Dimercaprol	8
10. Diagnosis of syphilis	8
11. Vitamins	9
12. Hormones	9
13. Antibiotics	11
14. Rh blood-typing sera	12
15. Enzymes	12
16. Consideration of problems referred to the committee by the Expert Committee on the International Pharmacopocia	13
17. Veterinary standards	15
18. National control centres	16
19. Standard for the opacity of bacterial suspensions	17
20. Confirmation of the establishment of new standards	17
21. Inspection of centres for the preparation of BCG vaccine	17
22. Proposed expert committee on diphtheria toxoid standardiza- tion	18
23. Recommended diagnostic methods	18
24. List of international standards	18
Annex 1. International biological standards	19

WORLD HEALTH ORGANIZATION

PALAIS DES NATIONS

GENEVA

JULY 1952

EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION

Fifth Session

Geneva, 3-8 December 1951

Members :

- Dr. J. H. Gaddum, Professor of Pharmacology, Edinburgh University, Edinburgh, United Kingdom
- Professeur E. Grasset, Directeur de l'Institut d'Hygiène ; Professeur de Bactériologie et d'Hygiène à l'Université de Genève, Geneva, Switzerland (*Vice-Chairman*)
- Dr. N. K. Jerne, Acting Chief, Department of Biological Standards, Statens Seruminstitut, Copenhagen, Denmark
- Dr. A. A. Miles, Director, Department of Biological Standards, National Institute for Medical Research (Medical Research Council), London, United Kingdom (*Chairman*)
- Dr. C. A. Morrell, Director, Food and Drugs Divisions, Department of National Health and Welfare, Ottawa, Canada
- Dr. J. Ørskov, Director, Statens Seruminstitut, Copenhagen, Denmark
- Dr. W. G. Workman, Chief, Biologics Control Laboratory, National Microbiological Institute, National Institutes of Health (US Public Health Service), Bethesda, Md., USA
- Dr. P. M. Wagle, Director, Haffkine Institute, Bombay, India, was unable to attend.

Advisers :

- *Sir Thomas Dalling, Chief Veterinary Officer, Animal Health Division, Ministry of Agriculture and Fisheries, London, United Kingdom (Representative of the Joint WHO/FAO Expert Group on Zoonoses)
- Dr. W. L. M. Perry, National Institute for Medical Research (Medical Research Council), London, United Kingdom

Consultants :

- *Dr. H. H. Green, Ministry of Agriculture and Fisheries Veterinary Laboratory, New Haw, Weybridge, Surrey, United Kingdom
- *Dr. A. W. Stableforth, Director, Ministry of Agriculture and Fisheries Veterinary Laboratory, New Haw, Weybridge, Surrey, United Kingdom

Secretariat :

- Dr. W. Aeg. Timmerman, Director, Division of Therapeutic Substances, WHO (*Secretary*)
- Dr. M. M. Kaplan, Chief Veterinary Officer, Division of Epidemiological Services, WHO
- Dr. R. Pollitzer, Consultant on Cholera, Division of Epidemiological Services, WHO

The report on the fifth session of this committee was originally issued in mimeographed form as document WHO/BS/136, 18 December 1951.

* Attended one day of the session to assist the committee with regard to special subjects.

EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION

Fifth Report ¹

The fifth session of the Expert Committee on Biological Standardization was held in Geneva from 3 to 8 December 1951.

The Deputy Director-General welcomed the experts, explained certain changes in the regulations for expert committees, and emphasized that the experts attended meetings in their capacity as individuals and not as representatives of countries. He had noted that the committee had an important agenda before it, which included studies on the standardization of diagnostic procedures, a function of WHO laid down in Article 2(*t*) of the Constitution. In discussing the problems of veterinary standards, the committee had taken the initiative in proving that WHO recognized no difference between veterinary and human problems in medicine. WHO was grateful to the experts for giving up their time in order to attend this session.

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

I. The Executive Board

1. NOTES the report of the Expert Committee on Biological Standardization on its fifth session ;
2. THANKS the members of the committee for their work, and
3. AUTHORIZES publication of the report.

II. Considering that direct contact between the international centres in Copenhagen and London and the national control centres in Member States has considerable advantages with regard to the functioning of national centres ;

Considering that regional control centres might lead to unnecessary complications and prejudice the efficient working of the national control centres,

The Executive Board

RECOMMENDS that no regional control centres be established.

III. Noting that considerable progress has been made in the establishment of international standard preparations for diphtheria toxoids ;

Considering that it is not therefore necessary to refer this matter to an expert committee,

The Executive Board

REQUESTS the Director-General not to convene in 1952 the expert committee on diphtheria toxoid standardization for which provision was made in the budget.

(Resolution EB9.R84, *Off. Rec. World Hlth Org.* 40, 30)

1. Cholera ²

The committee noted the progress made by the Statens Seruminstitut, Copenhagen, (1) in the establishment of dried standard preparations of the cholera vibrios to be used in the preparation of diagnostic antisera, and (2) in the collaborative assay of freeze-dried cholera vaccines in terms of the provisional reference vaccine.

The committee noted the recommendation made by the Expert Committee on Cholera that a single strain of cholera-susceptible mice should be made available for use in the assay of cholera vaccines.³ The committee recommended that breeding-stock of such a strain should be made available from a single source.

In answer to an observation of the Expert Committee on Cholera, that freeze-dried antiserum might be unsuitable as a standard because antisera sometimes lose potency during freeze-drying,³ the committee pointed out that the potency of a standard should always be assigned to the freeze-dried preparation after reconstitution, and that loss of potency during freeze-drying could, therefore, be ignored.

