Overview of ISO 17511 for 'Biologicales'

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Two EN ISO standards on MT
Why MT? Pressure and utility
Planning measurement
  - define measurand
  - set maximum MU
  - choose calibration hierarchy
WHO concepts & terminology
WHO assignment of quantity value
WHO and MU
EN ISO 17511


EN ISO 18153

EU Directive 98/79/EC on IVD MDs
Annex I, Essential requirements A.3

'The traceability of values assigned to calibrators and/or control materials must be assured through available reference measurement procedures and/or available reference materials of a higher order.'
CEN and ISO work related to metrological traceability of IVD MDs

Presentation of reference measurement procedures

Description of reference materials

Metrological traceability of values assigned to calibrators and control materials
(EN ISO 17511:2003)

Metrological traceability of values for catalytic concentration of enzymes
assigned to calibrators and control materials
(EN ISO 18153:2003)

Laboratory medicine - Requirements for reference measurement laboratories
(EN ISO 15195:2003)

(R.D. 2004-12-15)
Accreditation standards

General requirements for the competence of testing and calibration laboratories (EN ISO/IEC 17025:2000)

Medical laboratories - Particular requirements for quality and competence (ISO 15189:2003)

Laboratory medicine - Requirements for reference measurement laboratories (EN ISO 15195:2003)
EU & EC on WHO IS

The Competent Regulatory Authorities of the European Union and European Commission consider it essential that WHO International Standards are within the 'higher order' of reference materials.

[Report on WHO consultation 2004-06-07/08]
Why is metrological traceability important?

Prerequisite for reliability and spatio-temporal comparability of measured quantity values, thus allowing
- diagnosis
- monitoring
- therapy
- pooling of data
- avoidance of re-measurement in a new service having another metrological reference (or in a trade relationship)
A measured quantity value unaccompanied by measurement uncertainty is not only useless, but potentially dangerous because the value may be misinterpreted or misused.
metrological traceability

property of a measurement result relating the result to a stated metrological reference through an unbroken chain of calibrations of a measuring system or comparisons, each contributing to the stated measurement uncertainty

NOTE 1 - For this definition, a 'stated metrological reference' can be a definition of a measurement unit through its practical realization, or a measurement procedure, or a measurement standard.

NOTE 2 - A prerequisite to metrological traceability is a previously established calibration hierarchy.

Define measurand

Plasma–
Somatotropin;
arbitrary substance concentration
   (IS 80/505; procedure)
10⁻³ international unit/litre

NPU10357 (Coding scheme identifier and code value)

[Human growth hormone]
synonym

Component
- monomolecule or monoion
- common molecular part in a family of molecules
   (eg Fe for haemoglobins; epitope)
- reactivity of family of molecules
   (eg enzyme; hormone)

System--
Component (Analyte);
kind-of-quantity
(specification)
measurement unit

(R.D. 2004-12-15)
Guide to the
Expression of Uncertainty in Measurement

Corrected and reprinted edition

Published in the names of

BIPM : International Bureau of Weights and Measures
IEC : International Electrotechnical Commission
IFCC : International Federation of Clinical Chemistry
ISO : International Organization for Standardization
IUPAC : International Union of Pure and Applied Chemistry
IUPAP : International Union of Pure and Applied Physics
OIML : International Organization of Legal Metrology

(R.D. 2004-12-15)
Chemical calibration hierarchy - 1

**SI unit (definition)**
- **prim. ref.**
  - **prim.**
  - **second. ref.**
    - **Second:**
      - **mf.'s selected**
      - **mf.'s working**
      - **mf.'s product**
        - **routine**
          - **routine sample**
            - **RESULT**

**Metrological traceability**
- **RESP.**
  - **BODY**
    - **CGPM**
    - **BIPM, NMI, ARML**
    - **BIPM, NMI**
    - **NMI, ARML**
    - **NMI, ARML, ML**
    - **ML**
    - **ML**
    - **ML**
    - **MF**
    - **MF, user**
    - **user**

(R.D. 2004-12-15)
measurement unit

scalar quantity, defined and adopted by convention, with which other quantities of the same kind are compared in order to express their magnitudes

[Draft VIM3:2004-1.9]
(preliminary definition)
specificity of a measuring system

<chemistry> capability of a measuring system, using a specified measurement procedure, to provide a measurement result for a quantity involving a specified component in a system undergoing measurement, without interference from other components in the same system

[Draft VIM3:2004-2.43]
(preliminary definition)
selectivity of a measuring system

<chemistry> capability of a measuring system, using a specified measurement procedure, to provide measurement results for two or more quantities of the same kind involving different components in a system undergoing measurement, without interference from each other or from other quantities in the same system

[Draft VIM3:2004-2.42]
commutability of a material

closeness of agreement between the mathematical relationship of the measurement results obtained by two measurement procedures for a stated quantity in a given material, and the mathematical relationship obtained for the quantity in relevant samples

[≈EN ISO 17511-3.9 & 18153-3.4]
Chemical calibration hierarchy - 2

CALIBRATOR

MEASUREM. PROCED.

