JCTLM Symposium on
Reference Measurement Systems for Biologicals
International Bureau of Weights and Measures
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Overview of ISO 17511 for 'Biologicals'

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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

EUROPEAN STANDARD

NORME EUROPÉENNE

EUROPÄISCHE NORM

EN ISO 17511

August 2003

ICS 07.100.10

English version

In vitro diagnostic medical devices - Measurement of quantities in biological samples - Metrological traceability of values assigned to calibrators and control materials (ISO 17511:2003)

Dispositifs médicaux de diagnostic in vitro - Mesurage des grandeurs dans des échantillons d'origine biologique - Traçabilité métrologique des valeurs attribuées aux agents d'étalonnage et aux matériaux de contrôle (ISO 17511:2003)

In-vitro-Diagnostika - Messung von Größen in Proben biologischen Ursprungs - Metrologische Rückführbarkeit von Werten, die Kalibriermaterialien und Kontrollmaterialien zugeordnet sind (ISO 17511:2003)

This European Standard was approved by CEN on 11 March 2003.

CEN members are bound to comply with the CEN/CENELEC Internal Regulations which stipulate the conditions for giving this European Standard the status of a national standard without any alteration. Up-to-date lists and bibliographical references concerning such national standards may be obtained on application to the Management Centre or to any CEN member.

This European Standard exists in three official versions (English, French, German). A version in any other language made by translation under the responsibility of a CEN member into its own language and notified to the Management Centre has the same status as the official versions.

CEN members are the national standards bodies of Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Luxembourg, Malta, Netherlands, Norway, Portugal, Slovakia, Spain, Sweden, Switzerland and United Kingdom.

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COMITÉ EUROPÉEN DE NORMALISATION
EUROPÄISCHES KOMITEE FÜR NORMUNG

Management Centre: rue de Stassart, 36 B-1050 Brussels

Ref. No. EN ISO 17511:2003 E

EUROPEAN STANDARD

NORME EUROPÉENNE

EUROPÄISCHE NORM

EN ISO 18153

August 2003

ICS 07.100.10

English version

In vitro diagnostic medical devices - Measurement of quantities in biological samples - Metrological traceability of values for catalytic concentration of enzymes assigned to calibrators and control materials (ISO 18153:2003)

Dispositifs médicaux de diagnostic in vitro - Mesurage des grandeurs dans des échantillons d'origine biologique - Traçabilité métrologique des valeurs de concentration catalytique des enzymes attribuées aux agents d'étalonnage et aux matériaux de contrôle (ISO 18153:2003)

In-vitro-Diagnostika - Messung von Größen in Proben biologischen Ursprungs - Metrologische Rückführbarkeit von Werten der katalytischen Konzentration von Enzymen, die Kalibratoren und Kontrollmaterialien zugeordnet sind (ISO 18153: 2003)

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Ref. No. EN ISO 18153:2003 E

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.'

(R.D. 2004-12-15)

CEN and ISO work related to metrological traceability of IVD MDs

Presentation of **reference measurement procedures**
(EN 12286:1998 + 12286/A1:2000; ISO 15193:2002)

Description of **reference materials**
(EN 12287:1999, ISO 15194:2002)

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)

(R.D. 2004-12-15)

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]

(R.D. 2004-12-15)