2. Pertussis Vaccine ⁴

The committee noted the progress made by the Statens Seruminstitut in its investigation of the proposed standard preparation of pertussis vaccine, and of the best methods of assay.

3. Diphtheria Toxoid ⁵

The committee established as the international standard for diphtheria toxoid, plain, the provisional reference preparation of diphtheria toxoid, plain, which is a relatively highly purified toxoid and which had proved to be of the same order of potency as current therapeutic preparations in various countries. The committee also considered the relative merits of crude and partially-purified plain toxoids as standards, and decided that the new standard would serve adequately for the assay of diphtheria toxoids

² Statens Seruminstitut, Copenhagen, unpublished working document WHO/BS/130

³ *World Hlth Org. techn. Rep. Ser.* 1952, 52, 12

⁴ Statens Seruminstitut, Copenhagen, unpublished working document WHO/BS/123

⁵ Statens Seruminstitut, Copenhagen, unpublished working document WHO/BS/113

of all degrees of purity. The committee noted that the slopes of the dosage-response lines for plain diphtheria toxoids tended to become flatter as the purity increased, but considered that in practice such differences in slopes would not seriously affect the validity of the assays.

The committee authorized the Statens Seruminstitut to proceed with the establishment of an international reference preparation of diphtheria toxoid, adsorbed. The Statens Seruminstitut was authorized to obtain a sample of freeze-dried adsorbed toxoid similar to that at present in use at the Paul Ehrlich Institute, Frankfurt-on-Main, Germany, and to institute a collaborative examination of the material, including accelerated degradation tests.

The committee deferred assignment of unitage to both the international standard for diphtheria toxoid, plain, and the proposed international reference preparation of diphtheria toxoid, adsorbed, and asked the Statens Seruminstitut to collect data on the relation between the immunizing potency of plain and adsorbed toxoids in man, with a view to assigning to the international standard for diphtheria toxoid, plain, a unitage approximately equivalent to that of the proposed international reference preparation of diphtheria toxoid, adsorbed.

The committee re-affirmed the principle that the size of a new international unit should be assigned so as to avoid, as far as possible, any change in the size of existing well-established units. In cases where the international unit was made equivalent to an existing unit, the committee would expect either that the designation of the existing unit should be replaced by the term "international unit" or at least that the designation should include a definition of its relation to the international unit.

In this connexion the committee decided that in assigning a unitage to the proposed international reference preparation of diphtheria toxoid, adsorbed, every effort would be made to relate it to the "Schutzeinheit" of the German standard for diphtheria toxoid, held by the Paul Ehrlich Institute, Frankfurt-on-Main.

4. Tetanus Toxoid ⁶

The committee established the international standard for tetanus toxoid. The standard preparation had proved to have an immunizing potency similar to current therapeutic preparations of tetanus toxoid in various countries. Since there was evidence that the slopes of the dosage-response

⁶ Statens Seruminstitut, Copenhagen, unpublished working documents WHO/BS/125, WHO/BS/125 Add.1, WHO/BS/125 Add.2

lines for plain and adsorbed toxoids were closely similar, a single standard could at present be used for the assay of both plain and adsorbed preparations of tetanus toxoid. The committee defined the international unit of tetanus toxoid as the immunizing activity of 0.03 mg of the international standard for tetanus toxoid. In accordance with the principle re-affirmed in section 3 (page 5) of this report, this unit was made approximately equivalent to the "Schutzeinheit" of the standard tetanus toxoid held by the Paul Ehrlich Institute, Frankfurt-on-Main.

5. Streptococcus Antitoxin

The committee noted the progress made in the establishment of an international standard for streptococcus antitoxin and the different magnitudes of national unit potencies already established. There was evidence of heterogeneity of streptococcus antitoxins, similar to that observed in tetanus antitoxins. The committee decided to defer the establishment of this standard and authorized the National Institute for Medical Research, London, to continue the investigation of the heterogeneity and to obtain opinions about the unit potency to be assigned to the standard.

6. Enteric and Rickettsial Diagnostic Antisera

The committee noted that the preparations of *Salmonella* diagnostic antisera were ready for collaborative study of their suitability as international standards. The progress made in preparing *Proteus* diagnostic antisera was also noted.

7. Tuberculin

7.1 Mammalian PPD⁷

The committee established the batch of purified protein derivative (PPD) of tuberculin, prepared by Dr. Florence Seibert of the Henry Phipps Institute, Philadelphia, Pa., USA, from a human strain of the tubercle bacillus, as the international standard for purified protein derivative of mammalian tuberculin. The unitage of this standard will be assigned as soon as possible.

Although the committee intends that the standard shall serve for the assay of PPD tuberculins used in the diagnosis of both bovine and human infections, it recognized that for certain purposes the assay of bovine PPD

⁷ Green, H. H., unpublished working document WHO/BS/127

in terms of a human PPD standard might prove to be insufficiently specific. The committee, therefore, decided to include in the designation of the standard a statement that the international standard preparation is a specimen of PPD from a human strain of the tubercle bacillus.

7.2 *Avian PPD*⁸

The committee decided to establish an international standard preparation of PPD of avian tuberculin and accepted the offer by the Veterinary Laboratory of the Ministry of Agriculture and Fisheries (England and Wales), Weybridge, Surrey, United Kingdom, of the existing standard of that Ministry as the proposed international standard preparation. It authorized the Weybridge Veterinary Laboratory, in consultation with the appropriate committees of the Food and Agriculture Organization of the United Nations (FAO) and the International Office of Epizootics, to proceed with a collaborative examination of its suitability as an international standard preparation and of the unitage to be assigned to it.