RESP. BODY

international conventional reference

international conventional

mf.'s selected

mf.'s working

mf.'s standing

mf.'s product

routine

routine sample

RESULT

IScO, WHO

ML

MF

MF, user

user

user

Metrological traceability

(R.D. 2004-12-15)
reference measurement procedure

thoroughly investigated measurement procedure shown to yield values having an uncertainty of measurement commensurate with its intended use, especially in assessing the trueness of other measurement procedures for the same quantity and in characterizing reference materials

[EN ISO 17511-3.29]
Chemical calibration hierarchy - 3

CALIBRATOR | MEASUREM. PROCED. | RESP. BODY
--- | --- | ---
| international conventional reference | IScO, WHO | ML
mf.'s working | mf.'s standing | ML
mf.'s product | routine | MF
| routine sample | RESULT | user

Metrological traceability

(R.D. 2004-12-15)
Chemical calibration hierarchy - 4

INTERNATIONAL

METROLOGICAL TRACEABILITY

RESULT

CALIBRATOR

MEASUREMENT

RESPONSET

BODY

INTERNATIONAL

CONVENTIONAL

MF. 'S SELECTED

MF. 'S WORKING

MF. 'S PRODUCT

MF. 'S STANDING

ROUTINE

ROUTINE SAMPLE

USER

IScO, WHO

METROLOGICAL TRACEABILITY

(R.D. 2004-12-15)
'biological' (noun)

indicates a compound including
- antibody for prophylactic use
- antibody as an immunochemical reagent
- pharmaceutical compound

[WHO]

[historically relevant colloquialism for the first type; less appropriate for the second and third types]
**biological substance**

Material of biological, biotechnological or synthetic origin that cannot be characterized fully by biochemical and/or physical means alone

EXAMPLES - large, incompletely characterized proteins; antigens; vaccines; antisera; blood products; nucleic acid standards; small, well-characterized proteins

[WHO Draft Recommendations 2004]

[organic chemical compound; not necessarily occurring in biology]
international biological measurement standard

IS

preparation of a substance of biological, biotechnological or synthetic origin, the activity of which is defined by the World Health Organization in terms of an International Unit or another suitable unit of activity

EXAMPLES - material containing proteins, antigens, vaccines, antisera, blood products, or nucleic acids

[WHO Draft Recommendations 2004]

NOTE - This type of measurement standard is a reference material, usually functioning as a calibrator.

(R.D. 2004-12-15)
measurement standard

realization of the definition of a given quantity, with stated value and measurement uncertainty, used as a reference

NOTE 1 - The 'realization of the definition of a given quantity' can consist of a measuring system, a material measure, or a reference material.

[Draft VIM3:2004-5.1]
reference material
RM

material, sufficiently homogeneous and stable with respect to one or more specified quantities, used for the calibration of a measuring system, or for the assessment of a measurement procedure, or for assigning values and measurement uncertainties to quantities of the same kind for other materials

NOTE 1 - The term 'reference material' designates a family of materials without necessarily implying a hierarchy according to the magnitude of the measurement uncertainty.

[Draft VIM3:2004-5.13]
calibrator

measurement standard used in the calibration of a measuring system

[Draft VIM3:2004-5.13]
International Unit of WHO IU

biological activity corresponding to a given amount of a WHO international biological measurement standard (IS)

NOTE - The amount (mass, volume, ampoule content) providing one International Unit of a first international biological measurement standard is defined arbitrarily.

[based on WHO texts]
Metrological traceability to a WHO International Unit

'to a defined part of the content of an ampoule'

[WHO]

to the definition of a measurement unit through a stated metrological traceability chain

[Draft VIM3:2004-2.26]

The second meaning ensures applicability even when the physical material disappears.
biological assay

procedure which requires the use of some elements of a living system (examples include animals, tissues, cells, receptors, antibodies and enzymes) and where the quantity being measured is often defined by comparison to a biological reference preparation or, in some circumstances, may be defined in SI terms.

[WHO Draft Recommendation 2004]

[Measurement procedure]

- bioprocedure: entire animal, organ, cell
- (bio)chemical procedure: clotting, enzymatic, immunochemical, NA amplification, other]
thoroughly investigated measurement procedure shown to yield values having an uncertainty of measurement commensurate with its intended use, especially in assessing the trueness of other measurement procedures for the same quantity and in characterizing reference materials

[EN ISO 17511-3.29]
Multiprocedural assignment of quantity value to reference material

WHO/NIBSC standpoint
- assignment of imprecision is inappropriate
- minimising imprecision by single-method calibration is also inappropriate

[A.F. Bristow at JCTLM, BIPM 2002-06]

Different measurement procedures seem to give different measurement results due to different measurands defined by procedure; alternatively different specificity of the measuring systems.
**measurement uncertainty**

parameter that characterizes the dispersion of the quantity values that are being attributed to a measurand, based on the information used.

NOTE 1 - Measurement uncertainty quantitatively characterizes the knowledge about the measurand, based on the information used.

NOTE 2 - Measurement uncertainty characterizes the dispersion of a set or distribution of quantity values for the measurand, obtained by available information. The dispersion is due to definitional uncertainty of the measurand and random and systematic effects in the measurement.

Measurement uncertainty of First IS

No MU
  - arbitrary definition of IU
  - small relatively to use of IS

[WHO]

The arbitrary definition does not remove any definitional uncertainty and the MU of embodiment.

The decision of insignificance should be left to the user, and a stated estimate of MU from an uncertainty budget (on definition of measurand, aliquoting, homogeneity, and stability) would be both necessary information (EU Directive: measurement traceability) and good advertisement.
Measurement uncertainty of replacement IS

'... every effort is made in the collaborative study design to ensure that the IU defined by a replacement reference material is as similar as possible to the IU defined by the old reference material so that continuity of the IU is obtained over time.'

[WHO Draft Recommendation 2004]

The practical implication of this statement can only be judged by the user on the basis of an uncertainty budget incorporating the MU of the previous IS(s).
Using Material 2 as a calibrator allows measured quantity values with measurement uncertainty and metrological traceability to Material 1 and thereby comparability of measurement results over time (and space).

Severing the connection between 1 and 2 renders comparison between 'old' and 'new' results dubious.

The assigned quantity value of any material has a measurement uncertainty.