

An introduction to metrological traceability in laboratory medicine

CIRME 7th International Scientific Meeting
Metrological traceability and assay standardization

Stresa, Italy
Under the auspices of



Linda Thienpont
Linda.thienpont@ugent.be



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

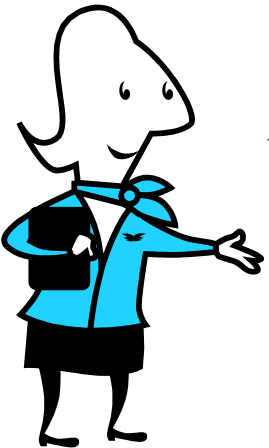
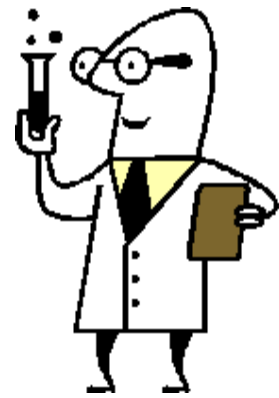
→ The logic itself

→ Metrological traceability!

Metrology

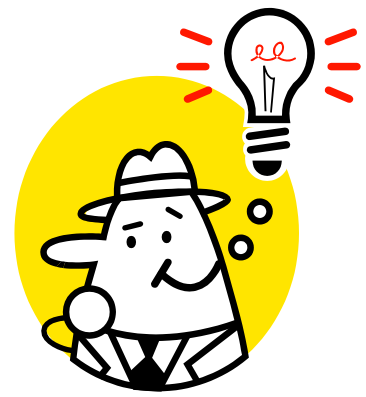


So, it's about rain and thunderstorms?

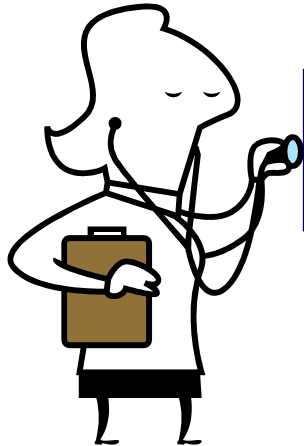


Oh, sorry, it's *metrology*, not meteorology!

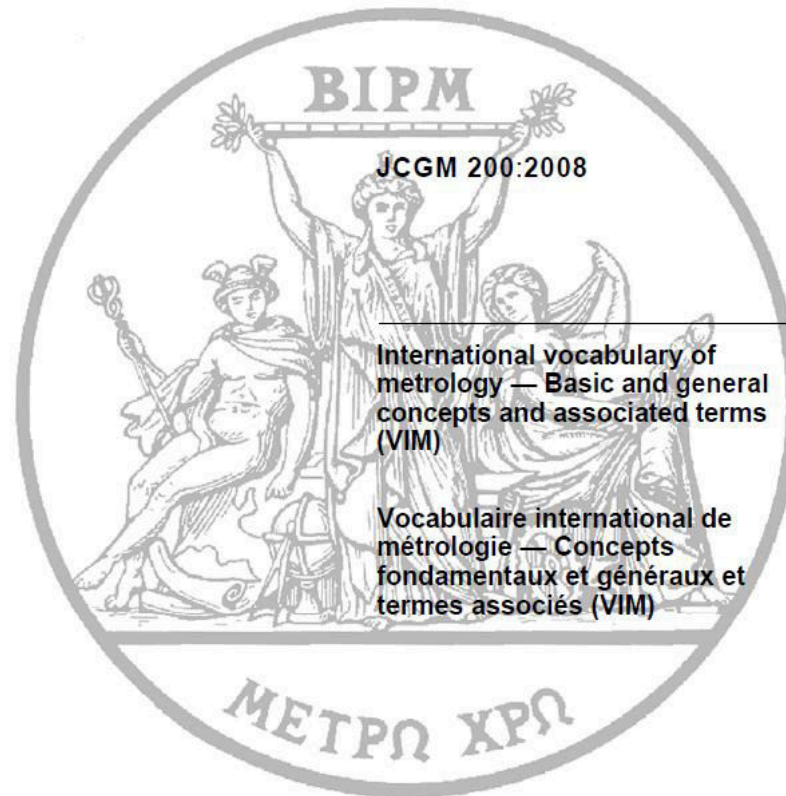
It will all be about measurement...



