



# Traceable and commutable calibrators

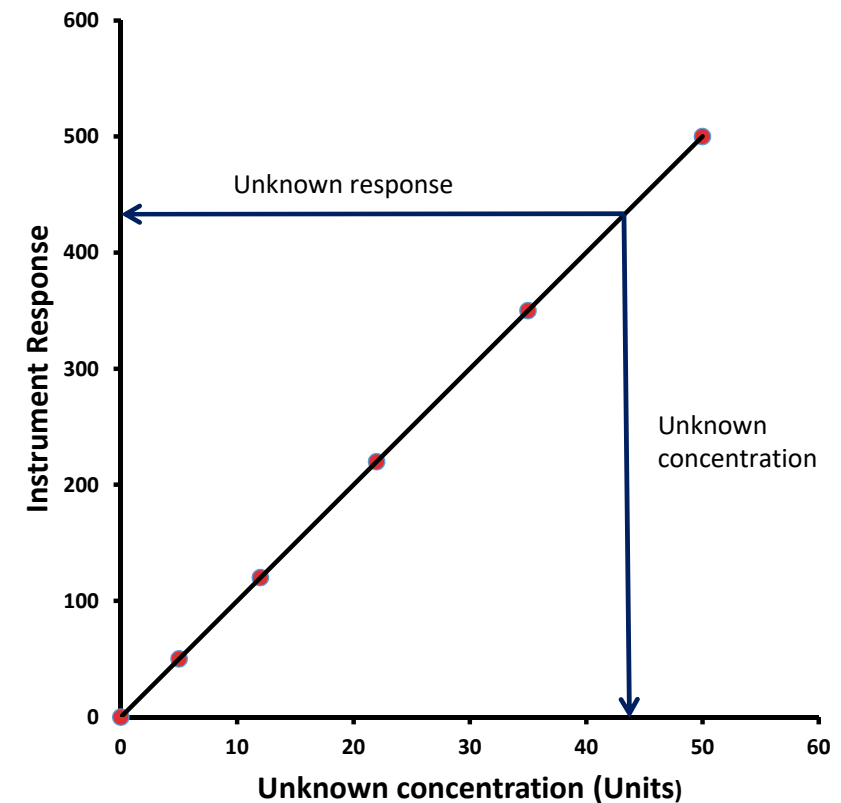
JCTLM Working Group for Traceability: Education and Promotion (WG-TEP)  
Area 2: Mini-presentations to explain scientific concepts

# Calibration

**Calibration:** the process of assigning a value, usually in concentration units, to an instrument response. This represents the functional relationship between the measured values and analytical quantities characterising the type(s) of measurand(s).

**Calibrator(s):** material of known quantity used to produce a calibration curve from which concentrations of unknowns can be derived. The instrument response changes with increased concentration of unknown.

For accurate patient results, such calibrators must be related to a known quantity: traceable



# Traceability

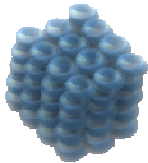
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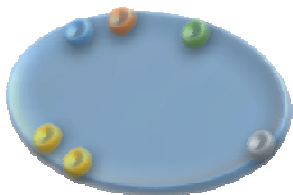
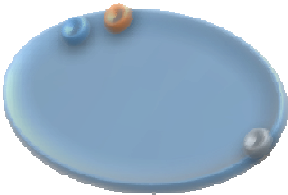
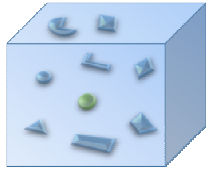
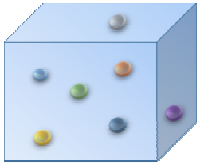
- *Trace*: path that someone or something takes
- *Traceable*: if something is traceable, you can find out where it came from, where it has gone, when it began or what its cause was
- Traceability means – comparability
- The ability to compare the results of measurements between different laboratories
- The use of a common reference
- Metrological traceability is **the property of a measurement result** which allows measurements made under different conditions (e.g. at different times, by different people, in different locations, using different measurement procedures) to be compared in a meaningful way

