



Examples of reference measurement procedures

JCTLM Working Group for Traceability: Education and Promotion (WG-TEP)

Area 2: Mini-presentations to explain scientific concepts



Standardization of Clinical Measurements

- Clinical measurements provide medical information for patient care
 - Health care providers use clinical measurements to make medical decisions for patients
- Therefore, high accuracy and standardization of clinical analytes is imperative for high quality medical practice
- A significant step towards achieving high quality and traceable measurements is via reference measurement procedures and reference materials
- Joint Committee for Traceability in Laboratory Medicine (JCTLM)
 - Plays a significant role in the standardization and global harmonization of clinical analytes
 - Establishes a database of available higher-order reference materials, available higher-order reference measurement procedures and reference measurement laboratories for laboratory medicine



JOINT COMMITTEE ON TRACEABILITY IN LABORATORY MEDICINE (JCTLM)



- International consortium established in 2002 and sponsored by the **International Bureau of Weights and Measures (BIPM)**, the **International Federation for Clinical Chemistry and Laboratory Medicine (IFCC)** and the **International Laboratory Accreditation Cooperation (ILAC)**
- JCTLM developed and maintains database of:
 - Available **Certified Reference materials (CRMs)** and **Reference Measurement Procedures (RMPs)** that can be used by manufacturers to meet the traceability requirements of the EC Directive
 - Laboratories worldwide providing **Reference Measurement Services (RMSs)** for the value-assignment of calibrators for the in vitro diagnostic (IVD) industry



Definition of a Reference Measurement Procedure (RMP)

- “Measurement procedure accepted as providing measurement results **fit for their intended use** in assessing measurement trueness of measured quantity values obtained from other measurement procedures for **quantities of the same kind**, in calibration, or in characterizing reference materials” [VIM3 JCGM 200:2012]
- **In simpler terms, a RMP is a measurement procedure which:**
 - Provides measurements which have been thoroughly assessed for bias
 - Has been validated to measure what it is intended to measure
 - Provides the results that we need



Uses of Reference Measurement Procedures (RMPs)

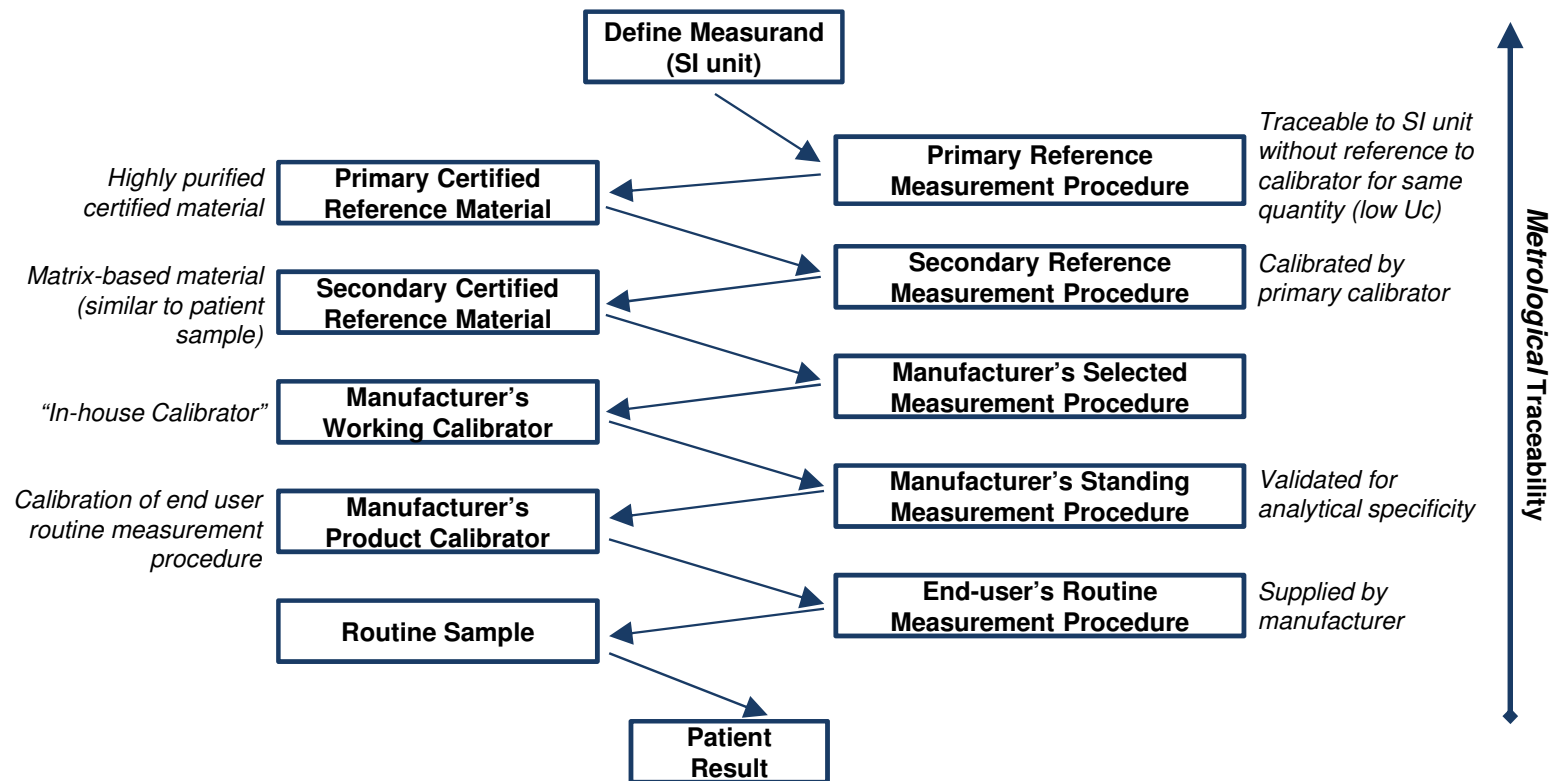
- Value-assignment of certified reference materials (CRMs)
- Comparison of routine assays
- Assessment of the performance characteristics of routine assay systems (instrumentation and reagents)
- Detection of analytical biases on quantities in routine samples