The committee also noted that the Weybridge Veterinary Laboratory is prepared to make available to interested workers the strain (D4) of avian tubercle bacillus which was used in the manufacture of the proposed international standard preparation.

7.3 *Assay of tuberculin*⁹

The committee noted certain improved methods of assay of tuberculin which make possible the calculation of fiducial limits of error of the estimated potency of tuberculin from the internal evidence of the assay.

8. Organic Arsenical Substances

8.1 *Oxophenarsine*¹⁰

On the basis of the results of a collaborative examination of the existing joint Canadian-British standard for oxophenarsine, the committee decided to establish it as the international standard for oxophenarsine. The committee authorized the National Institute for Medical Research to obtain opinions from interested workers about the necessity for this standard in the light of the definitive chemical constitution of preparations of oxophenarsine.

⁸ Green, H. H., unpublished working document WHO/BS/126

⁹ Long, D. A., Miles, A. A. & Perry, W. L. M., unpublished working document WHO/BS/120

¹⁰ Department of Biological Standards, National Institute for Medical Research, London, unpublished working document WHO/BS/133

8.2 *Melaminyl trypanocides*¹¹

The committee considered the request of the International Scientific Committee for Trypanosomiasis Research that standard preparations should be provided for melaminyl trypanocides.

The committee decided to establish international reference preparations of two of these substances, namely Melarsen (the sodium salt of *p*-(2:4-diamino-*s*-triazinyl-6-)-aminophenylarsonic acid) and its polymerized antimonial analogue, designated "MSb", and authorized the National Institute for Medical Research to obtain preparations of these two substances and to institute a collaborative study of their suitability as international reference preparations.

9. Dimercaprol

The committee noted the progress made by the National Institute for Medical Research in obtaining opinions of interested workers about the suitability of the British standard for dimercaprol as an international standard.

10. Diagnosis of Syphilis

10.1 *Syphilitic sera*

The committee noted the progress made by the Subcommittee on Serology and Laboratory Aspects of the Expert Committee on Venereal Infections and Treponematoses in the establishment of a group of reference syphilitic sera for the calibration of various serological tests for syphilis. The results of a pilot experiment indicated that freeze-dried sera were suitable for the preservation of specific and non-specific reactivity. The committee recommended to the Subcommittee on Serology and Laboratory Aspects that further tests be made of the stability of preparations at temperatures above 37°C.

10.2 *Cardiolipin and lecithin*¹²

The committee established provisional international reference preparations of cardiolipin and lecithin. It authorized the Statens Seruminstitut to consult with the New York State Department of Health, Albany, N.Y., USA, about the suitability for this purpose of the preparations already

¹¹ Lourie, E. M., unpublished working document WHO/BS/134

¹² Pangborn, M. C., Maltaner, F., Tompkins, V. N., Beecher, T., Thompson, W. R. & Flynn, M. R. (1951) *Cardiolipin antigens*, Geneva (*World Health Organization: Monograph Series*, No. 6); unpublished working document WHO/Pharm/Mon/465 Rev. 2

held at the Statens Seruminstitut, and to replace these preparations when necessary by fresh preparations that had also been tested for suitability in Albany and Copenhagen. The committee recommended that the Subcommittee on Serology and Laboratory Aspects of the Expert Committee on Venereal Infections and Treponematoses should determine the conditions under which standard preparations of cardiolipin and lecithin might be expected to retain their potency for long periods, but recognized that this information can best be obtained when suitable reference preparations of syphilitic sera are available.

11. Vitamins

11.1 Vitamin A

The committee noted that about half of the international standard preparation of vitamin A acetate had been used since its establishment as the international standard for vitamin A two years ago.¹³ The committee authorized the National Institute for Medical Research to proceed with the establishment of the third international standard for vitamin A when this proves necessary. (See also section 16.7, page 14.)

11.2 Vitamin B₁₂¹⁴

The committee noted the progress made by the National Institute for Medical Research in the establishment of an international standard for Vitamin B₁₂. Two preparations will be blended to form the proposed standard. Investigations of the suitability of these batches and of the form of the standard preparation are in progress.

12. Hormones

12.1 Adrenocorticotrophic hormone (*corticotrophin*)

Since the stock of the international standard for adrenocorticotrophic hormone (ACTH) is small, the committee authorized the National Institute for Medical Research to proceed with the establishment of the second international standard for adrenocorticotrophic hormone. It was decided that, provided that batches of ACTH could be blended without serious loss of potency, the contributions for the proposed second international standard should be blended to form a large batch of material. The committee

¹³ See *World Hlth Org. techn. Rep. Ser.* 1950, 2, 10; 3, 3.

¹⁴ Miles, A. A., unpublished working document WHO/BS/118

recommended that the collaborative assay of the second standard in terms of the first should be done by as many different methods as possible, and agreed that, if necessary, the whole stock of the first standard should be expended for this purpose.

12.2 *Thyrotrophin*

The committee noted the progress made by the National Institute for Medical Research in the establishment of an international standard for thyrotrophin. The standard preparation will be a blend of two contributions diluted with an inert substance and put up in tablet form. It is proposed to make the international unit similar to that of the USP (Pharmacopeia of the United States of America) reference preparation. The committee recommended that the National Institute for Medical Research should obtain opinions from interested workers about the maximum permissible contents of other pituitary hormones in the proposed standard preparation.

12.3 *Growth hormone*

The committee noted the progress made by the National Institute for Medical Research in obtaining material for an international standard for growth hormone.