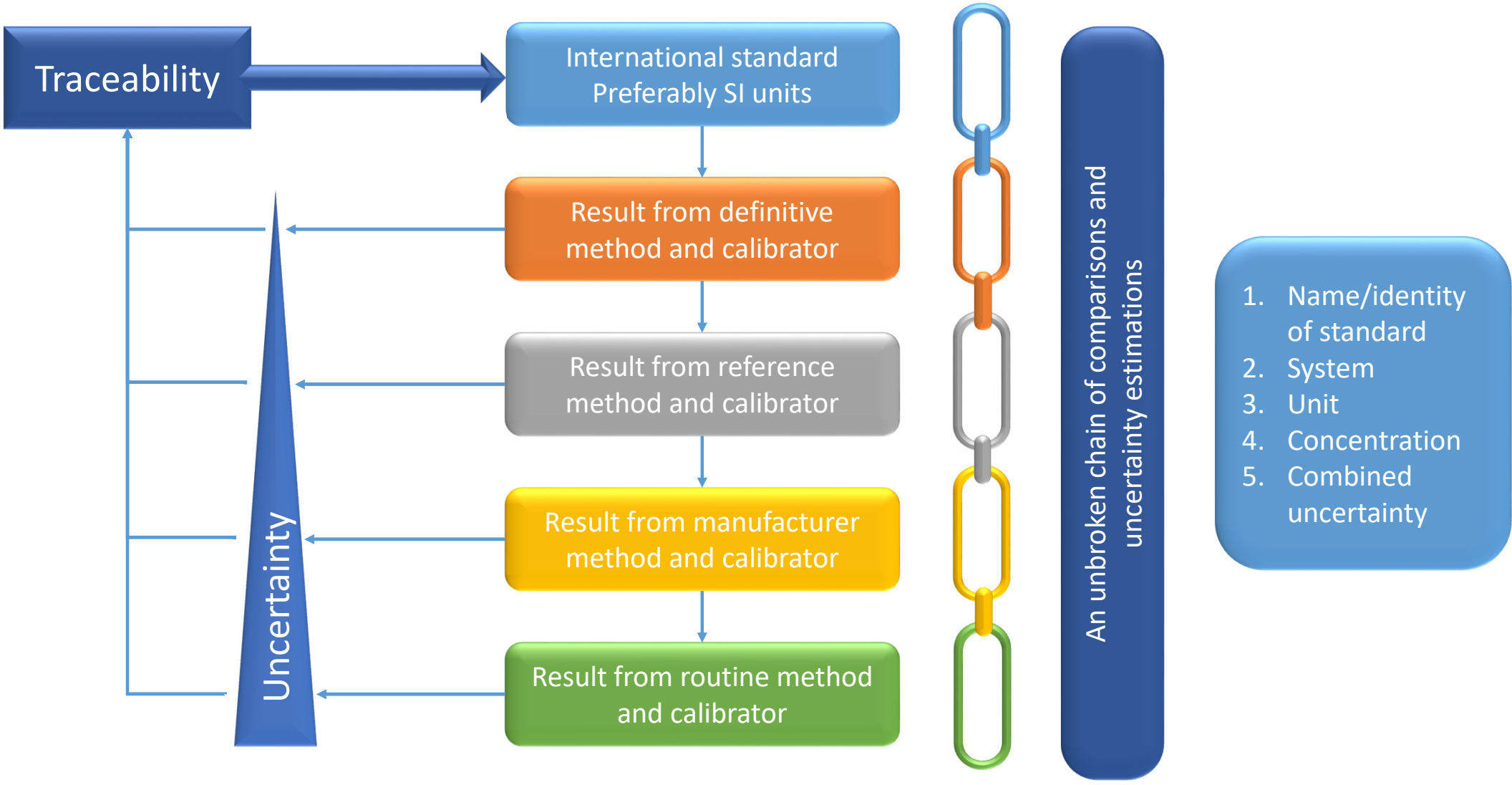
# Traceability to SI vs traceability in general