Reference Measurement System

Traceability of Measurements (ISO 17511)

- Metrological Traceability** [VIM3 JCGM 200:2012]: 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



Adapted from:
ISO 17511:2003(E)



Relevant ISO Standards for Higher-Order CRMs and RMPs

- **ISO 17511:** *In vitro* diagnostic medical devices -- Measurement of quantities in biological samples -- Metrological traceability of values assigned to calibrators and control materials
- **ISO 15193:** *In vitro* diagnostic medical devices -- Measurement of quantities in samples of biological origin -- Requirements for content and presentation of reference measurement procedures
- **ISO 15194:** *In vitro* diagnostic medical devices -- Measurement of quantities in samples of biological origin -- Requirements for certified reference materials and the content of supporting documentation
- **ISO 15195:** Laboratory medicine -- Requirements for reference measurement laboratories
- **ISO 18153:** *In vitro* diagnostic medical devices -- Measurement of quantities in biological samples -- Metrological traceability of values for catalytic concentration of enzymes assigned calibrators and control materials



Higher-order RMP Recognized by JCTLM

- **Accuracy**
 - Purity assessment of primary standard
 - Recovery of added analyte
 - Comparison with certified value of CRM
- **Repeatability (3 independent sets)**
 - Within-set CV
 - Between-set CV
- **Interference Testing**
 - Structural analogues of metabolites
 - Structure analogues of synthetic compounds
- **Uncertainty Estimation**
- **Inter-laboratory Comparison**



Reference: ISO 15193

Elements of a Reference Measurement Procedure [ISO 15193:2009]

Mandatory Descriptive Elements for RMPs:

- Title
- Forward
- Warning and safety precautions
- Scope
 - *Type of materials to which the RMP will be applied*
 - *Objective of the RMP*
 - *Limits for values*
 - *Interferences*
- Reagents (description and use)
- Apparatus (description, preparation and use)
- Principle and method of measurement
- Sampling and Samples:
 - *Pre-analytical factors that influence measurement*
 - *Sample storage*
 - *Sample preparation*
- Data processing
- Analytical performance
- Inter-laboratory validation
- References
- Dates of authorization and revision



Sources of Certified Reference Material and Reference Methods

- JCTLM website hosted by BIPM (<http://www.bipm.org/jctlm/>)

- Reference Materials
- Reference Measurement Methods
- Reference Measurement Services



Sources of Certified Reference Material and Reference Methods

JCTLM website hosted by BIPM (<http://www.bipm.org/jctlm/>)

Various Reference Measurement Procedures for Creatinine in different matrices

The screenshot displays the JCTLM website interface. At the top, it identifies the Bureau International des Poids et Mesures and the JCTLM project. The main content area shows the results of a search for reference measurement methods/procedures. A table lists three results for creatinine, detailing the measurement principle/technique and the matrix/material used.

Select	Analyte	Measurement principle/technique	Matrix/Material
<input type="checkbox"/>	creatinine	Isotope dilution mass spectrometry	Urokinase
<input type="checkbox"/>	creatinine	Isotope dilution mass spectrometry	Urine
<input type="checkbox"/>	creatinine	Isotope dilution mass spectrometry	Urokinase



Sources of Certified Reference Material and Reference Methods

- List of reference measurement procedure associated with desired analyte/matrix can be generated
- Allows user to easily compare reference measurement procedures submitted by different institutions

Result of the search: list of reference measurement methods/procedures

View search criteria: reference measurement methods/procedures; Analyte: matrix; Analyte category: Other category

Sort as PDF file | Filter your selection

Results of the search

Reference method for serum uric acid	Applicable matrix(es)	Applicable matrix(es)	Applicable matrix(es)
Full description of technique(s)	ICP-MS/MS	ICP-MS/MS	ICP-MS/MS
Quantity	Amount of substance concentration	Amount of substance concentration	Amount of substance concentration
Applicable range	0.05 mmol/L to 0.80 mmol/L	0.05 mmol/L to 0.80 mmol/L	0.05 mmol/L to 0.80 mmol/L
Expected uncertainty (level of confidence 95%)	0.5% to 0.5%	0.5% to 0.5%	0.5% to 0.5%
Reference(s)	Sekizawa et al., J. Clin. Chem. Clin. Biochem., 1985, 33, 137-144	Sekizawa et al., J. Clin. Chem. Clin. Biochem., 1985, 33, 137-144	Sekizawa et al., J. Clin. Chem. Clin. Biochem., 1985, 33, 137-144
Compendium assessment study (s)	WHOCC/2012.40.1407-1410, 18899	WHOCC/2012.40.1407-1410, 18899	WHOCC/2012.40.1407-1410, 18899
JCTLM ID identification number	NR1024-17	NR1024-17	NR1024-17
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Role of RMPs in the clinical measurements

- In order to achieve standardization in clinical chemistry measurements, the measurement system must allow for reliable transfer of the measurement values from the highest metrological order to methods that are routinely used in clinical laboratories.
- Key requirements of the measurement system are reference measurement procedures and reference materials.
- Clinical laboratories use routine procedures with validated calibrators to establish traceability and standardization.





Accurate results
for patient care

