An introduction to metrological traceability in laboratory medicine

CIRME 7th International Scientific Meeting
Metrological traceability and assay standardization

Stresa, Italy
Under the auspices of

JCTLM

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Overview

- Introduction
- Metrology
- Regulatory environment
  - Directive & ISO 17511, ISO 18513
  - Joint Committee for Traceability in Laboratory Medicine
- Concept of Reference Measurement System
- Traceability models (SI- & non-SI analytes)
- Standardization – Harmonization
- Summary

Introduction

Measurement paradigm

Procedures that claim the same measurand should give comparable/equivalent measurement results (within clinically relevant constraints)

Measurement results should be independent of

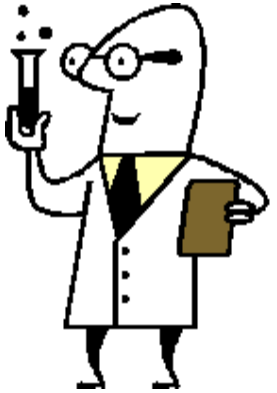
- **Time**
- **Location/laboratory**
- **Procedure**

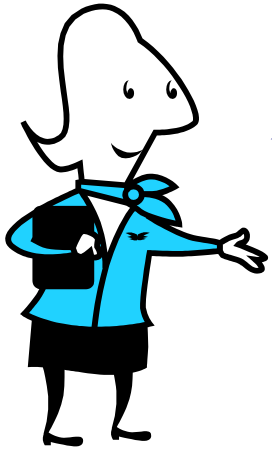
➔The logic itself

➔Metrological traceability!

Metrology

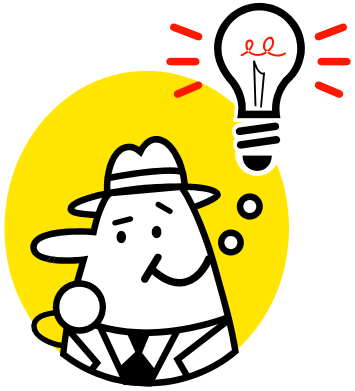
So, it's about rain and thunderstorms?



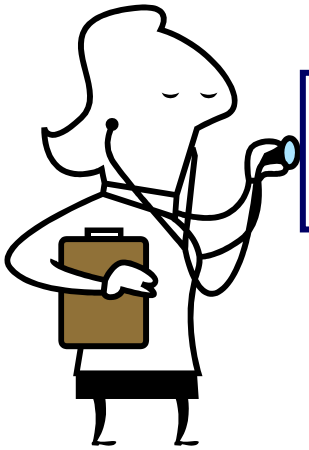


Oh, sorry, it's *metrology*, not meteorology!

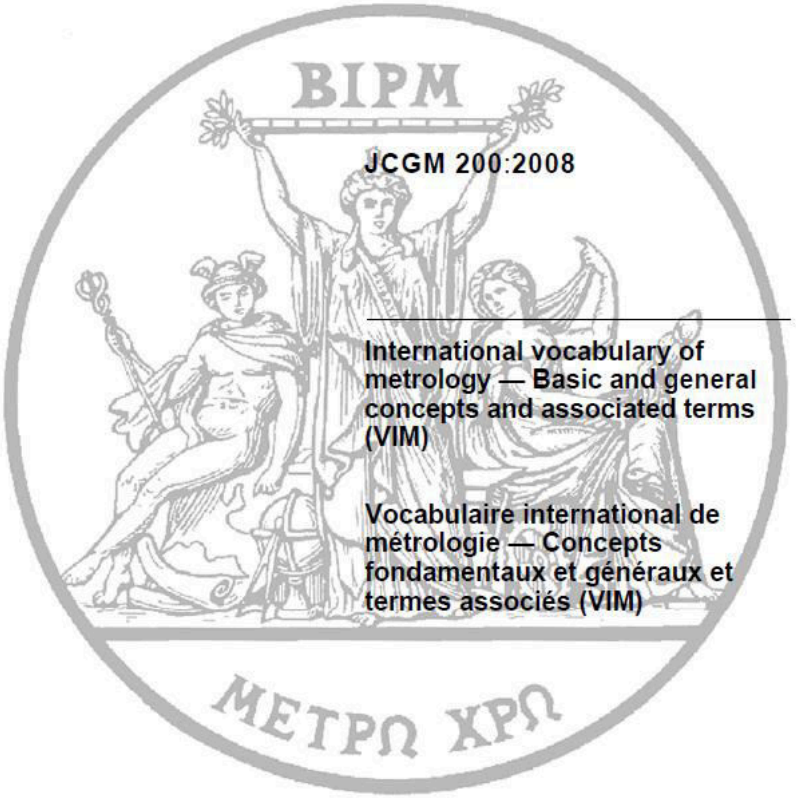
It will all be about measurement…



VIM – The metrologist's bible



International vocabulary of metrology (VIM)#



#http://www.bipm.org/en/publications/guides/vim.html

Metrology

Metrological traceability#

"Property of a measurement result whereby the result can be related to a reference through a documented unbroken chain of calibrations, each contributing to the measurement uncertainty#"

