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APPLICATION OF IUPAC–IFCC RECOMMENDATIONS ON QUANTITIES AND UNITS TO WHO BIOLOGICAL REFERENCE MATERIALS FOR DIAGNOSTIC USE

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Names of countries given after Members' names are in accordance with the *IUPAC Handbook 1991–93*; changes will be effected in the *1994–95* edition.

Applications of IUPAC–IFCC recommendations on quantities and units to WHO biological reference materials for diagnostic use

This document deals with the nature of WHO biological reference materials, their development for the control of therapeutic substances and recommendations to improve their application in diagnosis. The nature of international units specified by WHO biological reference materials is contrasted with that of SI units, and the method for assigning values in international units to such reference materials is described. The document recommends the use of SI units (mole) with existing and proposed WHO biological reference materials whenever the elementary entity of the stated component can be recognized. It also recommends that the description of quantities having no recognized kind-of-quantity with a definable dimension should be clearly distinguished by the term "arbitrary" and include a reference to the procedure and calibrator used. The WHO is urged to involve appropriate non-governmental organizations in advising on the need for, and the suitability of international reference materials.

1 Introduction

1.1 Biological reference materials together with reference measurement procedures are well established foundations for the characterization and measurement of quantities involving biologicals. Biologicals are defined by WHO as substances used in prophylaxis, therapy and diagnosis whose identity, purity or amount cannot be characterized adequately by physicochemical means alone. The inclusion of substances in this category at any particular time depends on the methods available for their synthesis or isolation (and hence their perceived purity), as well as the perceived selectivity of the methods available for their characterization.

1.2 Since the 1920s, biological standardization has been promoted under programmes organized first by the League of Nations (Ref. 5.1) and later by the World Health Organization (Ref. 5.2). The main initial objective was to ensure that the potency and quality of therapeutic biological products (such as insulin) could be standardized world-wide. However, over the last twenty-five years, biological standardization has been applied increasingly also to clinical laboratory investigations.

1.3 Over this latter period, the IFCC and IUPAC have adopted and developed a comprehensive and coherent system of quantities and units for use in laboratory medicine (Ref. 5.3). This system, which is based on a sound theoretical framework shared with other physical and chemical sciences, has resulted in the world-wide introduction of the International System of Units (SI) into laboratory medicine.

1.4 Workers in clinical laboratory sciences have therefore become increasingly conversant with SI and with IUPAC/IFCC recommendations on quantities and units. However, difficulties arise in the use of the quantities and international units specified for some WHO biological reference materials. This is largely because these quantities and units are not readily reconciled with those of the IUPAC–IFCC recommendations. There is also often a lack of understanding about the relevant WHO standard to be used and the mode of expression of results. These difficulties lead to the incorrect use of biological standards in clinical laboratory sciences resulting in the presentation of erroneous or insufficient data.

1.5 Through the initiatives of the IFCC Committee on Quantities and Units and the IUPAC Commission on Quantities and Units in Clinical Chemistry and following consultations with representatives of WHO, a Consulting Working Group was set up to consider these issues. This Group met at WHO (Geneva) in January 1991 and October 1992.

The statements and recommendations below were agreed, based upon references 5.3, 5.4 and 5.5.

2 Quantities and units

2.1 A quantity measured in the clinical laboratory must be described in terms of the following elements and structure (Ref. 5.3).

Elements and structure	Example
System—	Blood(of individual N.N. at stated time)—
Component;	Haemoglobin(Fe);
kind-of-quantity	substance concentration*

*Based on ICSH 1965 (Ref. 5.6)

The component is also commonly designated "analyte".

The magnitude of the quantity is expressed by the product of numerical value and unit . Thus,

quantity = numerical value · unit

The concept of quantity applies more particularly to that property of a reference material that is assigned a value. Where applicable, the unit should be of the International System of Units (SI). The assigned value should be accompanied by a statement of its uncertainty.

2.2 SI units have recognized dimensions that are defined by the kind-of-quantities for which they are used (e.g. mole per litre and substance concentration have the dimension $L^{-3}N$) and are independent of measurement procedure. By contrast, international units are defined by reference materials and in terms of appropriate respective measurement procedures without being traceable to SI units.

2.3 The clinical laboratory usually does not use biological procedures, and international units based on such procedures are therefore not necessarily relevant to immunological (or biochemical or chemical) procedures, unless for a given pair of biological and immunological (or biochemical or chemical) procedures an acceptable correlation between results makes transformation permissible.

3 Reference materials

3.1 WHO has published guidelines for the preparation, characterization and establishment of international and other standards and reference reagents for biological substances (Ref. 5.7). These describe various characteristics, such as precision of fill, stability and, for a primary reference material, capacity to reduce inter-laboratory variability, which need to be examined in the process of characterizing candidate biological reference materials. The document also reviews various appropriate steps such as a pilot study, measurement phase in the main collaborative study, statistical analysis of results, official submission and, finally, establishment by the WHO Expert Committee on Biological Standardization.

3.2 When a reference material is made for the first time and cannot be characterized by a kind-of-quantity used with the SI, its assigned value (in terms of an international unit) is arbitrary. Replacement preparations are assigned values based on that of the preceding preparation.

3.3 When "procedure-dependent" international units have to be used, it may be necessary to assign the value on the basis of only one reference measurement procedure utilized by all laboratories participating in the collaborative trial. In changing into a kind-of-quantity of well known dimension and an SI unit, there is metrological strength in employing different methods and even principles of measurement.

4 Recommendations

4.1 In the field of laboratory medicine, the use of an international unit in measured values of a quantity is a way of circumventing the problem of having a component (analyte) that does not have a known elementary entity. When an elementary entity for the stated component can be recognized, a kind-of-quantity based on amount-of-substance (unit: mole) is preferred, e.g. for a given polypeptide.

4.2 The information relating to each existing and proposed WHO reference material should be examined to see whether knowledge about the system and component(s) would allow defining a kind-of-quantity based on amount-of-substance (unit: mole) and assigning a value with an SI unit.

4.3 For quantities having no recognized kind-of-quantity with a definable dimension, the term "arbitrary" should precede the usual kind-of-quantity name and a reference to the "procedure" and to the calibrator should follow the kind-of-quantity in the systematic name. Thus kind-of-quantities of an arbitrary nature always need specifications. Example: For concentration of lutropin, the kind-of-quantity could be "arbitrary substance concentration(immunoprocedure X; IS 80/552)".

4.4 Guidelines for the use of a reference material should state the procedure(s) for which the material has been found suitable.

4.5 WHO is urged to form a group involving appropriate non-governmental organizations to advise on the need for international reference materials for clinical laboratory investigations and to review and advise on documentation submitted to the Expert Committee on Biological Standardization in support of certification.

4.6 WHO is urged to continue and to expand its programme for the production of international reference materials suitable for clinical diagnosis (Ref. 5.8).

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