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#**”*

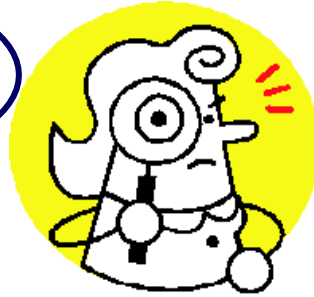
Note: a **‘reference’** can be

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

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

Metrology

Measurand



Measurand

Quantity **intended** to be measured

Quantity format: “System–Component (analyte); Kind of quantity”

Serum–creatinine; amount-of-substance concentration, x $\mu\text{mol/L}$

I knew it would be about thunderstorms!



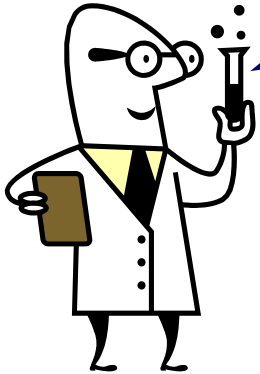
<http://www.bipm.org/en/publications/guides/vim.html>

Component/Measurand

S-creatinine



Alkaline picrate active substances! (Jaffe)



Creatinine! (Enzymatic)



You see that I was right when I said "thunderstorms"!



Regulatory environment

Directive 98/79/EC#

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

Note: demonstration means establishment and verification of success!

- 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 biological samples – 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

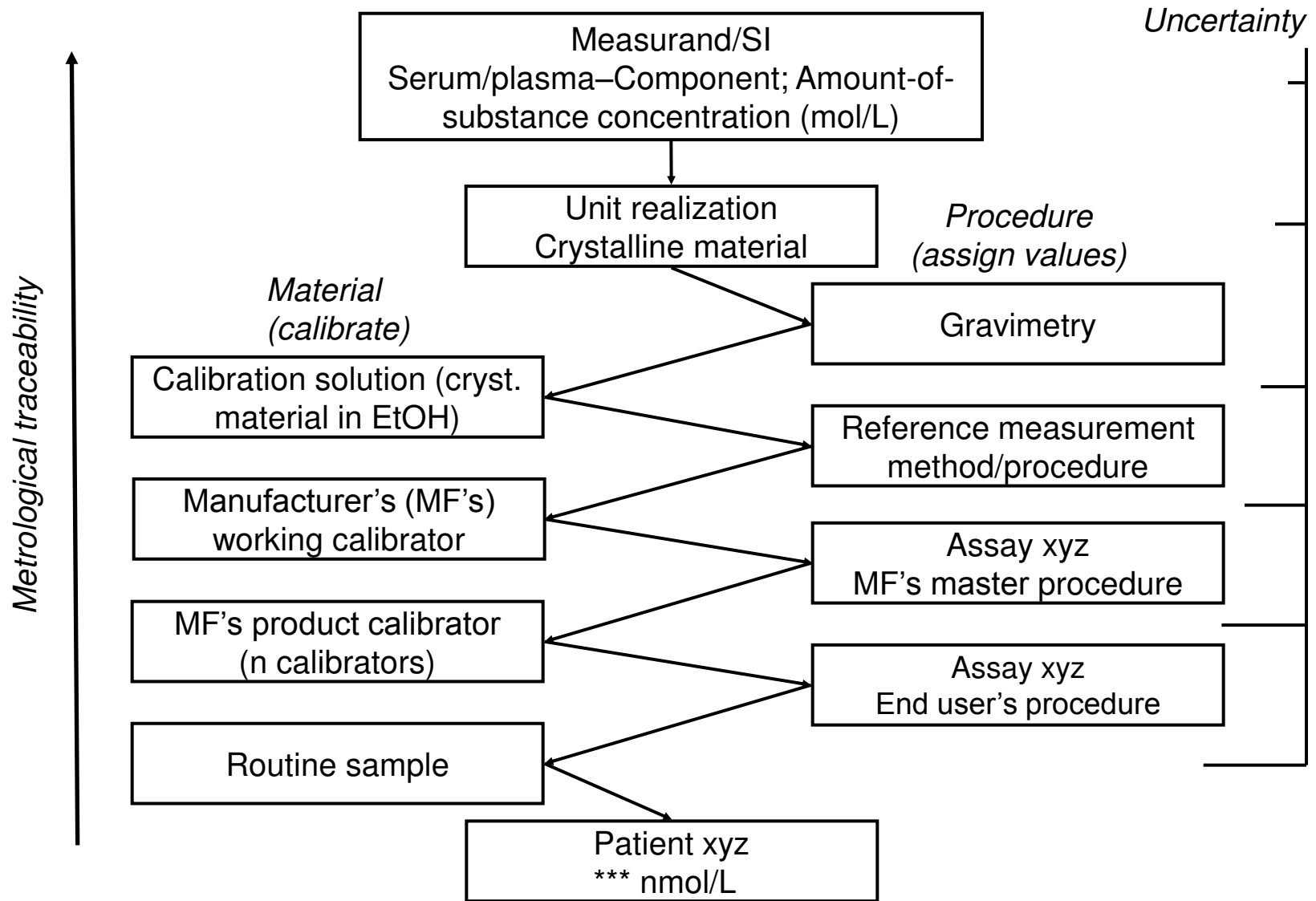
Requirements for reference measurement laboratories

