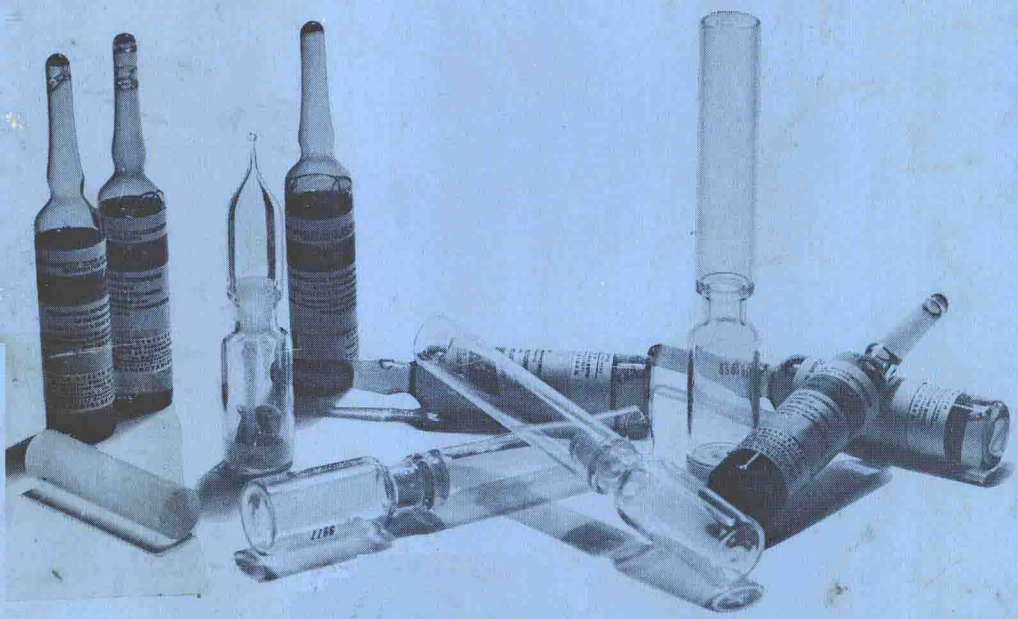
Biological Substances

International Standards, Reference Preparations, and Reference Reagents

1982



WORLD HEALTH ORGANIZATION
GENEVA 1982

LISTS OF INTERNATIONAL BIOLOGICAL STANDARDS, INTERNATIONAL BIOLOGICAL REFERENCE PREPARATIONS, AND INTERNATIONAL BIOLOGICAL REFERENCE REAGENTS

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The World Health Organization is a specialized agency of the United Nations with primary responsibility for international health matters and public health. Through this organization, which was created in 1948, the health professions of more than 155 countries exchange their knowledge and experience with the aim of making possible the attainment by all citizens of the world by the year 2000 of a level of health that will permit them to lead a socially and economically productive life.

By means of direct technical cooperation with its Member States, and by stimulating such cooperation among them, WHO promotes the development of comprehensive health services, the prevention and control of diseases, the improvement of environmental conditions, the development of health manpower, the coordination and development of biomedical and health services research, and the planning and implementation of health programmes.

These broad fields of endeavour encompass a vide variety of activities, such as developing systems of primary health care that reach the whole population of Member countries; promoting the health of mothers and children; combating malnutrition; controlling malaria and other communicable diseases, including tuberculosis and leprosy; having achieved the eradication of smallpox, promoting mass immunization campaigns against a number of other preventable diseases; improving mental health; providing safe water supplies; and training health personnel of all categories.

Progress towards better health throughout the world also demands international cooperation in such matters as establishing international standards for biological substances, pesticides and pharmaceuticals; formulating environmental health criteria; recommending international nonproprietary names for drugs; administering the International Health Regulations; revising the International Classification of Diseases, Injuries, and Causes of Death; and collecting and disseminating health statistical information.

Further information on many aspects of WHO's work is presented in the Organization's publications.