12.4 *Assay of chorionic gonadotrophin*

The committee noted the progress made by the National Institute for Medical Research in initiating a collaborative investigation of the accuracy and precision of current assay methods for chorionic gonadotrophin.

12.5 *Insulin*¹⁵

The committee noted its oversight at its fourth session in failing to initiate consultation with the Insulin Committee of the University of Toronto, Canada, about the establishment of the third international standard preparation. The Insulin Committee had been appointed by the Permanent Commission on Biological Standardization of the Health Organization of the League of Nations as distributor for North America. The committee asked WHO to apologize on its behalf to the Insulin Committee of the University of Toronto.

¹⁵ Mussett, M. V. & Perry, W. L. M., unpublished working document WHO/BS/119

The committee authorized the National Institute for Medical Research, after consultation with the Insulin Committee of the University of Toronto, to establish the third international standard for insulin and to assign to it a unitage on the basis of the result of the collaborative assay. The committee recommended that the Insulin Committee of the University of Toronto should be invited to be distributor for North America of the third international standard for insulin.

The committee discussed the recommendations made by the Insulin Advisory Board of the Pharmacopeia of the United States of America about the size and quality of future insulin standards and expressed its agreement with the principle that, whenever possible, international standards should be made from preparations large enough to provide, in addition, material for national standards. The committee agreed with the suggestion made by the above-mentioned body that, in the case of an insulin standard, the batch should be large enough to provide also for standards of preparations of insulin such as protamine-zinc insulin.

13. Antibiotics

13.1 *Penicillin*

13.1.1 The committee authorized the National Institute for Medical Research to establish the second international standard for penicillin and to assign to it a unitage on the basis of the results of the collaborative assay already carried out.¹⁶

13.1.2 *Penicillin K*.¹⁷ The committee established the international reference preparation of penicillin K, but did not define a unit because at present this preparation is likely to be used mainly for research.

13.2 *Dihydrostreptomycin*¹⁸

The committee noted the progress made by the National Institute for Medical Research in obtaining material for an international standard for dihydrostreptomycin.

¹⁶ Department of Biological Standards, National Institute for Medical Research, London, unpublished working document WHO/BS/121

¹⁷ Department of Biological Standards, National Institute for Medical Research, London, unpublished working document WHO/BS/132

¹⁸ Department of Biological Standards, National Institute for Medical Research, London, unpublished working document WHO/BS/122

13.3 *Aureomycin and terramycin*¹⁹

The committee noted the progress made by the National Institute for Medical Research in the establishment of international standards for aureomycin and terramycin, for which materials have already been obtained.

13.4 *Chloramphenicol*

The committee noted the progress made by the National Institute for Medical Research in obtaining material for an international reference preparation of chloramphenicol.

13.5 *Bacitracin*¹⁹

The committee noted the progress made by the National Institute for Medical Research in obtaining material for an international reference preparation of bacitracin.

13.6 *Collection of "author's preparations" of new antibiotics*

The committee discussed the best ways of initiating the collection of author's preparations of antibiotics that have at least been shown to cure experimental infections, and decided that, in general, author's preparations should be obtained at the specific request of WHO, acting on the advice of members of the Expert Advisory Panels on Antibiotics and on Biological Standardization. On obtaining an author's preparation, WHO would consult the author about the nature and size of the provisional unitage to be assigned to it.

14. Rh Blood-typing Sera

The committee noted the progress made by the Lister Institute of Preventive Medicine, London, in obtaining materials for international standard preparations of Rh antisera.

15. Enzymes

15.1 *Hyaluronidase*²⁰

The committee noted the report on the British standard for hyaluronidase submitted by the National Institute for Medical Research. It decided

¹⁹ Department of Biological Standards, National Institute for Medical Research, London, unpublished working document WHO/BS/122

²⁰ Jaques, R., unpublished working document WHO/BS/135

to proceed with the establishment of an international standard for hyaluronidase, and authorized the National Institute for Medical Research to institute a collaborative examination of preparations of bovine testicular hyaluronidase and to select a preparation or a blend of several preparations to serve as the international standard. The examination will include tests of activity in the skin, upon which the final selection should principally be based, and characterization by physico-chemical methods.

15.2 *Thrombin*

The committee noted the progress made by the National Institute for Medical Research, London, in consultation with the National Institutes of Health, Bethesda, Md., USA, in obtaining material for an international standard for thrombin.

16. Consideration of Problems Referred to the Committee by the Expert Committee on the International Pharmacopoeia ²¹

The committee commented (subsections 16.1, 16.3, 16.4) on the problems referred to it by the Expert Committee on the International Pharmacopoeia but authorized WHO to modify these comments in the light of information that members of the Expert Committee on Biological Standardization might submit before 31 January 1952.

16.1 *Pyrogens* ²²

The committee authorized the National Institute for Medical Research to proceed with the establishment of an international reference preparation of pyrogens. After consultation with interested workers about its nature, material will be collected and subjected to collaborative examination for its suitability (a) as a standard for tests of the potency of therapeutic preparations of pyrogens, and (b) for determining the sensitivity of rabbits used in tests designed to exclude the presence of pyrogenic contaminants in other preparations.

16.2 *Taeniocidal drugs*

The committee discussed the need for biological tests of oleoresin of male fern and authorized the National Institute for Medical Research to

²¹ *World Hlth Org. techn. Rep. Ser.* 1952, **50**, 11

²² Unpublished working documents WHO/Pharm/116 Rev.1, WHO/Pharm/116 Rev.1 Add.1, WHO/Pharm/116 Rev.1 Add.2, WHO/Pharm/116 Rev.1 Add.3

institute collaborative tests of preparations of male fern with a view to comparing the results of biological assays with those of the chemical tests at present required by the *Pharmacopoea Internationalis*.