→ 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	<i>“Networks”</i>	Application of RMPs

Reference Measurement System



→ SI traceability – Trueness – Standardization

Pitfalls in SI traceability

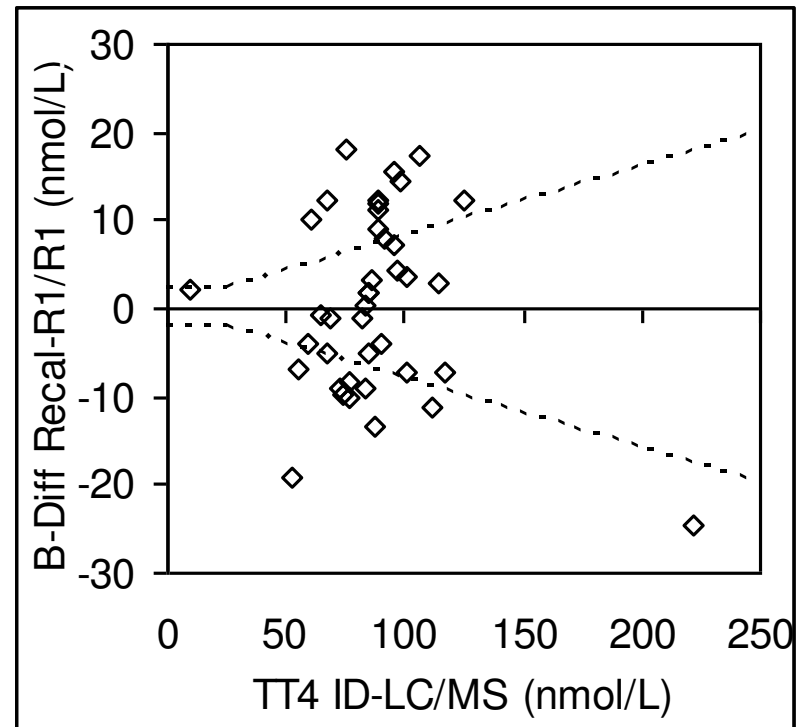
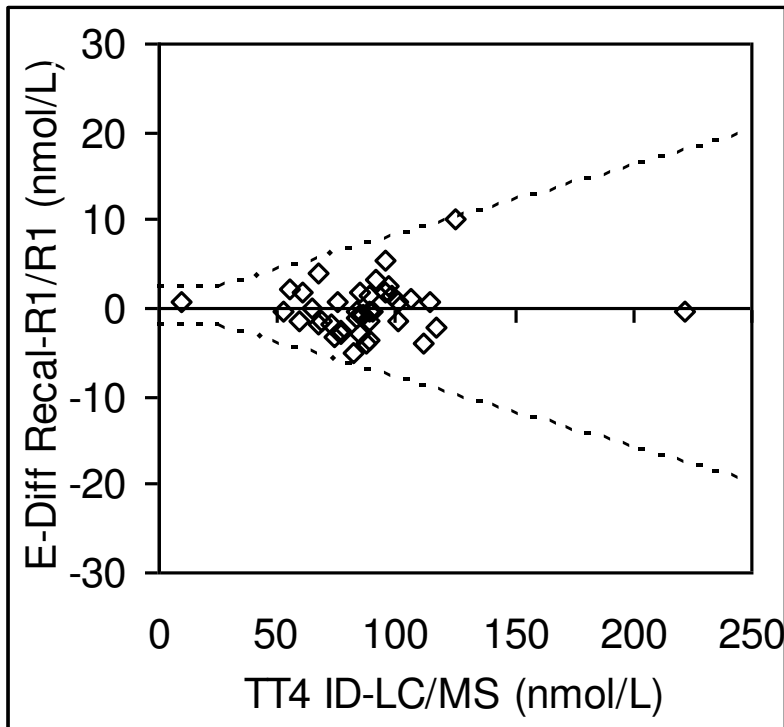
Potential causes