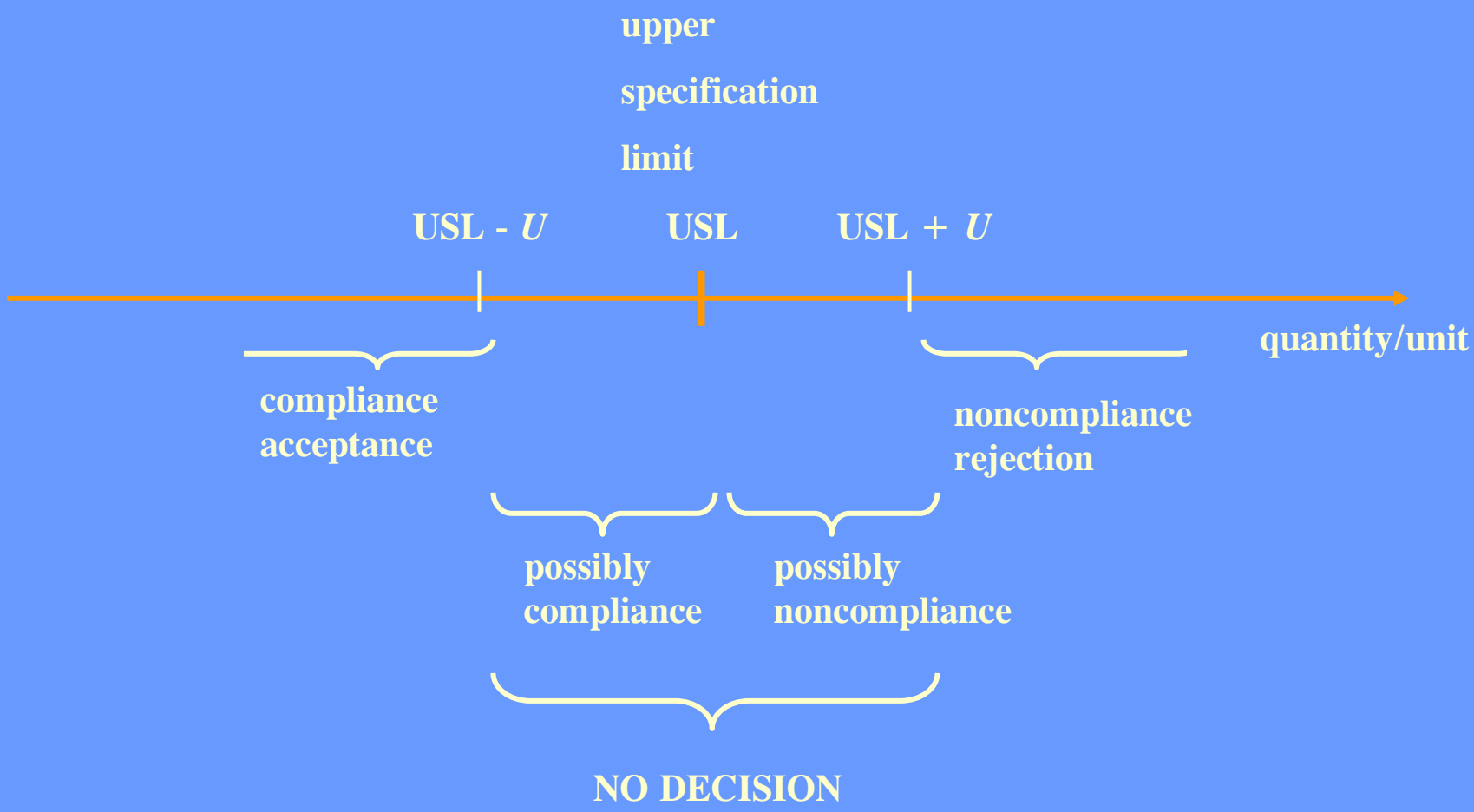
Why is metrological traceability important?

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)

(R.D. 2004-12-15)

A measured quantity value unaccompanied by measurement uncertainty is not only useless, but potentially dangerous because the value may be misinterpreted or misused.



(R.D. 2004-12-15)

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.

[Draft VIM3:2004-2.24]

(R.D. 2004-12-15)

Define measurand

Plasma–	System--
Somatotropin;	Component (Analyte);
arbitrary substance concentration	kind-of-quantity
(IS 80/505; procedure)	(specification)
10^{-3} international unit/litre	measurement unit

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)

(R.D. 2004-12-15)