Note: a 'reference' can be

- **Definition of a measurement unit**
- **Measurement procedure**
- **Measurement standard**

#http://www.bipm.org/en/publications/guides/gum.html

Metrology

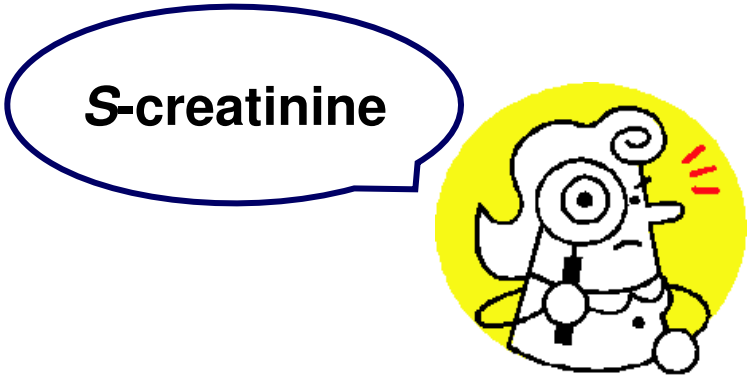
Measurand
Quantity intended to be measured

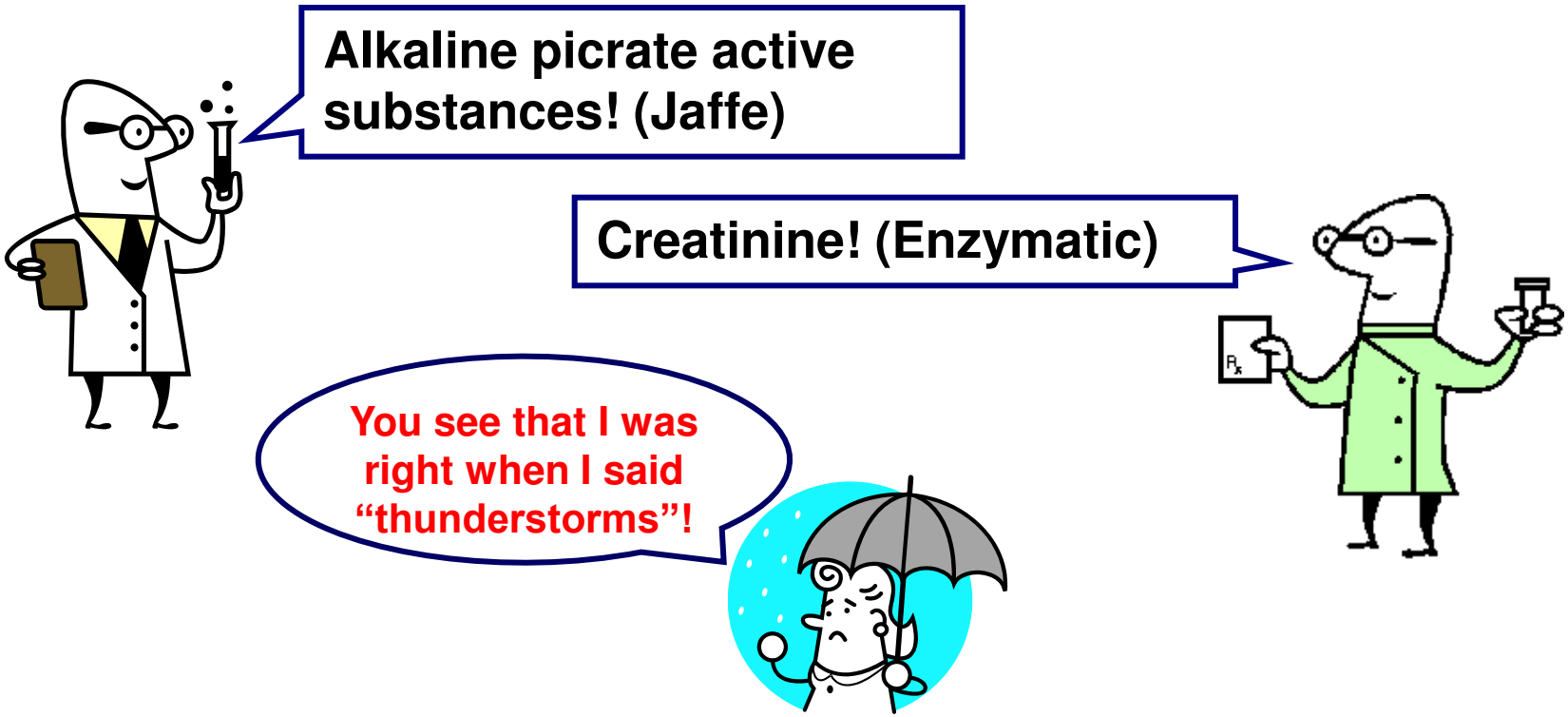
Quantity format: **"System–Component (analyte); Kind of quantity"**