16.3 Sterility tests²³

The committee suggested that the Expert Committee on the International Pharmacopoeia should reconsider whether hydroxylamine was a suitable inactivator of streptomycin in the sterility test for streptomycin. The committee approved the appendix on the sterility tests for dihydrostreptomycin and for benzylpenicillin, after suggesting modifications of the latter.

16.4 D-Tubocurarine²⁴

The committee suggested modifications of the drafts of both the rabbit-head-drop and the rat-diaphragm methods of assay and recommended that both should be included as suggested methods of assay in the *Pharmacopoea Internationalis*.

16.5 Insulin preparations

The committee considered that there was no decisive evidence to justify the inclusion in the monograph on insulin in the first edition of the *Pharmacopoea Internationalis* of a test for the presence of glycogenolytic factors. At the request of the committee, the National Control Centre of Canada agreed to seek evidence whether therapeutic preparations of insulin containing a substantial proportion of glycogenolytic factors had any adverse clinical effects, and to investigate methods of testing for the presence of glycogenolytic factors in preparations of insulin.

16.6 Biological preparations for the Pharmacopoea Internationalis²⁵

The committee agreed that members should obtain the opinions of interested workers about biological preparations that should be included in the *Pharmacopoea Internationalis*.

16.7 Collection of authentic chemical substances

The committee recommended that the Expert Committee on the International Pharmacopoeia consider the establishment of a collection of authentic chemicals, which would include :

²³ Unpublished working documents WHO/Pharm/100, Who/Pharm/100 Add. 1, WHO/Pharm/108 Rev.1

²⁴ Unpublished working documents WHO/Pharm/102, WHO/Pharm/102 Rev.1

²⁵ Unpublished working documents WHO/Pharm/89 Rev.1, WHO/Pharm/114 Rev.1, WHO/Pharm/158

(a) biological 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 and vitamin A);

(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).

The committee further recommended that the holding and distribution of these reference preparations of authentic chemicals would best be carried out by an institute engaged in active research in relevant fields, which would deal with the problem, on behalf of WHO, in a manner analogous with the holding and distribution of the biological standards by the Statens Seruminstitut and the National Institute for Medical Research.

17. Veterinary Standards

The committee noted the request of the Joint WHO/FAO Expert Group on Zoonoses and of the International Office of Epizootics that the existing biological standards should be available for veterinary use, and that the Expert Committee on Biological Standardization should extend its scope to include standards needed for practice and research in veterinary medicine.

The committee welcomed the initiative of these bodies in offering to join in its work of establishing standards for holding and distribution from the two international centres, and recommended that veterinary experts be added to the Expert Advisory Panel on Biological Standardization.

17.1 *Rickettsial antisera*

The committee agreed to establish an international standard preparation of Q-fever antiserum for use in the complement-fixation test, and if possible in the agglutination test, for the serological diagnosis of Q fever. The committee authorized the Ministry of Agriculture and Fisheries Veterinary Laboratory, Weybridge, and WHO, in consultation with the Statens Seruminstitut, to proceed with the collection and characterization of a standard preparation of pooled human antisera.

The committee advised that the serum, which should be freeze-dried, should on reconstitution have a titre in the range 1/32 - 1/64 in the commonly used complement-fixation tests for Q fever, and should have assigned to it a unitage approximately equal to the reciprocal of the titre as finally determined.

17.2 *Brucella abortus antiserum*²⁶

The committee decided to establish an international standard for *Brucella abortus* antiserum for use in the agglutination tests for brucella infections.

The committee decided to accept as the standard preparation a batch of bovine antiserum equivalent in potency to the existing standard of the International Office of Epizootics, at present held at the Ministry of Agriculture and Fisheries Veterinary Laboratory, Weybridge. The standard preparation will be freeze-dried. The committee decided to assign to it a unitage such that 1 ml of this material as reconstituted will have an activity of 1,000 units. This unitage is chosen because 1/1,000 is the average titre obtained in commonly used tube-agglutination tests.

The committee authorized the Weybridge Veterinary Laboratory to obtain the opinions of interested medical workers about the suitability of this standard in the diagnosis of human infections. In view of the proved worth of this material for veterinary purposes, the committee agreed that it would be unnecessary to obtain further veterinary opinions about its suitability.

18. National Control Centres²⁷

The committee considered that the system of having regional centres for the distribution and control of biological standards was not only no improvement on the existing system but would be an unnecessary and distracting complication which might well prejudice its efficient working. The committee recommended that the regional system of administration should not apply to the distribution and control of biological standards, but that direct contact between the international centres in Copenhagen and London and the national control centres in each Member State should be maintained.

In order that the fullest benefits might be obtained from the system of national control centres, the committee recommended that personal contacts should be extended by the visits of a technical expert on biological standardization, preferably attached to WHO, to national control centres, to inform them of developments initiated by the Expert Committee on Biological Standardization and to facilitate the work of biological standardization in their respective countries. The expert should also encourage the establishment of national control centres in countries where they do not now exist.

²⁶ *World Hlth Org. techn. Rep. Ser.* 1951, 37, 19; Stableforth, A. W., unpublished working documents WHO/Bruc/18, WHO/BS/128

²⁷ Miles, A. A., unpublished working document WHO/BS/115

As a preliminary step the committee decided that the international centres in Copenhagen and London should report to it on the present status and activity of all national control centres.