1. Traceability to SI

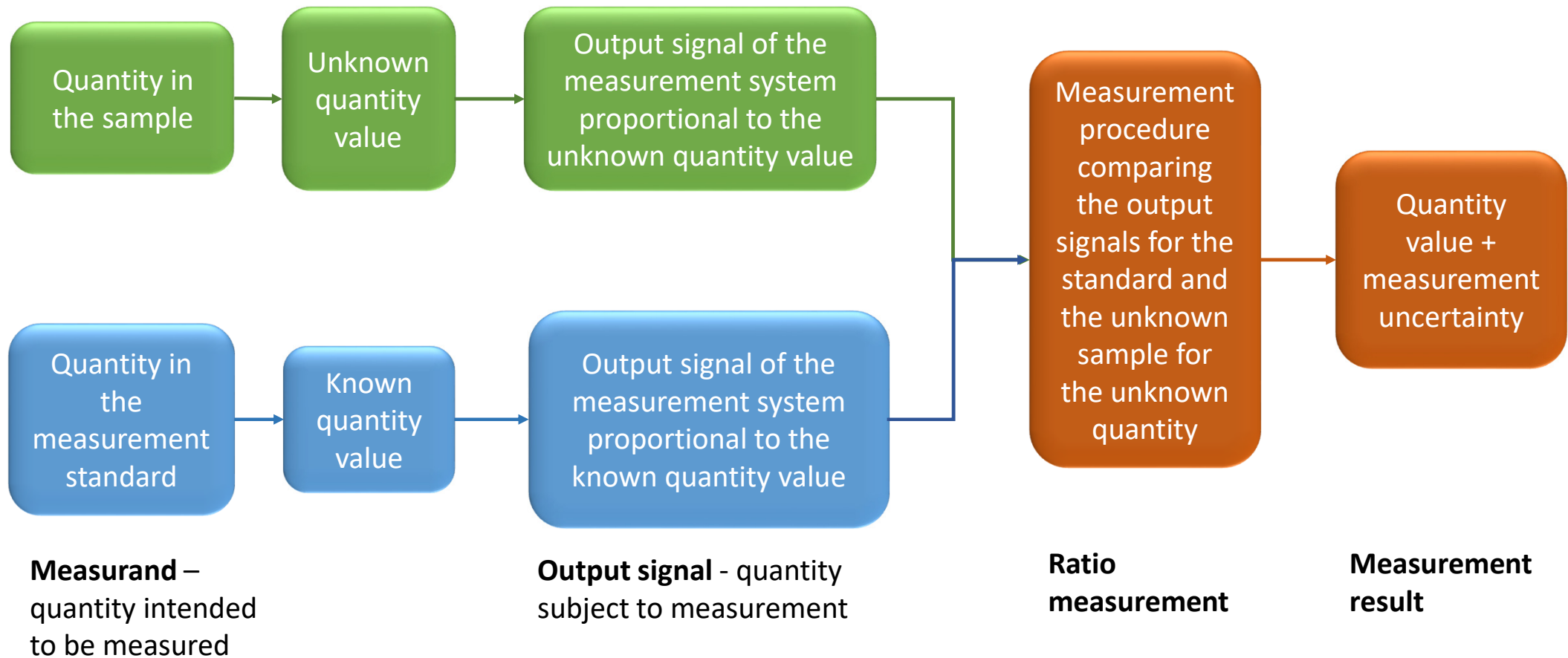


2. Traceability in general





# Measuring means comparing



# Measurand Categories

## Type A Measurands (SI traceable)

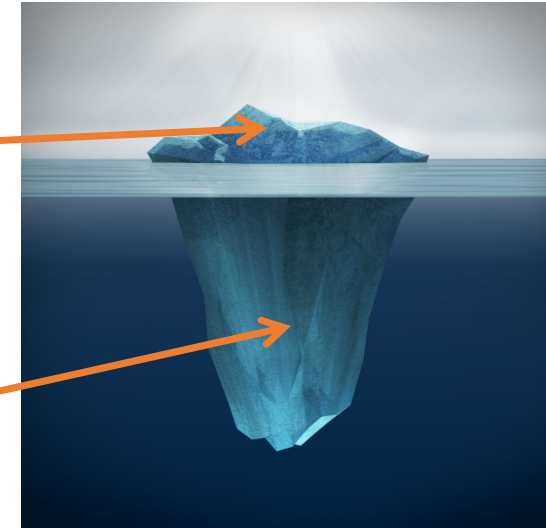
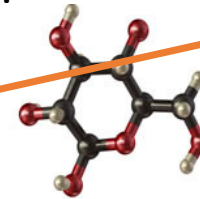
- Well defined compounds available in pure form that are traceable to the SI Unit

e.g. electrolytes, urea, glucose, creatinine, uric acid, etc.

Traceable and expressed in molar units (SI unit).

~10%

~90%



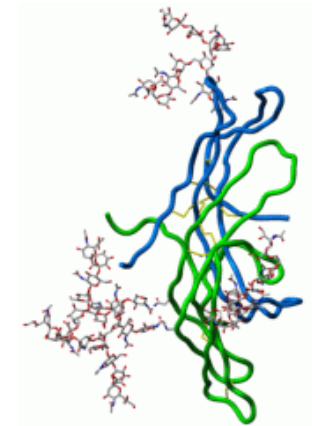
## Type B Measurands (Not SI traceable)

- Not a uniform substance: a heterogeneous mixture of substances which may differ from person to person as well as within the same person depending on health and disease status

e.g. human chorionic gonadotropin (hCG), tumour markers, cardiac troponin, etc.

These are not traceable to the SI Unit and are expressed in arbitrary units such as mass units or WHO International units

