Biological Substances

International Standards and Reference Reagents

1990

World Health Organization
Geneva

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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 some 165 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 wide 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 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.

OTHER WHO PUBLICATIONS ON BIOLOGICALS AND PHARMACEUTICALS

	Price* (Sw. fr.)
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* Prices in developing countries are 70% of those listed here.

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Contents

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 diseases, 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 most standards established by the 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.*

For standards containing 50 mg or more of material (e.g., standards for many antibiotics and the human, bovine and porcine insulins), it has not been possible to depart from a definition of the International Unit on the basis of weight.

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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.

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., according to the form in which the standard is available). The World Health Assembly has recommended[3] 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,[4] 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,[5] 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; another custodian laboratory is the Anti-Viral Research Branch of the National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA. They distribute samples of these standards, free of charge, to national control laboratories for biological products[6] and, with small handling charges, to other organizations such as manufacturers and hospital laboratories. These preparations are intended for use in the calibration of the activity of national or working

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[3] *WHO handbook of resolutions and decisions. Volume II, 1973-1984.* Geneva, World Health Organization, 1985, p. 135 (resolution WHA37.27).
[4] WHO Technical Report Series, No. 700, 1984, pp. 7-8.
[5] WHO Technical Report Series, No. 760, 1987, p. 15.
[6] WHO Technical Report Series, No. 463, 1971, p. 8.

standards and for the expression of their biological activity in International Units; in almost all cases such samples are made for use in laboratory assays only and should 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, as well as other reagents used to calibrate certain reference materials used in the assay of a variety of biological substances; international units are not assigned to them.

Requests for international reference materials should be addressed directly to the custodian laboratories, together with a statement of intended use. Address, telephone, fax and telex numbers of WHO custodian laboratories are as follows:

International Laboratories for Biological Standards

- Central Laboratory, Netherlands Red Cross Blood Transfusion Service, Plesmanlaan 125, Amsterdam, Netherlands (Tel. (20) 512 9222; Telex 13159 BLOOD NL; Fax (20) 512 3332).
- Central Veterinary Laboratory, New Haw, Weybridge, Surrey KT15 3NB, England (Tel. (9323) 41111; Telex 262318; Fax (9323) 47046).
- National Institute for Biological Standards and Control,[7] South Mimms, Potters Bar, Herts. EN6 3QG, England (Tel (707) 54753/54763; Telex 21911 NIBSAC G; Fax (707) 46730).
- Statens Seruminstitut, 80 Amager Boulevard, 2300 Copenhagen S, Denmark (Tel. (45) 31 95 2817; Telex 31316 SERUM DK; Fax (45) 31 95 5822).

Other laboratories

- Anti-Viral Research Branch, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892, USA (Tel. (301) 496 9088; Telex 248232; Fax (301) 496 8030).
- Centers for Disease Control, Atlanta, GA 30333, USA (Tel. (404) 639 3355; Telex 549571 CDC ATL; Fax (404) 639 3037/3296).

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[7] The NIBSC has its own catalogue, which is available on request.

- Rijksinstituut voor Volksgezondheid en Milieuhygiene, Postbus 1, 3720 BA, Bilthoven, Netherlands
  (Tel. (30) 749111; Telex 47215 RIVM NL; Fax (30) 742971).
- WHO/FAO Collaborating Centre for Reference and Research on Leptospirosis, Laboratory of Tropical Hygiene, Royal Tropical Institute, Meibergdreef 39, 1105 AZ Amsterdam, Netherlands
  (Tel. (20) 566 5438; Telex 15080 KIT NL; Fax (20) 668 4579).

The list printed on the following pages has been revised to show all the changes made since the publication of the previous edition in 1987, including those contained in the thirty-seventh, thirty-eighth,[8] thirty-ninth[9] and fortieth[10] reports of the WHO Expert Committee on Biological Standardization.

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

[8] WHO Technical Report Series, No. 771, 1988.
[9] WHO Technical Report Series, No. 786, 1989.
[10] WHO Technical Report Series, No. 800, 1990.

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.

Allergens

Held and distributed by
International Laboratory for Biological Standards, National Institute for Biological Standards and Control, Potters Bar

Preparation	IU per ampoule	Form in which available
Birch pollen (*Betula verrucosa*) extract	100 000	Ampoules containing about 1g of lyophilized extract of birch pollen
Dog (*Canis domesticus*) hair and dander extract	100 000	Ampoules containing about 2.36 mg of lyophilized dog hair and dander extract
House-dust mite (*Dermatophagoides pteronyssinus*) extract	100 000	Ampoules containing the freeze-dried residue of 1 ml of house-dust mite extract
Short ragweed pollen (*Ambrosia elatior*) extract	100 000	Ampoules containing the freeze-dried residue of 0.3 ml aqueous extract of defatted short ragweed pollen
Timothy grass pollen (*Phleum pratense*) extract	100 000	Ampoules containing the freeze-dried residue of 1 ml aqueous extract of Timothy grass pollen

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 1986	WHO Technical Report Series, 1987, **760**, 19; WHO/BS 1512
1st Standard 1986	WHO Technical Report Series, 1987, **760**, 19; 1989, **786**, 27; WHO/BS 1513, 1547
1st Standard 1984	WHO Technical Report Series, 1985, **725**, 16; WHO/BS 1417
1st Standard 1983	WHO Technical Report Series, 1985, **626**, 16; 1984, **700**, 16
1st Standard 1983	WHO Technical Report Series, 1978, **626**, 16; 1984, **700**, 17