19. Standard for the Opacity of Bacterial Suspensions²⁸

The committee noted the progress made by the Statens Seruminstitut in the investigation of the suitability of the material provided by the National Institutes of Health, Bethesda, Md., USA, as an international standard for opacity for use in the direct visual characterization of bacterial suspensions, and authorized the Statens Seruminstitut to establish this material as the international standard after obtaining opinions from interested workers in various countries.

20. Confirmation of the Establishment of New Standards

The committee confirmed the establishment, authorized at its fourth session,²⁹ of the following standards :

The second international standard for histolyticus antitoxin, which is now available at the Statens Seruminstitut, Copenhagen.³⁰

The third international standard for sulfarsphenamine and the international standard for D-tubocurarine, both of which are now available at the National Institute for Medical Research, London.³¹

21. Inspection of Centres for the Preparation of BCG Vaccine³²

After considering a report by Dr. Poul Lind of the International Tuberculosis Campaign, the committee ratified the approval given by WHO of the BCG laboratory of the Agouza Serum and Vaccine Institute, Cairo.

The committee also authorized the inspection, on its behalf, of the BCG laboratory of the Institut Pasteur hellénique, Athens, by Dr. Lind and authorized WHO to approve this laboratory subject to a satisfactory report.

²⁸ Statens Seruminstitut, Copenhagen, unpublished working document WHO/BS/124

²⁹ *World Hlth Org. techn. Rep. Ser.* 1951, 36, 5, 7, 13

³⁰ Department of Biological Standards, Statens Seruminstitut, Copenhagen, unpublished working documents WHO/BS/91, WHO/BS/131

³¹ National Institute for Medical Research, Department of Biological Standards (1949) *Bull. World Hlth Org.* 2, 65; Davies, M. G., Miles, A. A. & Perry, W. L. M. (1951) *Bull. World Hlth Org.* 4, 563

³² Lind, P., unpublished working document WHO/BS/114

22. Proposed Expert Committee on Diphtheria Toxoid Standardization

The committee recommended that no meeting of the proposed expert committee on diphtheria toxoid standardization should be held in 1952. It was felt that most of the technical difficulties in the way of establishing a standard, which had been anticipated when this meeting was requested, had now been overcome.

23. Recommended Diagnostic Methods

The committee recommended that WHO should investigate the desirability of publishing a collection of "recommended methods" or diagnostic tests; and cited, as examples, methods which had been referred to it by other expert committees, such as methods for the bacteriological diagnosis of tuberculosis and for the serological diagnosis of syphilis.

24. List of International Standards

The committee recommended that a definitive list of the international standards held in the Statens Seruminstitut, Copenhagen, and in the National Institute for Medical Research, London, should be annexed to the present report.³³

³³ This list is given as Annex 1.

Annex 1
INTERNATIONAL BIOLOGICAL STANDARDS¹

<i>Preparation</i>	<i>Adopted</i>	<i>Reference</i>	<i>Unit mg</i>	<i>Form in which dispensed</i>
<i>Antitoxins and antisera</i>				
Diphtheria antitoxin	1922	<i>Quart. Bull. Hlth Org. L.o.N. 1936, 5, 728</i>	0.0628	In 66% glycerol, 10 international units (IU)/ml. Bottles containing approx. 10 ml.
Diphtheria antitoxin for flocculation test	1935	<i>Bull. Hlth Org. L.o.N. 1938, 7, 859</i>	—	Dilution of hyperimmune horse serum in phosphate buffered saline, containing 0.01% merthiolate, 500 IU/ml. Bottles containing approx. 10 ml.
Tetanus antitoxin	1928	<i>World Hlth Org. techn. Rep. Ser. 1950, 2, 5</i>	0.3094	In 66% glycerol, 5 IU/ml. Bottles containing approx. 10 ml.
Gas-gangrene antitoxin (perfringens)	1931	<i>Bull. Hlth Org. L.o.N. 1943, 10, 97</i>	0.1135	In 66% glycerol, 20 IU/ml. Bottles containing approx. 5 ml.
Gas-gangrene antitoxin (vibrien septique)	1934	<i>Bull. Hlth Org. L.o.N. 1943, 10, 97</i>	0.0974	In 66% glycerol, 50 IU/ml. Bottles containing approx. 5 ml.
Gas-gangrene antitoxin (oedematiens)	1934	<i>Quart. Bull. Hlth Org. L.o.N. 1935, 4, 42</i>	0.2681	In 66% glycerol, 20 IU/ml. Bottles containing approx. 5 ml.
Gas-gangrene antitoxin (histolyticus)	1935	<i>World Hlth Org. techn. Rep. Ser. 1952, 56, 17</i>	0.2000	In 66% glycerol, 20 IU/ml. Bottles containing approx. 5 ml.
Gas-gangrene antitoxin (Sordelli)	1938	<i>Bull. Hlth Org. L.o.N. 1939, 8, 856</i>	0.1334	In 66% glycerol, 20 IU/ml. Bottles containing approx. 10 ml.

¹ Additional references, and a historical account of standards adopted before 1945, may be found in: Gautier, R. (1935) *Quart. Bull. Hlth Org. L.o.N. 4, 497*; Gautier, R. (1946) *Bull. Hlth Org. L.o.N. 12, 1*.