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INTRODUCTION

The primary purpose underlying the establishment of International Biological Standards and International Biological Reference Preparations is to provide a means of ensuring uniformity throughout the world in the designation of the potency or activity of preparations that are used in the prophylaxis, therapy, or diagnosis of human and some animal disease, and that cannot be expressed directly in terms of chemical and physical quantities. For this purpose, International Units have been assigned, wherever possible, to biological substances.[1]

The International Unit (IU) for a specific substance has been defined, in the past, as the biological activity contained in a defined weight of the current International Standard for that substance. However, difficulties have been experienced when attempting to weigh small amounts of materials with great accuracy, particularly hygroscopic powders. In this connexion the thirtieth report of the WHO Expert Committee on Biological Standardization,[2] which met in November 1978, stated:

> "The problem may be largely avoided by distributing an international standard in freeze-dried form and assigning a defined number of international units per ampoule, thus making it unnecessary to weigh quantities of the standard preparation. The total contents of the ampoule are removed with an appropriate solvent and the final volume is accurately adjusted."

For certain standards newly established by that Committee, the unitage has therefore been defined on the basis of the total contents of the ampoule, rather than on the basis of weight, and is shown in this way in the present edition of *Biological Substances.* In keeping with a recommendation of the Committee, definitions of unitage of previously established standards have also been restated here on the basis of the ampoule contents wherever the distribution of the standard into the ampoules is known to have been done with sufficient precision (i.e., $\pm 1.0\%$). For some years, indeed, recipients of ampoules of standards that have been accurately filled have been instructed to use them on the basis of the total number of units stated to be in each ampoule; and for these standards, the number of IU per ampoule has been given parenthetically in previous editions of the present work.

For some standards, on the other hand, it has not been possible to depart from a definition of the International Unit on the basis of weight. For some reference preparations, there is no assigned unitage (as shown by dashes in both the second and the third column in the following tables).

The standard is the material as it exists in the ampoules; the "material" thus includes the active ingredients together with all the other constituents that may be present (moisture, carrier, buffer salts, etc.,

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[1] WHO Technical Report Series, No. 486, 1972, pp. 7-8.

[2] WHO Technical Report Series, No. 638, 1979, pp. 7-8.

according to the form in which the standard is available). The World Health Assembly has recommended[1] that Member States of the Organization give official recognition to existing international standards and units. A secondary purpose of these standards is the facilitation of work out of which clinical application may arise. International Reference Preparations, although not covered by resolutions of the World Health Assembly, are provided as a service; for most of them, international units are defined.

The main custodians of International Biological Standards and International Biological Reference Preparations are the International Laboratories for Biological Standards at the State Serum Institute, Copenhagen, Denmark, at the National Institute for Biological Standards and Control, London, England, at the Central Veterinary Laboratory, Weybridge, Surrey, England, and at the Central Laboratory of the Red Cross Blood Transfusion Service, Amsterdam, Netherlands, as well as the National Institute of Public Health, Bilthoven, Netherlands, the International Agency for Research on Cancer, Lyon, France, the National Institutes of Health, Bethesda, MD, USA, and the Centers for Disease Control, Atlanta, GA, USA. They distribute samples of these preparations, free of charge, to national control laboratories for biological products.[2] These preparations are intended for use in the calibration of the activity of national or working standards and for the expression of their biological activity in International Units; such samples are made for use in laboratory assays only and must not be administered to human beings.

International Biological Reference Reagents are established for the purpose of providing biological diagnostic reagents of high specificity for the identification of microorganisms or their products (specific antisera), as well as other important biological materials used in the diagnosis of disease. Since these reference reagents are not used for the quantitative assay of the activity of biological products, an international unit is not assigned to them. However, they serve usefully for long-term reference purposes.

The list printed on the following pages has been revised to show all the changes made since the publication of the previous edition in 1979, including those contained in the thirty-first[3] and thirty-second[4] reports of the WHO Expert Committee on Biological Standardization, which met in April 1980 and September 1981.