Type B measurands are generally more suited to harmonisation



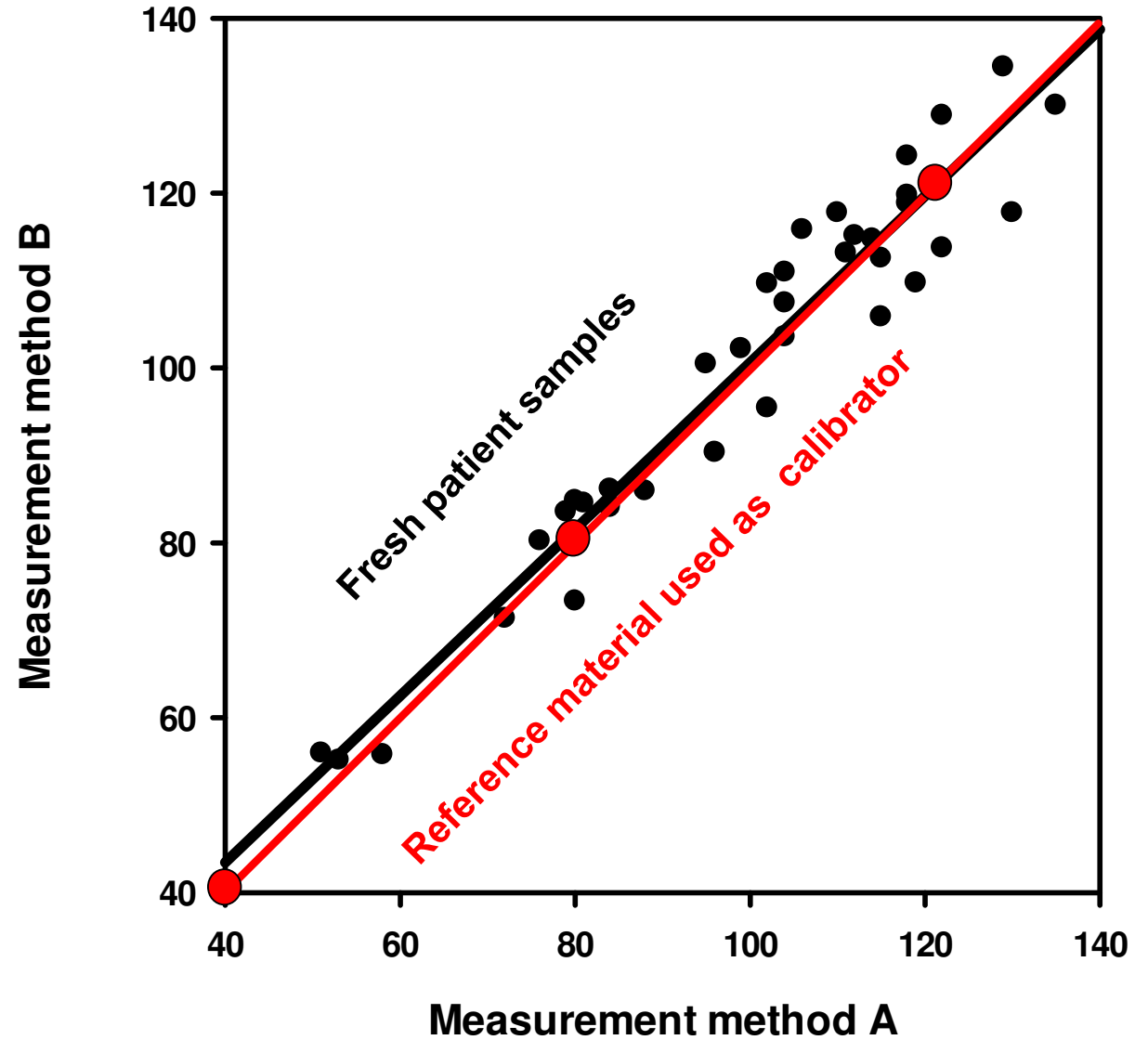
# Commutability of a reference material

- Property of a **reference material**, demonstrated by the closeness of agreement between the relation among the **measurement results** for a stated **quantity** in this material, obtained according to two given **measurement procedures**, and the relation obtained among the measurement results for other specified materials
  - **NOTE 1** The reference material in question is usually a calibrator and the other specified materials are usually routine samples.
  - **NOTE 2** The measurement procedures referred to in the definition are the one preceding and the one following the reference material (calibrator) in question in a calibration hierarchy (see ISO 17511).
  - **NOTE 3** The stability of commutable reference materials should be monitored regularly.