Serum–creatinine; amount-of-substance concentration, *x* µmol/L

#http://www.bipm.org/en/publications/guides/vim.html

Component/Measurand





Regulatory environment

Directive 98/79/EC#

Requires that IVD manufacturers demonstrate traceability of in vitro-diagnostic medical devices

Note: demonstration means establishment and <u>verification of success</u>!

-Implementation of traceability: is the IVD industry's approach really fulfilling obligations? *D.A. Armbruster*

-Survey assay and laboratory performance in the traceability era. *G. Jones*

➔How?

#Directive 98/79/EC of the European Parliaments and of the Council of 27 October 1998 on in vitro diagnostic medical devices. L331. Off J Eur Comm 1998;41:1–37.

Regulatory environment

ISO 17511 (2003)

In vitro diagnostic medical devices (IVD MD) – Measurement of quantities in biological samples – Metrological traceability of values assigned to calibrators and control materials

ISO 18153 (2003)

IVD MD – Measurement of quantities in biologicalsamples – Metrological traceability of assigned values for catalytic concentration of enzymes in calibrators and control materials

➔Make use of hierarchically higher reference materials and measurement procedures

Regulatory environment

Joint Committee for Traceability in Laboratory Medicine (JCTLM)#

➔Overarching control of the key elements for traceability!

#http://www.bipm.org/en/committees/jc/jctlm/

Regulatory environment

ISO 17511 ISO 18153

ISO 15193

Requirements for content and presentation of reference measurement procedures

Reference measurement procedures of higher metrological order. *D. Bunk*

ISO 15194

Requirements for certified reference materials and the content of supporting documentation

Role of primary and secondary reference materials. *H. Schimmel*

ISO 15195

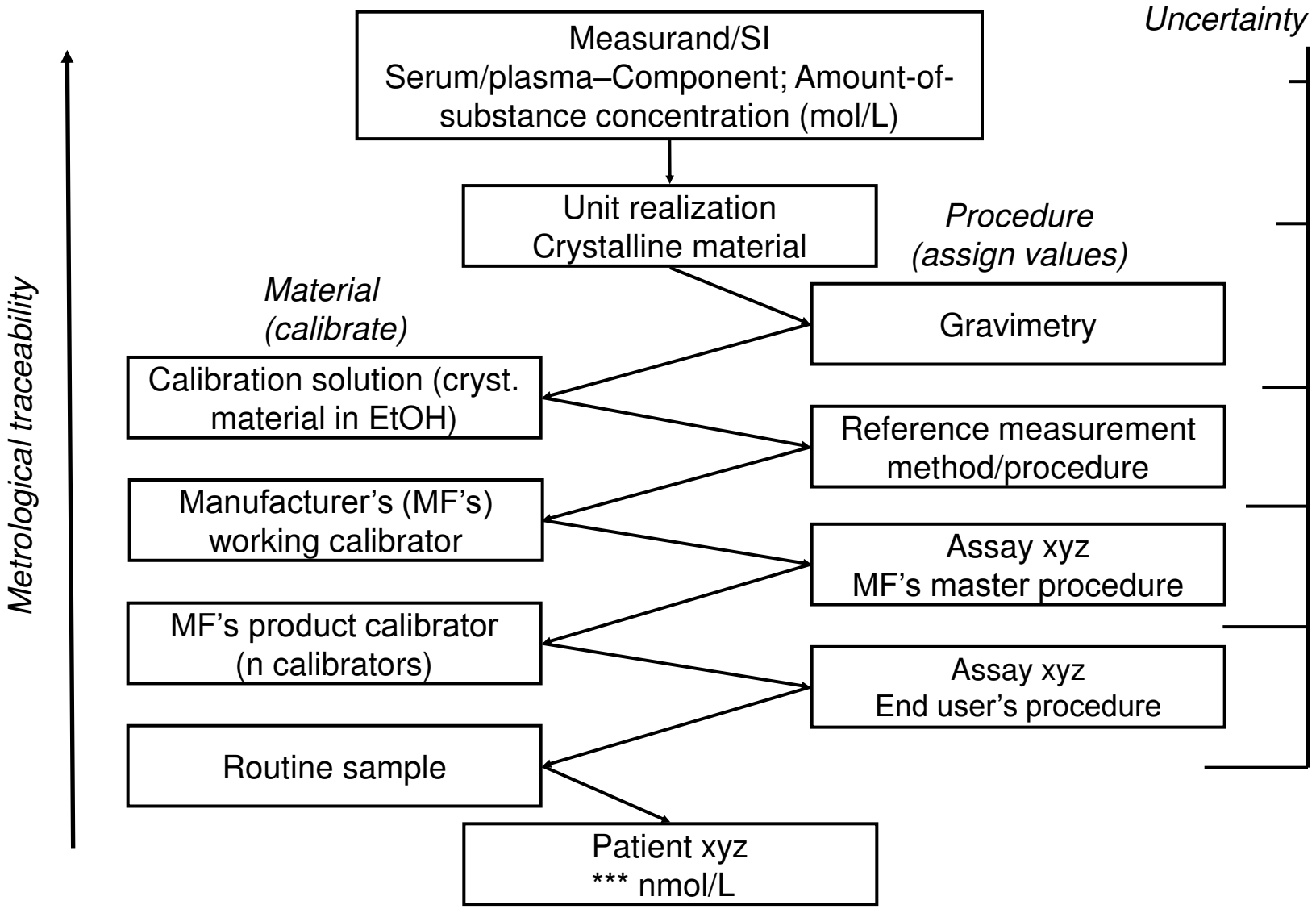
Requirements for reference measurement laboratories