- **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!

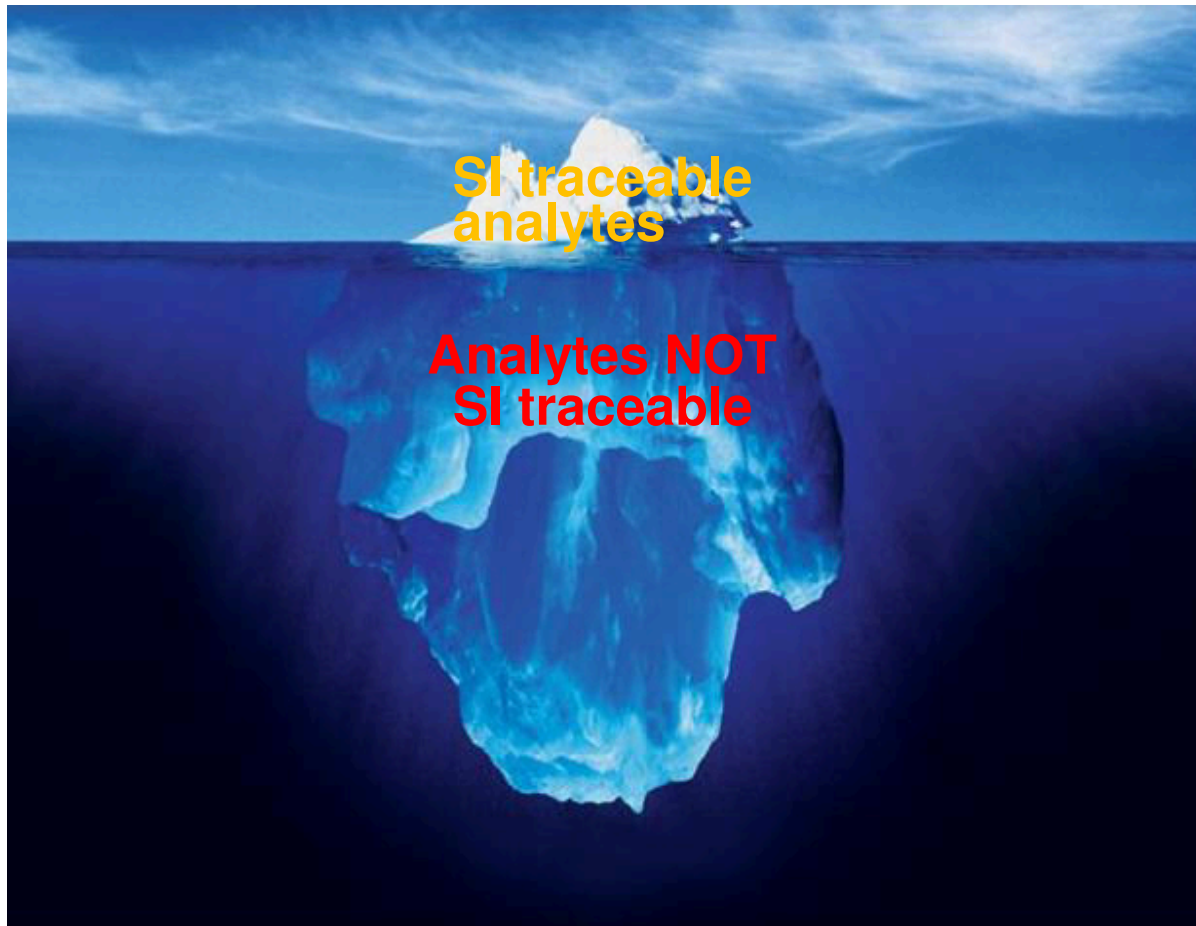
Traceability models

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”