Guide to the Expression of Uncertainty in Measurement

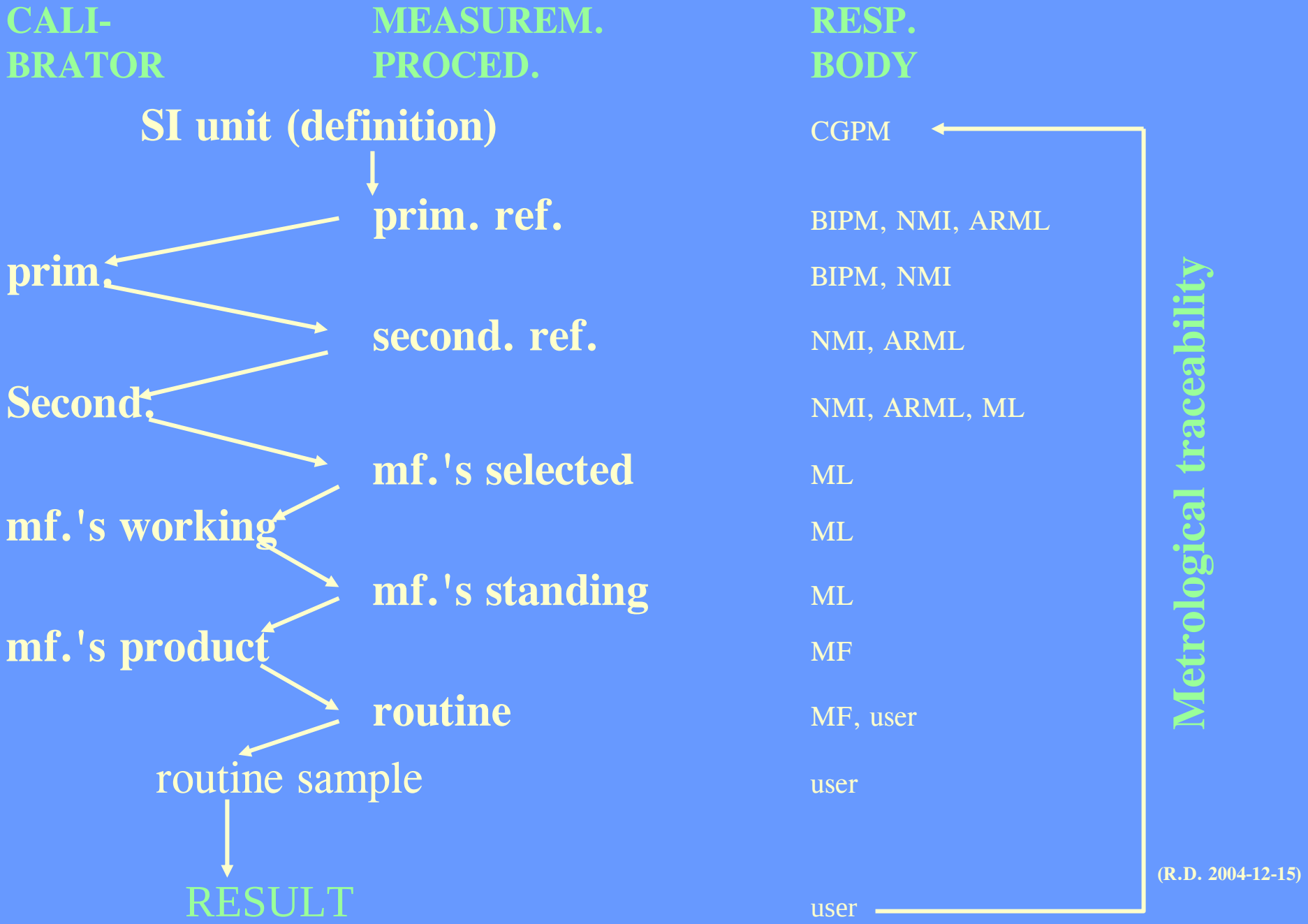
Corrected and reprinted edition
Geneva: ISO 1995:viii + 101 pp.

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



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]

(R.D. 2004-12-15)

(*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]

(R.D. 2004-12-15)

(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]

(R.D. 2004-12-15)