<i>Preparation</i>	<i>Adopted</i>	<i>Reference</i>	<i>Unit mg</i>	<i>Form in which dispensed</i>
Staphylococcus α antitoxin	1934	<i>Bull. Hlth Org. L.o.N.</i> 1938, 7, 845	0.2376	In phosphate buffered saline, containing 0.01% merthiolate, 20 IU/ml. Bottles containing approx. 5 ml.
Antidysentery serum (Shiga)	1928	<i>Quart. Bull. Hlth Org.</i> <i>L.o.N.</i> 1936, 5, 728	0.0500	In 66% glycerol, 200 IU/ml. Bottles con- taining approx. 8 ml.
Antipneumococcus serum (type I)	1934	<i>Quart. Bull. Hlth Org.</i> <i>L.o.N.</i> 1935, 4, 48	0.0886	In 66% glycerol, 200 IU/ml. Bottles con- taining approx. 10 ml.
Antipneumococcus serum (type II)	1934	<i>Quart. Bull. Hlth Org.</i> <i>L.o.N.</i> 1935, 4, 65	0.0894	In 66% glycerol, 200 IU/ml. Bottles con- taining approx. 10 ml.

Blood-typing sera

Anti-A blood-typing serum	1950	<i>Bull. World Hlth Org.</i> 1950, 3, 301	0.3465	Ampoules containing approx. 90 mg.
Anti-B blood-typing serum	1950	<i>Bull. World Hlth Org.</i> 1950, 3, 301	0.3520	Ampoules containing approx. 90 mg.

Antigens

Old tuberculin	1931	<i>Quart. Bull. Hlth Org.</i> <i>L.o.N.</i> 1936, 5, 728	0.0100	100,000 IU/ml. Ampoules containing approx. 2 ml.
Purified protein deriva- tive of mammalian tuberculin	1951	<i>World Hlth Org. techn.</i> <i>Rep. Ser.</i> 1952, 56, 6	—	Awaiting decision on unitage. Ampoules con- taining approx. 10 mg.
Diphtheria toxoid, plain	1951	<i>World Hlth Org. techn.</i> <i>Rep. Ser.</i> 1952, 56, 4	—	Awaiting decision on unitage. Ampoules con- taining approx. 50 mg.
Tetanus toxoid	1951	<i>World Hlth Org. techn.</i> <i>Rep. Ser.</i> 1952, 56, 5	0.0300	Ampoules containing approx. 25 mg.

PROVISIONAL INTERNATIONAL REFERENCE PREPARATIONS

Cardiolipin	1951	<i>World Hlth Org. techn.</i> <i>Rep. Ser.</i> 1952, 56, 8	—	7.2 mg/ml. Bottles containing 10 ml.
-------------	------	--	---	---

<i>Preparation</i>	<i>Adopted</i>	<i>Reference</i>	<i>Unit mg</i>	<i>Form in which dispensed</i>
Beef-heart lecithin	1951	<i>World Hlth Org. techn. Rep. Ser. 1952, 56, 8</i>	—	30 mg/ml. Bottles containing 30 ml.
Egg lecithin	1951	<i>World Hlth Org. techn. Rep. Ser. 1952, 56, 8</i>	—	30.2 mg/ml. Bottles containing 30 ml.

**B. HELD BY THE DEPARTMENT OF BIOLOGICAL STANDARDS,
NATIONAL INSTITUTE FOR MEDICAL RESEARCH, LONDON**

Vitamins

Provitamin A (pure β -carotene)	1949	<i>World Hlth Org. techn. Rep. Ser. 1950, 3, 6</i>	0.0006	In vegetable oil, 200 IU/g. Bottles containing approx. 10 g.
Vitamin A (pure vitamin A acetate)	1949	<i>World Hlth Org. techn. Rep. Ser. 1950, 3, 3</i>	0.000344	In cotton-seed oil, 10,000 IU/g. Gelatin capsules containing 0.25 ml.
Vitamin B (pure synthetic vitamin B ₁)	1938	<i>Bull. Hlth Org. L.o.N. 1938, 7, 882</i>	0.003	Ampoules containing approx. 20 mg.
Vitamin C (L-ascorbic acid)	1934	<i>Quart. Bull. Hlth Org. L.o.N. 1934, 3, 428</i>	0.05	Ampoules containing approx. 550 mg.
Vitamin D (pure vitamin D ₂)	1949	<i>World Hlth Org. techn. Rep. Ser. 1950, 3, 7</i>	0.000025	In vegetable oil, 1,000 IU/g. Bottles containing approx. 10 g.
Vitamin E (α -tocopheryl acetate)	1941	<i>Bull. Hlth Org. L.o.N. 1941, 9, 443</i>	1.0	In olive oil, 10 IU/g. Bottles containing approx. 10 g.

Hormones, etc.

Insulin (pure crystalline insulin)	1935	<i>Quart. Bull. Hlth Org. L.o.N. 1936, 5, 584</i>	0.0455	Ampoules containing approx. 20 mg.
Progesterone	1935	<i>Bull. Hlth Org. L.o.N. 1943, 10, 86</i>	1.0	Ampoules containing approx. 65 mg.
Chorionic gonadotrophin (active principle from human urine of pregnancy, dried and diluted with lactose)	1938	<i>Bull. Hlth Org. L.o.N. 1939, 8, 884</i>	0.1	Ampoules containing twenty-five 10-mg tablets.