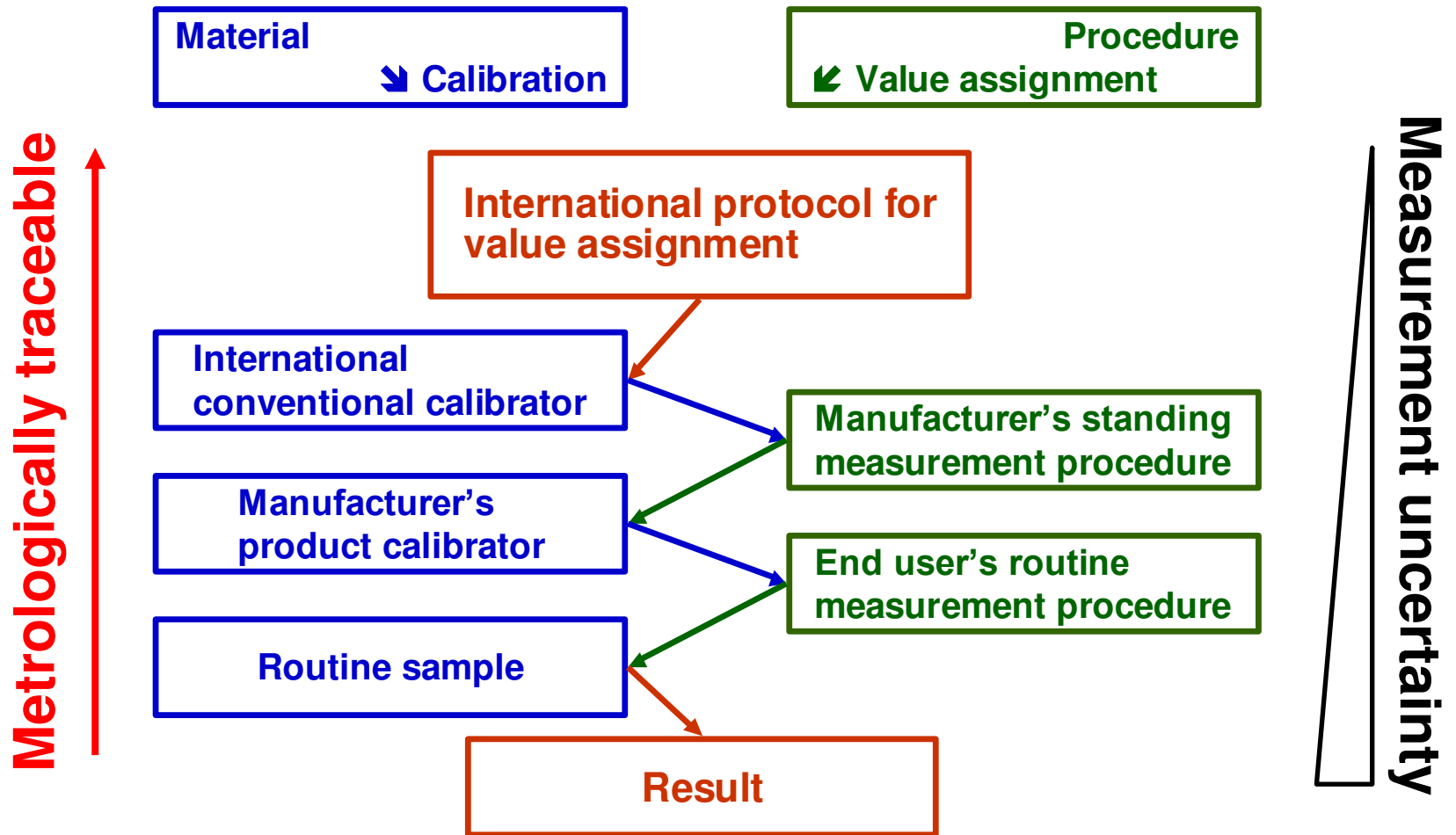


Traceability models in ISO 17511

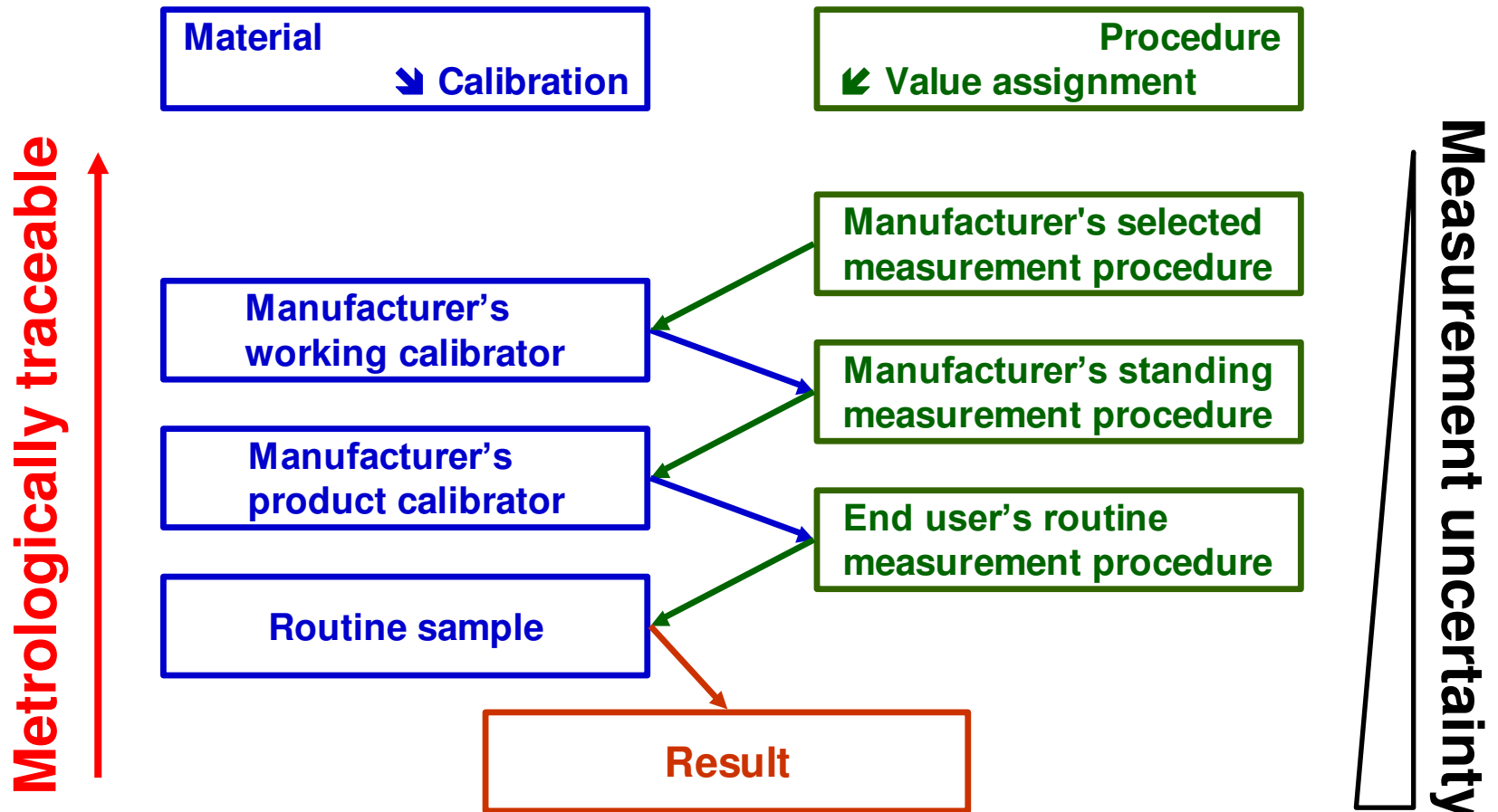
Category	RMP	Reference material	Example
1 (SI)	X (primary)	X (primary)	Cortisol
2 (non-SI)	X#	X#	
3 (non-SI)	X	–	Hemostatic factors
4 (non-SI)	–	X	hCG
5 (non-SI)	–	–	Tumor markers

#International conventional RMP & RM

Category 4 (only intern. cRM)