➔ Reference Measurement System

Reference Measurement System

Element	Organization	Task
Unit (preferred: SI unit)	Conférence Générale des Poids et Mesures (CGPM)	Establishment of a coherent system of units (mole)
Component (analyte)/measurand	IFCC	Definition of the relevant component/measurand
Reference materials (RMs)	National Metrology Institutes (IRMM, NIST)	Realization of SI units: production and certification of RMs
Reference measurement procedures (RMPs)	Reference laboratory or other competent analytical laboratory	Development and validation of RMPs
Reference laboratories	*"Networks"*	Application of RMPs

Reference Measurement System



➔ **SI traceability – Trueness – Standardization**

Pitfalls in SI traceability

Potential causes

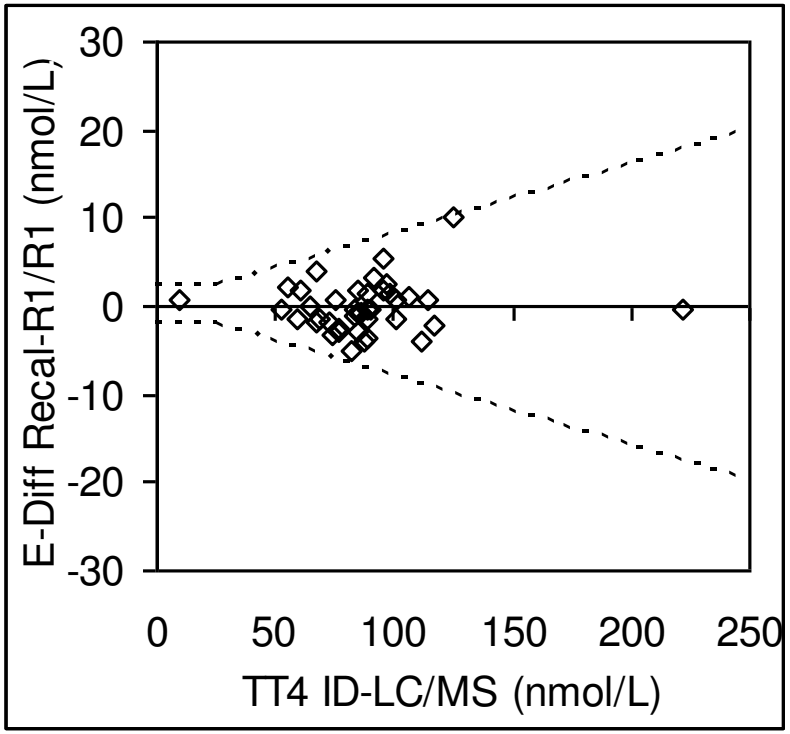
- **Manufacturer's working calibrator not commutable**
  ➔Use native, single donation sera
- **Analytical issues in the hierarchically lower methods**
  - **Insufficient specificity**
  - **Incapability of equimolar measurement (mixture analysis)**
  - **Sample-related effects (part of random error components)**
- **Lack of specifications for the extent of traceability**