This list is brought up to date every few years. Any changes between revisions will be listed cumulatively in annexes to the reports of the WHO Expert Committees on Biological Standardization.

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[1] WHO Official Records No. 143, 1965, p. 5 (resolution WHA18.7); No. 209, 1973, p. 15 (resolution WHA26.32).

[2] WHO Technical Report Series, No. 463, 1971, p. 8.

[3] WHO Technical Report Series, No. 658, 1981.

[4] WHO Technical Report Series, No. 673, 1982.

INTERNATIONAL BIOLOGICAL STANDARDS
AND
INTERNATIONAL BIOLOGICAL REFERENCE PREPARATIONS

IMPORTANT

Wherever possible, the biological activity of a substance has been expressed as the total number of international units per ampoule. In these cases the entire contents of the ampoule should be removed with an appropriate solvent and the final volume accurately adjusted. It is neither necessary nor advisable to weigh the entire material, or a portion of it, contained in the ampoule.

In other cases, where the weight definition of the unit has been unavoidable, the material should be weighed with particular care, especially as some of the reference materials are hygroscopic.

ANTIBIOTICS I Held and

International Laboratory for Biological Standards, National Institute for

Preparation	IU per ampoule	mg/IU (if relevant)	Form in which available
Amphotericin B	—	0.001064	Ampoules containing approximately 50 mg of amphotericin B (940 IU per mg)
Bacitracin	—	0.01351	Ampoules containing approximately 100 mg of zinc bacitracin (74 IU per mg)
Bleomycin complex A_2/B_2	8910	—	Ampoules containing 5 mg of bleomycin complex
Candicidin	—	0.0004766	Ampoules containing approximately 50 mg of candicidin (2098 IU per mg)
Capreomycin	—	0.001087	Ampoules containing approximately 80 mg of capreomycin sulfate (920 IU per mg)
Cefalotin	—	0.0010661	Ampoules containing approximately 50 mg of sodium cefalotin (938 IU per mg)
Chlortetracycline	—	0.001	Ampoules containing approximately 75 mg of chlortetracycline hydrochloride (1000 IU per mg)
Clindamycin	—	0.0011947	Ampoules containing approximately 50 mg of clindamycin hydrochloride (837 IU per mg)
Colistin	—	0.00004878	Ampoules containing approximately 75 mg of colistin sulfate (20 500 IU per mg)
Colistin methane sulfonate[1]	—	0.00007874	Ampoules containing approximately 75 mg of colistin methane sulfonate (12 700 IU per mg)

[1] In some countries this antibiotic is known as 'colistin sulphomethate' or 'colistimethate'.