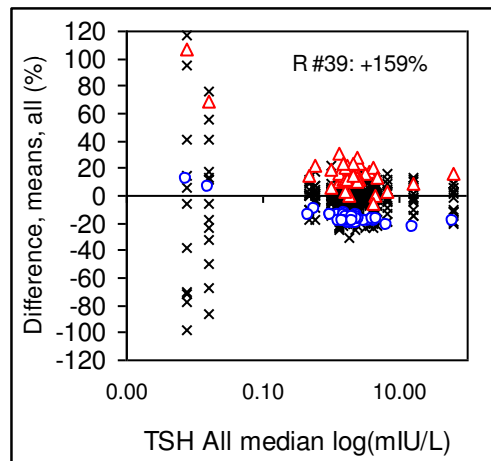
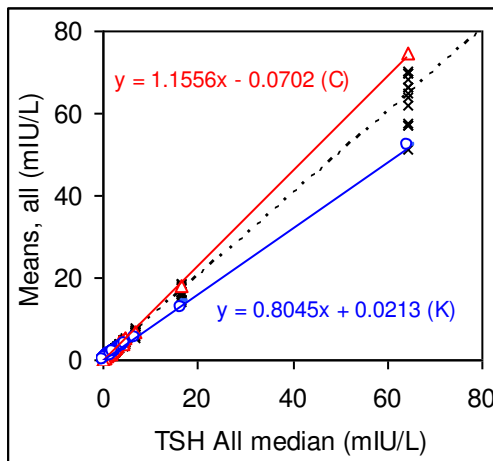
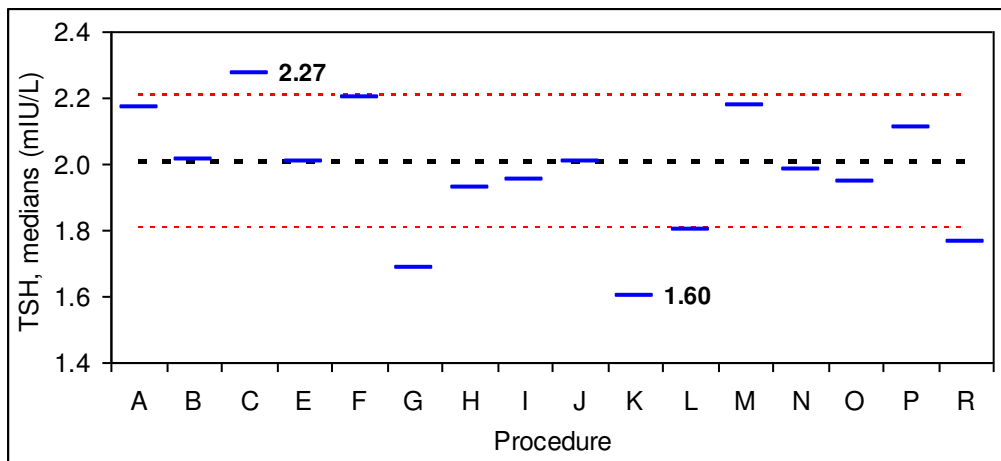
Category 5 (neither RMP nor RM)



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

Thienpont - CIRME 7th International Scientific Meeting 2013

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 invariable 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



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Steering Committee

The **Steering Committee** is responsible for overall guidance of the implementation of the harmonization program and for developing collaborations to create the International Consortium for Harmonization of Clinical Laboratory Results. The steering committee appointed three task forces to assist in developing processes and tools needed for the infrastructure.

- **Task Force for Planning the Harmonization Oversight Group**
This task force developed procedures for operation of the Harmonization Oversight Group and its management of harmonization activities. This work is now complete and this task force has been dissolved.
- **Task Force for Developing Checklists**
This task force developed checklists for submitting measurands to be considered for prioritization, for the assessment of priority and feasibility for harmonization, and for reporting the recommendation for prioritization and feasibility. This work is now complete and this task force has been dissolved.
- **Task Force for Developing a Toolbox of Technical Processes for Harmonization**
This task force will create a toolbox of well developed processes appropriate for harmonization when there is no reference measurement procedure. These processes are intended as a starting point and may be modified as needed for a particular measurand. This task force is continuing to develop the toolbox.

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1850 K Street, NW Suite 625
Washington, DC 20006
Phone: (800) 892-1400 | Fax: (202) 887-5093
Email: webmaster@aacc.org

<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!!!**