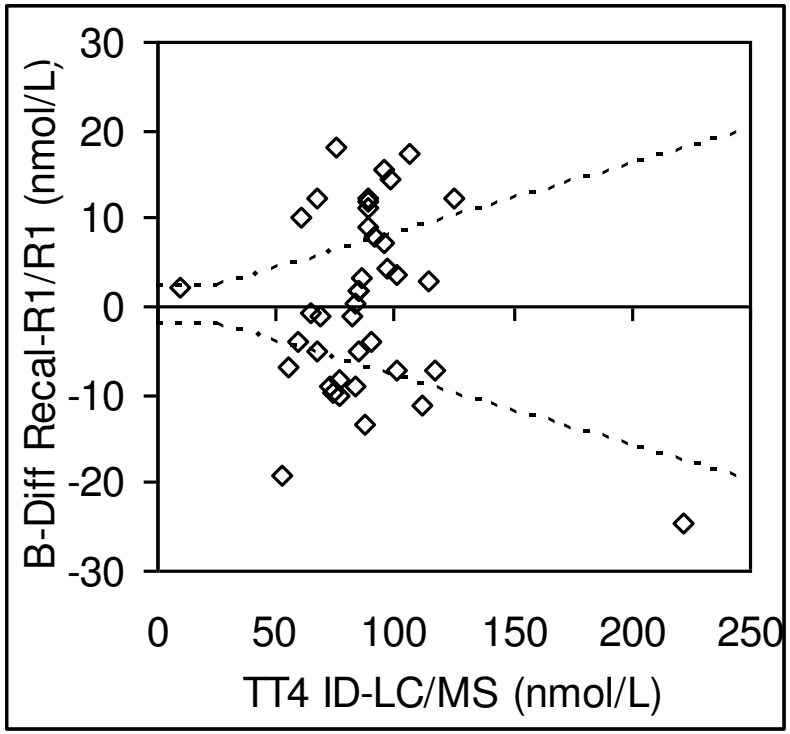
Define performance goals in standardization.
D. Stöckl

Pitfalls in SI traceability

Sample-related effects

Absolute difference plot after recalibration: best and worst assay (Thienpont LM et al. Clin Chem 2010; 56:921-9)





➔No standardization without attention to analytical quality!