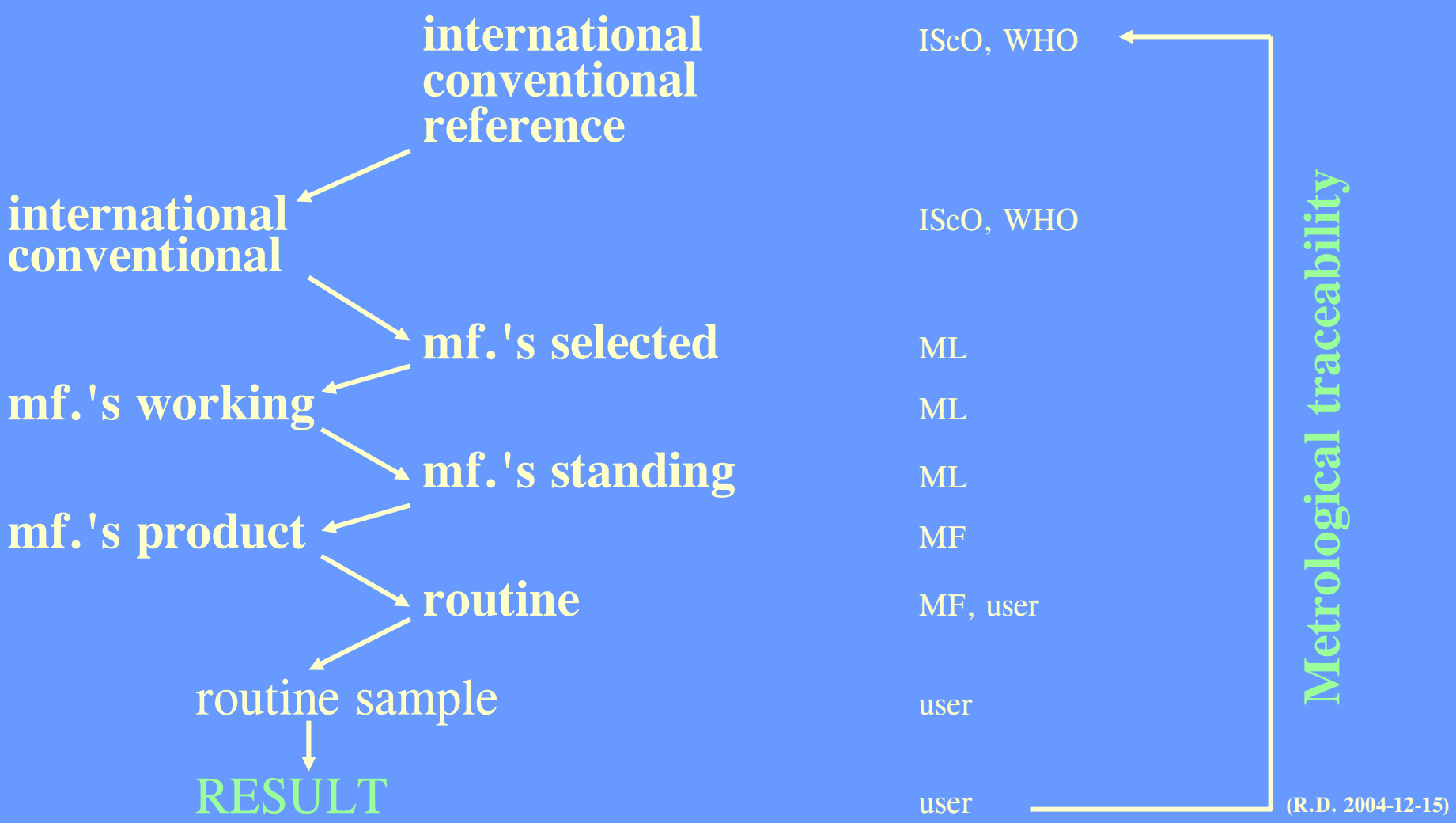
commutability of a material

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]

(R.D. 2004-12-15)