<i>Preparation</i>	<i>Adopted</i>	<i>Reference</i>	<i>Unit mg</i>	<i>Form in which dispensed</i>
Serum gonadotrophin (active principle from serum of pregnant mares, dried and diluted with serum)	1938	<i>Bull. Hlth Org. L.o.N.</i> 1939, 8 , 898	0.25	Ampoules containing ten 25-mg tablets.
Prolactin	1938	<i>Bull. Hlth Org. L.o.N.</i> 1939, 8 , 909	0.1	Ampoules containing ten 10-mg tablets.
Pituitary, posterior lobe powder (dry powdered acetone-extract of posterior lobes of ox pituitary)	1940	<i>Bull. Hlth Org. L.o.N.</i> 1943, 10 , 89	0.5	Ampoules containing approx. 30 mg.
Adrenocorticotrophic hormone (active principle from pig pituitary, dried)	1950	<i>World Hlth Org. techn. Rep. Ser.</i> 1951, 36 , 7	1.0	Ampoules containing approx. 1.3 mg and 5.0 mg.
Heparin (dried sodium salt)	1942	<i>Bull. Hlth Org. L.o.N.</i> 1943, 10 , 151; <i>Bull. World Hlth Org.</i> 1947-8, 1 , 7	0.0077	Ampoules containing approx. 50 mg.

Glycosides and alkaloids

Digitalis (dry powdered leaves of <i>Digitalis purpurea</i>)	1949	<i>Bull. World Hlth Org.</i> 1950, 2 , 655	76.0	Ampoules containing approx. 2.5 g.
Ouabain (pure crystalline)	1928	<i>Quart. Bull. Hlth Org. L.o.N.</i> 1935, 4 , 497	—	Ampoules containing approx. 100 mg.
D-Tubocurarine chloride (pure crystalline)	1951	<i>Bull. World Hlth Org.</i> 1949, 2 , 65; <i>World Hlth Org. techn. Rep. Ser.</i> 1952, 56 , 17	1.0	Ampoules containing approx. 30 mg.

Arsenicals

Neoarsphenamine	1940	<i>Quart. Bull. Hlth Org. L.o.N.</i> 1935, 4 , 497	—	Ampoules containing approx. 0.3 g.
Sulfarsphenamine	1951	<i>Bull. World Hlth Org.</i> 1951, 4 , 563; <i>World Hlth Org. techn. Rep. Ser.</i> 1952, 56 , 17	—	Ampoules containing approx. 0.3 g.

<i>Preparation</i>	<i>Adopted</i>	<i>Reference</i>	<i>Unit mg</i>	<i>Form in which dispensed</i>
Oxophenarsine	1951	<i>World Hlth Org. techn. Rep. Ser. 1952, 56, 7</i>	—	(a) Ampoules containing approx. 60 mg or 20 mg oxophenarsine hydrochloride. (b) Ampoules containing approx. 100 mg anhydrous sodium carbonate. (c) Ampoules containing approx. 500 mg anhydrous sodium sucrose.

Antibiotics

Penicillin (benzylpenicillin, sodium salt)	1944	<i>Bull. Hlth Org. L.o.N. 1946, 12, 181</i>	0.0006	Ampoules containing approx. 30 mg.
Streptomycin (streptomycin sulfate)	1949	<i>World Hlth Org. techn. Rep. Ser. 1950, 2, 11</i>	0.001284	Ampoules containing approx. 25 mg.

INTERNATIONAL REFERENCE PREPARATION

Penicillin K (<i>n</i> -heptylpenicillin, sodium salt)	1951	<i>World Hlth Org. techn. Rep. Ser. 1952, 56, 11</i>	—	Ampoules containing approx. 20 mg.
---	------	--	---	------------------------------------

**WORLD HEALTH ORGANIZATION
TECHNICAL REPORT SERIES**

	Number		Price	
Antibiotics, Expert Committee on				
Report on the first session	26	9d.	\$0.10	Sw. fr. 0.40
Biological Standardization, Expert Committee on				
Report on the third session	2	1/6	\$0.20	Sw. fr. 0.80
Report on the fourth session	36	9d.	\$0.10	Sw. fr. 0.40
Fifth report	56	1/3	\$0.15	Sw. fr. 0.60
Report of the Subcommittee on Fat-Soluble Vitamins	3	9d.	\$0.10	Sw. fr. 0.40
Drugs Liable to Produce Addiction, Expert Committee on				
Report on the second session	21	9d.	\$0.10	Sw. fr. 0.40
Third report	57	9d.	\$0.10	Sw. fr. 0.40
International Pharmacopoeia, Expert Committee on (formerly Expert Committee on the Unification of Pharmacopoeias)				
Report on the fourth session	1	9d.	\$0.10	Sw. fr. 0.40
Report on the fifth session	12	9d.	\$0.10	Sw. fr. 0.40
Report on the sixth session	29	1/3	\$0.15	Sw. fr. 0.60
Report on the seventh session (including report on the first session of the Subcommittee on Non-Proprietary Names)	35	1/6	\$0.20	Sw. fr. 0.80
Report on the eighth session (including report on the second session of the Subcommittee on Non-Proprietary Names)	43	2/-	\$0.25	Sw. fr. 1.—
Ninth report (including third report of the Subcommittee on Non-Proprietary Names)	50	2/-	\$0.25	Sw. fr. 1.—
Tuberculosis, Expert Committee on				
Report on the fourth session	7	1/3	\$0.15	Sw. fr. 0.60
Report on the fifth session	32	9d.	\$0.10	Sw. fr. 0.40
Venereal Infections and Treponematoses, Expert Committee on				
Report on the third session	13	1/6	\$0.20	Sw. fr. 0.80
Subcommittee on Serology and Laboratory Aspects				
Report on the first session	14	2/-	\$0.25	Sw. fr. 1.—
Report on the second session	33	1/6	\$0.20	Sw. fr. 0.80

Bulk Orders

A discount of 20 % will be given to health organizations for orders of 100 copies or more. Such orders should be sent direct to the World Health Organization, Sales Section, Palais des Nations, Geneva, Switzerland.