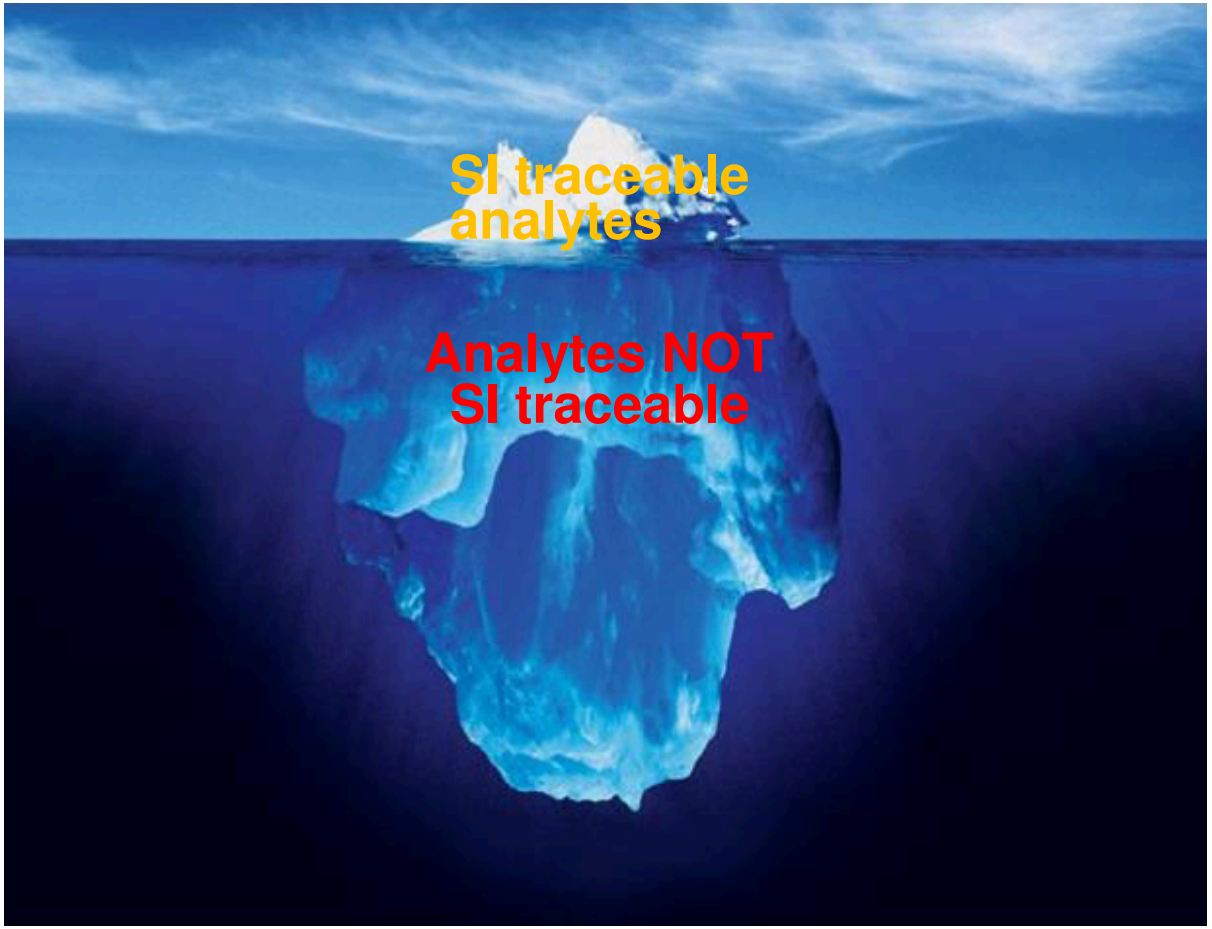
Traceability models

Complexity of measurements in laboratory medicine

- Laboratory medicine routinely provides results for 400 to 700 types of quantity (= analytes)
- Only for a minority of (well-defined) analytes there exist reference measurement procedures
- Many analytes are not or poorly defined; they are heterogeneous, thus measurement is mixture analysis (arbitrary units)
- Recognized in ISO 17511: different analytes require different calibration chains/traceability models

Traceability models

SI traceability – “Tip of the iceberg”