Chemical calibration hierarchy - 2



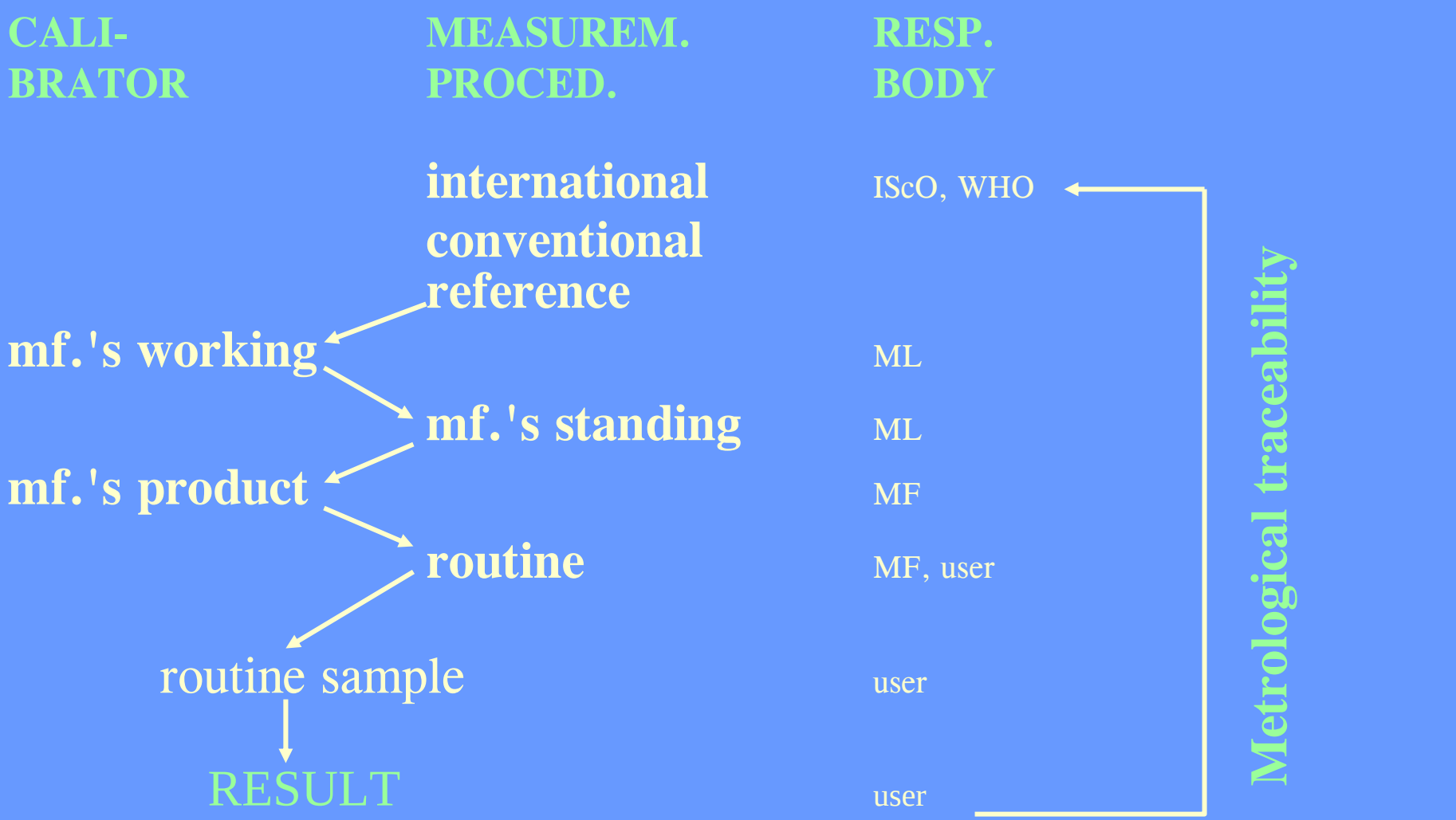
reference measurement procedure

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]

