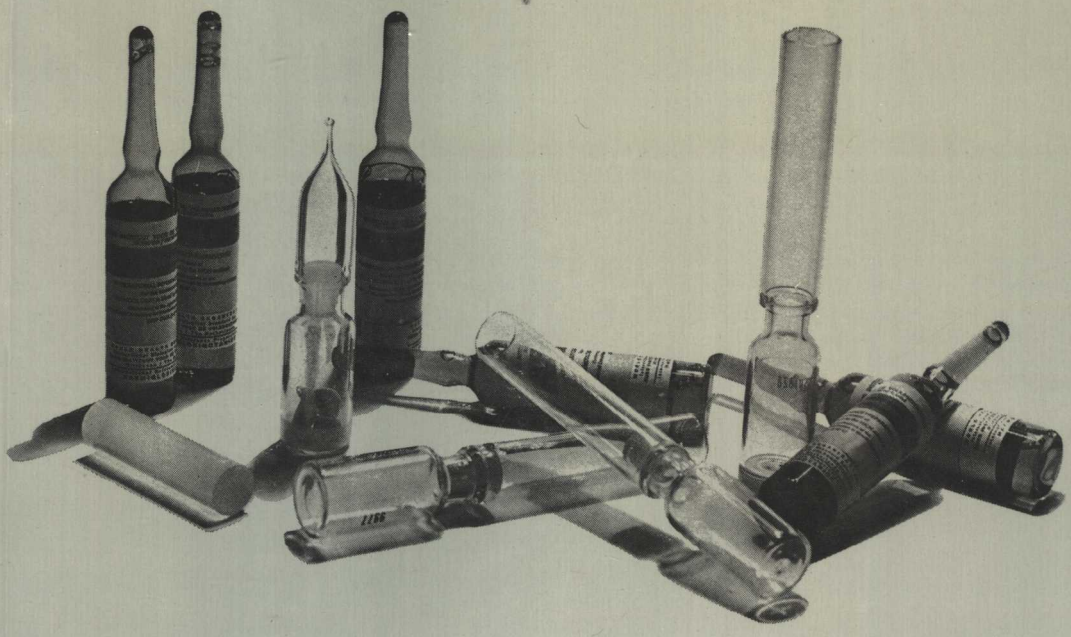
# Biological Substances

International Standards
and Reference Reagents
1986



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# BIOLOGICAL SUBSTANCES

## INTERNATIONAL STANDARDS AND REFERENCE REAGENTS

1986

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## INTRODUCTION

The primary purpose underlying the establishment of International Biological Standards and International Biological Reference Reagents is to provide a means of ensuring uniformity throughout the world in the designation of the potency, activity, or specificity 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 necessary, 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 connection 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., ± 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.

The standard is the material as it exists in the ampoules; the "material" thus includes the active ingredients together with all the other

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

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

constituents that may be present (moisture, carrier, buffer salts, etc., 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.

At the thirty-fourth meeting of the WHO Expert Committee on Biological Standardization in 1983, it was agreed that International Reference Preparations to which an activity had been assigned in the form of International Units should be considered functionally to be international standards. The question of whether it would be desirable to rename the international biological reference preparations already established as international biological standards was discussed, and it was agreed that to do so would probably cause confusion because of the extensive scientific literature in which the existing names had been used.

At its thirty-seventh meeting, in 1986, the WHO Expert Committee on Biological Standardization decided that, in the future, new or replacement International Biological Reference Materials would be established either as International Standards or as International Reference Reagents.

The main custodians of International Biological Standards are the International Laboratories for Biological Standards at the State Serum Institute, Copenhagen, Denmark, at the National Institute for Biological Standards and Control, Potters Bar, Hertfordshire, 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 National Institutes of Health, Bethesda, MD, USA, and the Centers for Disease Control, Atlanta, GA, USA. They distribute samples of these standards, free of charge, to national control laboratories for biological products.[3] 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 mainly (but not solely) for the purpose of providing biological diagnostic reagents of high specificity for the identification of microorganisms or their products, as well as other important biological materials used in the diagnosis of disease; international units are not assigned to them.

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[1] WHO handbook of resolutions and decisions. Volume II, 1973-1984. Geneva, World Health Organization, 1985, p. 135 (resolution WHA37.27).

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

The list printed on the following pages has been revised to show all the changes made since the publication of the previous edition in 1984, including those contained in the thirty-fifth[1] and thirty-sixth[2] reports of the WHO Expert Committee on Biological Standardization, which met in June 1984 and November 1985.

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 Committee on Biological Standardization.

[1] WHO Technical Report Series, No. 725, 1985.

[2] WHO Technical Report Series, No. 745, 1987.

# INTERNATIONAL BIOLOGICAL STANDARDS

## 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

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**International Laboratory for Biological Standards, National Institute for**

| Preparation | IU per ampoule | mg/IU (if relevant) | Form in which available |
|---|---|---|---|
| Amikacin | 50 600 | — | Ampoules containing approximately 50.9 mg of amikacin base |
| 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, Potters Bar, Herts. EN6 3QG, 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 Committee on Biological Standardization) |
|---|---|
| *1st Standard* 1983 | WHO Technical Report Series, 1978, **626**, 12; 1979, **638**, 12; 1981, **658**, 12; 1982, **673**, 16; 1983, **687**, 16; 1984, **700**, 12; WHO/BS 1173, 1224, 1274, 1316, 1355, 1398 |
| *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)<br>*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)<br>*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 |

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**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 demethylchlortetracyline 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 IU per mg) |
| Gramicidin | — | 0.001 | Ampoules containing approximately 55 mg of gramicidin (1000 IU per mg) |
| Kanamycin | 10345 | — | Ampoules containing approximately 12,7 mg of kanamycin sulfate |
| Lincomycin | — | 0.0011351 | Ampoules containing approximately 50 mg of lincomycin hydrochloride (881 IU per mg) |

[1] The International Nonproprietary Name of this substance is demeclocycline.

[2] The International Nonproprietary Name of this substance is gentamicin.

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| Years of establishment (in brackets, weight of previous standard containing one IU) | References (WHO/BS refers to unpublished working documents of the WHO Expert Committee 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)<br>*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)<br>*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; 1983, **687**, 18; 1984, **700**, 12; WHO/BS 263, 322, 368, 397, 397 Annex 1, 1228, 1413; *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<br>*2nd Standard* 1985 | *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; 1985, **725**, 15; WHO/BS 450, 478, 592, 648, 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 | .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 | — | 0.0002059 | Ampoules containing approximately 100 mg of nystatin (4855 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.