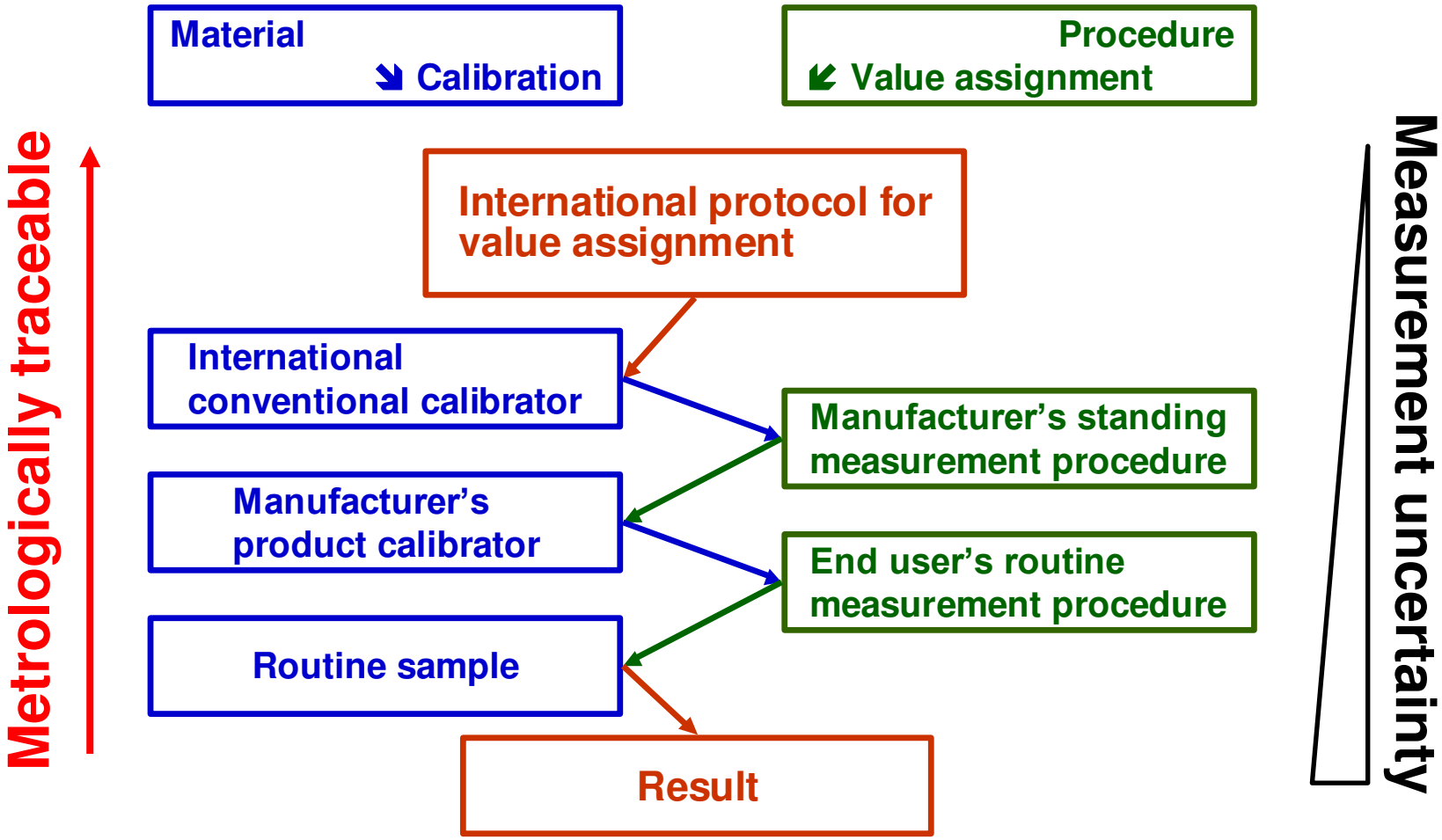


Traceability models in ISO 17511

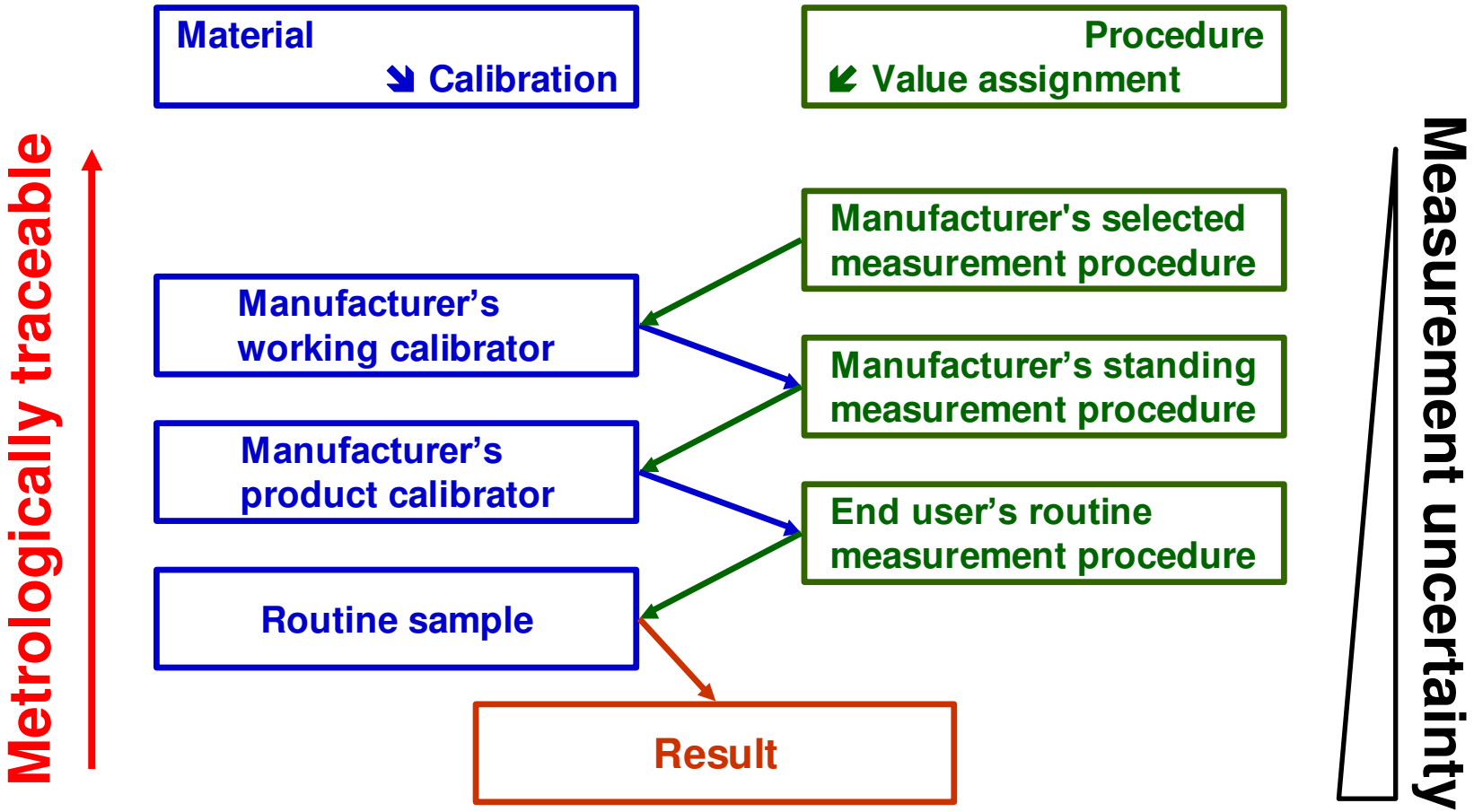
Category	RMP	Reference material	Example
1 (SI)	X (primary)	X (primary)	Cortisol
2 (non-SI)	X#	X#	
3 (non-SI)	X	–	Hemostatic factors
4 (non-SI)	–	X	hCG
5 (non-SI)	–	–	Tumor markers

#International conventional RMP & RM

Category 4 (only intern. cRM)