distributed by

Biological Standards and Control, Hampstead, London NW3 6RB, England

	Years of establishment (in brackets, weight of previous standard containing one IU)	References (WHO/BS refers to unpublished working documents of the WHO Expert Committees on Biological Standardization)
	1st Standard 1963	*Bull. World Health Organ.*, 1972, **47**, 343; WHO Technical Report Series, 1959, **172**, 8; 1960, **187**, 5; 1963, **259**, 10; 1964, **274**, 8; WHO/BS 450, 478, 592, 648
	1st Standard 1953 (0.0182 mg) *2nd Standard* 1964	*Bull. World Health Organ.*, 1953, **9**, 861; 1964, **31**, 101; WHO Technical Report Series, 1951, **36**, 9; 1952, **56**, 12; 1953, **68**, 16; 1954, **86**, 15; 1960, **187**, 6; 1963, **259**, 8; 1964, **293**, 8; WHO/BS 122, 144, 236, 481, 593, 642, 642 Add. 1, 681
	1st Reference Preparation 1980	WHO Technical Report Series, 1977, **610**, 16; 1978, **626**, 11; 1979, **638**, 13; 1981, **658**, 13; WHO/BS 1196, 1276; *J. biol. Stand.*, 1981, **9**, 253
	1st Reference Preparation 1978	WHO Technical Report Series, 1968, **384**, 12; 1969, **413**, 13; 1971, **463**, 12; 1976, **594**, 9; 1977, **610**, 16; 1978, **626**, 11; 1979, **638**, 11; WHO/BS 913, 1011, 1108, 1131, 1171, 1193
	1st Reference Preparation 1967	*Bull. World Health Organ.*, 1972, **47**, 343; WHO Technical Report Series, 1964, **293**, 11; 1968, **384**, 10; WHO/BS 731, 759, 884
	1st Reference Preparation 1965	*Bull. World Health Organ.*, 1972, **47**, 343; WHO Technical Report Series, 1964, **293**, 11; 1966, **329**, 8; 1967, **361**, 9; WHO/BS 731, 762, 821
	1st Standard 1953 (0.001 mg) *2nd Standard* 1969	*Bull. World Health Organ.*, 1953, **9**, 851; 1972, **47**, 635; WHO Technical Report Series, 1951, **36**, 9; 1952, **56**, 12; 1953, **68**, 16; 1954, **86**, 14; 1967, **361**, 10; 1969, **413**, 11; 1970, **444**, 8; WHO/BS 122, 143, 245, 857, 983
	1st Reference Preparation 1971	WHO Technical Report Series, 1971, **463**, 12; 1972, **486**, 10; WHO/BS 1052
	1st Standard 1968	*Bull. World Health Organ.*, 1973, **48**, 65; WHO Technical Report Series, 1961, **222**, 9; 1964, **274**, 8; 1964, **293**, 9; 1966, **329**, 7; 1967, **361**, 11; 1969, **413**, 11; WHO/BS 530, 647, 724, 764, 923
	1st Reference Preparation 1966	*Bull. World Health Organ.*, 1973, **48**, 75; WHO Technical Report Series, 1964, **274**, 8; 1964, **293**, 10; 1966, **329**, 7; 1967, **361**, 11; 1969, **413**, 11; WHO/BS 725, 764, 828, 924

ANTIBIOTICS I (*contd*) Held and

International Laboratory for Biological Standards, National Institute for

Preparation	IU per ampoule	mg/IU (if relevant)	Form in which available
Demethylchlortetracycline[1]	—	0.001	Ampoules containing approximately 80 mg of demethylchlortetracycline hydrochloride (1000 IU per mg)
Dihydrostreptomycin	—	0.001219	Ampoules containing approximately 200 mg of dihydrostreptomycin sulfate (820 IU per mg)
Doxycycline	—	0.0011494	Ampoules containing approximately 75 mg of doxycycline hydrochloride hemiethanolate hemihydrate (870 IU per mg)
Erythromycin	—	0.001087	Ampoules containing approximately 75 mg of erythromycin A base (920 IU per mg)
Gentamycin[2]	—	0.00156	Ampoules containing approximately 50 mg of gentamycin sulfate (641 mg IU per mg)
Gramicidin	—	0.001	Ampoules containing approximately 55 mg of gramicidin (1000 IU per mg)
Kanamycin	—	0.001232	Ampoules containing approximately 50 mg of kanamycin sulfate (812 IU per mg)
Kanamycin B[3]	—	—	Ampoules containing approximately 5 mg of kanamycin B
Lincomycin	—	0.0011351	Ampoules containing approximately 50 mg of lincomycin hydrochloride (881 IU per mg)

[1] The International Nonproprietary Name of this substance has been changed to demeclocycline.

[2] The International Nonproprietary Name of this substance has been changed to gentamicin.

[3] The International Nonproprietary Name of this substance is bekanamycin.