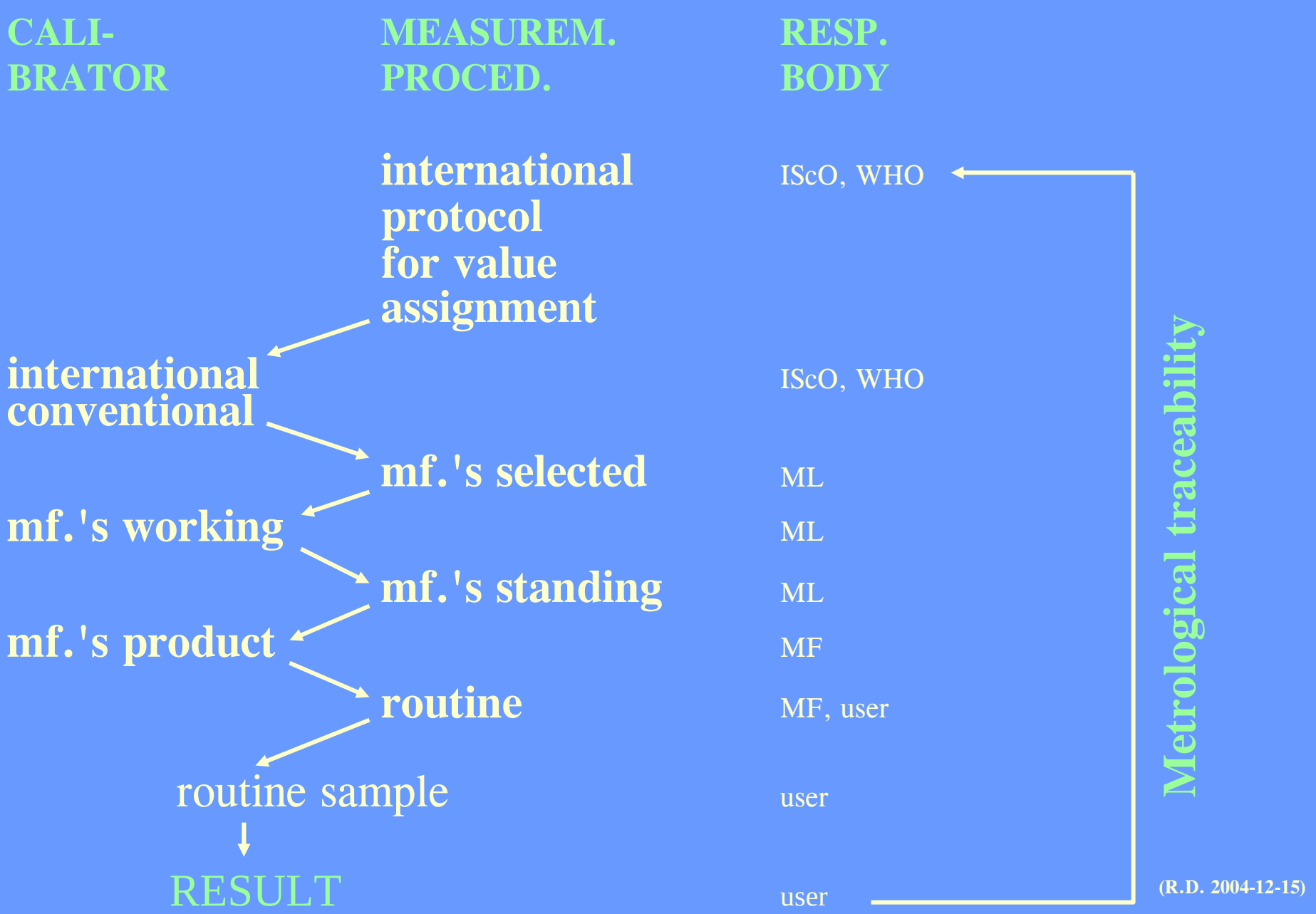
(R.D. 2004-12-15)

Chemical calibration hierarchy - 3



(R.D. 2004-12-15)

Chemical calibration hierarchy - 4



'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]

(R.D. 2004-12-15)

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]

(R.D. 2004-12-15)

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]

(R.D. 2004-12-15)

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]

(R.D. 2004-12-15)

calibrator

measurement standard used in the calibration of a measuring system

[Draft VIM3:2004-5.13]

(R.D. 2004-12-15)

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]

(R.D. 2004-12-15)

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.

(R.D. 2004-12-15)

biological assay

bioassay

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]

(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]

(R.D. 2004-12-15)

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.

(R.D. 2004-12-15)

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.

[Draft VIM3:2004-2.11]

(R.D. 2004-12-15)

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.

(R.D. 2004-12-15)

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).

(R.D. 2004-12-15)

Uncertainty budget

Material 1
with arbitrarily assigned
quantity value

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definition of measurand 1
homogeneity 1
aliquoting 1
stability 1

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u_c 1
$U_{0,95}$ 1

Material 2
with metrologically traceable
quantity value

---

definition of measurand 2
calibrator 1
repeatability 2
reproducibility 2
homogeneity 2
aliquoting 2
stability 2

---

u_c 2
$U_{0,95}$ 2

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.

(R.D. 2004-12-15)