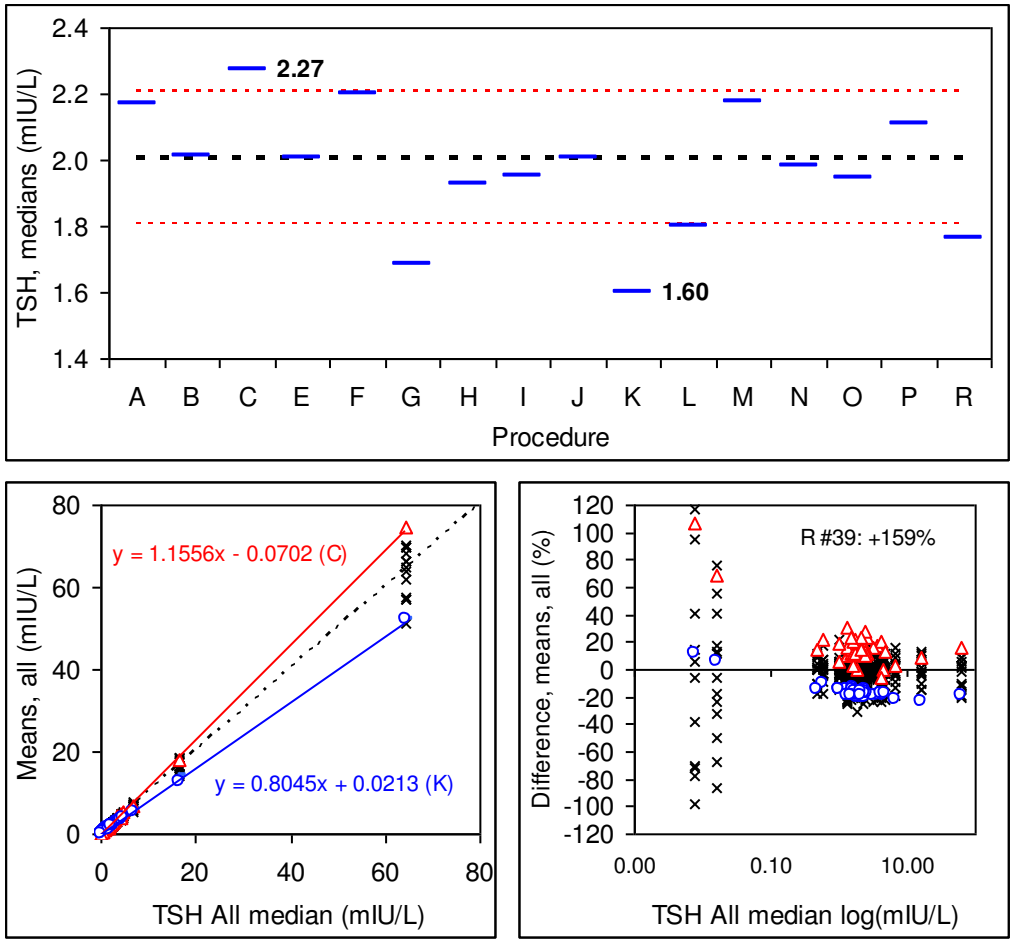


Category 5 (neither RMP nor RM)



Non-SI analytes in category 4 or 5

Example: Assays for TSH traceable to WHO 80/558 ➔Comparability an issue#



#Thienpont LM et al. Clin Chem 2010; 56:902-11

Pitfalls for non-SI analytes

Potential causes

- Heterogeneity of components in measurand (mixture analysis)
- Measurands insufficiently defined, and/or defined measurand not measured in practice
- Measurement procedures do not measure the components in the mixture in an equimolar way
- Composition of standards in terms of mixture components different from serum, e.g., WHO 80/558 is a material obtained from purified cadaver pituitary
- WHO standards in reduced matrix not commutable

➔Harmonization!

Harmonization

Requirements for harmonization of mixture analysis#

Analytical –

- **Procedures should measure the components of a mixture in an equimolar way**
- **Equimolarity to the diagnostic relevant extent**
- **To achieve by defining a "quasi surrogate component" in the measurand, e.g., epitopes at invariate peptide sequences that immunoassays should recognize**

Medical –

Each component of the mixture should contribute significantly to the assay's diagnostic application

#Thienpont LM, Van Houcke SK. Traceability to a common standard for protein measurements by immunoassay for in-vitro diagnostic purposes. Clin Chim Acta 2010;411:2058-61

Harmonization

"Surrogate" Reference Measurement System#

- **Dynamic, updatable according to scientific progress and technical possibilities**
- **Definition of the measurand commensurate with its realization by a measurement standard (and vice versa)**
- **"Surrogate" reference measurement procedure**

#Thienpont LM, Van Houcke SK. Traceability to a common standard for protein measurements by immunoassay for in-vitro diagnostic purposes. Clin Chim Acta 2010;411:2058-61

Harmonization – AACC

harmonization.net

AACC

http://www.harmonization.net/Pages/default.aspx

Summary

Establishment of metrological traceability is regulated

- **Concept of Reference Measurement System**
- **Traceability models different for SI- and non-SI analytes**
- **Traceability for SI analytes: standardization**
- **Traceability for non-SI analytes: harmonization**
- **Quality specifications required for the extent of traceability; if not defined, implementation will remain an issue!!!**