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Biological Standards and Control, Hampstead, London NW3 6RB, England

Years of establishment (in brackets, weight of previous standard containing one IU)	References (WHO/BS refers to unpublished working documents of the WHO Expert Committees on Biological Standardization)
1st Reference Preparation 1962	*Bull. World Health Organ.*, 1972, **47**, 343; WHO Technical Report Series, 1961, **222**, 9; 1963, **259**, 9; WHO/BS 530, 592
1st Standard 1953 (0.001316 mg) *2nd Standard* 1966	*Bull. World Health Organ.*, 1954, **10**, 901; 1966, **34**, 429; WHO Technical Report Series, 1950, **2**, 11; 1951, **36**, 9; 1952, **56**, 11; 1953, **68**, 17; 1954, **86**, 15; 1963, **259**, 9; 1964, **274**, 7; 1967, **361**, 8; WHO/BS 67, 122, 146, 241, 242, 592, 638, 829
1st Reference Preparation 1973	WHO Technical Report Series, 1970, **444**, 11; 1972, **486**, 9; 1973, **530**, 5; 1976, **594**, 8; WHO/BS 1012, 1050, 1099
1st Standard 1957 (0.001053 mg) *2nd Standard* 1978	*Bull. World Health Organ.*, 1957, **17**, 527; WHO Technical Report Series, 1955, **96**, 12; 1956, **108**, 13; 1957, **127**, 13; 1958, **147**, 6; 1978, **626**, 10; 1979, **638**, 12; WHO/BS 263, 322, 368, 397, 397 Annex 1, 1228; *J. biol. Stand.*, 1981, **9**, 209
1st Reference Preparation 1968	*Bull. World Health Organ.*, 1972, **47**, 343; WHO Technical Report Series, 1964, **293**, 11; 1966, **329**, 9; 1967, **361**, 12; 1969, **413**, 12; WHO/BS 763, 925
1st Reference Preparation 1966	*Bull. World Health Organ.*, 1967, **36**, 447; WHO Technical Report Series, 1960, **187**, 6; 1961, **222**, 9; 1964, **293**, 7; 1967, **361**, 8; WHO/BS 493, 682, 858
1st Reference Preparation 1959	*Bull. World Health Organ.*, 1972, **47**, 343; WHO Technical Report Series, 1959, **172**, 8; 1960, **187**, 6; 1963, **259**, 10; 1964, **274**, 9; 1964, **293**, 8; WHO/BS 450, 478, 592, 648, 687
1st Reference Preparation 1964	*Bull. World Health Organ.*, 1972, **47**, 343; WHO Technical Report Series, 1964, **293**, 8; WHO/BS 687
1st Reference Preparation 1965	*Bull. World Health Organ.*, 1972, **47**, 343; WHO Technical Report Series, 1964, **293**, 11; 1966, **329**, 8; 1967, **361**, 10; WHO/BS 731, 762, 854

ANTIBIOTICS I (*contd*) Held and

International Laboratory for Biological Standards, National Institute for

Preparation	IU per ampoule	mg/IU (if relevant)	Form in which available
Lymecycline	—	0.0010548	Ampoules containing approximately 100 mg of lymecycline (948 IU per mg)
Methacycline[1]	—	0.001082	Ampoules containing approximately 50 mg of methacycline hydrochloride (924 IU per mg)
Minocycline	—	0.0011587	Ampoules containing approximately 75 mg of minocycline hydrochloride (863 IU per mg)
Neomycin	—	0.0012903	Ampoules containing approximately 50 mg of neomycin sulfate (775 IU per mg)
Neomycin B[2]	16756	0.001492	Ampoules containing approximately 25 mg of neomycin B sulfate (670 IU per mg)
Novobiocin	—	0.001031	Ampoules containing approximately 100 mg of novobiocin acid (970 IU per mg)
Nystatin	—	0.000333	Ampoules containing approximately 75 mg of nystatin (3000 IU per mg)
Oleandomycin	—	0.001176	Ampoules containing approximately 75 mg of oleandomycin chloroform adduct (850 IU per mg)

[1] The International Nonproprietary Name of this substance is metacycline.
[2] The International Nonproprietary Name of this substance is framycetin.