# Commutability

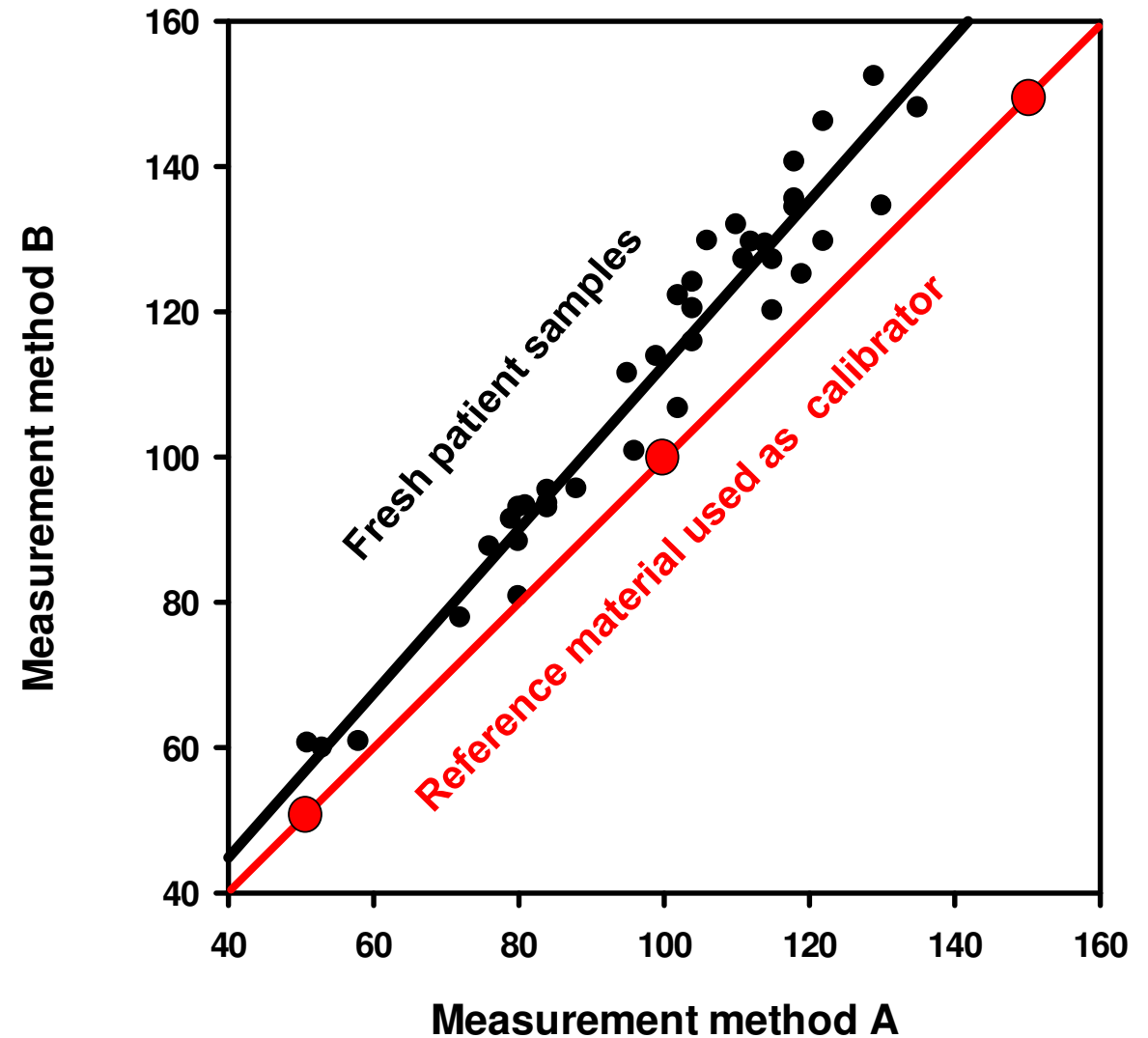
A commutable reference material and fresh patient specimens will show the same analytical response when tested using two (or more) different methods



# Lack of commutability

A non-commutable reference material and fresh patient specimens show a different analytical response when tested using two (or more) different methods

It is important to ensure Reference Materials are commutable and suitable for use where they are to be used for calibration of a method



# Commutability of the materials

Material	Primary Reference	Secondary Reference	Working Calibrator	Product Calibrator	Patient Sample
<b>Commutable?</b>	<b>Commutable?</b>	<b>Commutable?</b>	<b>Commutable?</b>	<b>Commutable?</b>	<b>Commutable!</b>
Measurement Procedure	Primary Reference Measurement	Secondary Reference Measurement	Manufacturer's Measurement		Routine measurement in a Clinical Laboratory
Provider	BIPM, National Metrology Institutes, Accredited Reference Laboratories	National Metrology Institutes, Accredited Reference Laboratories	Manufacturer's Laboratory		End User
Uncertainty					
Uncertainty					

Patient result



# Manufacturer Traceability

Traceability of Method



Calibrator Target Value and Uncertainty

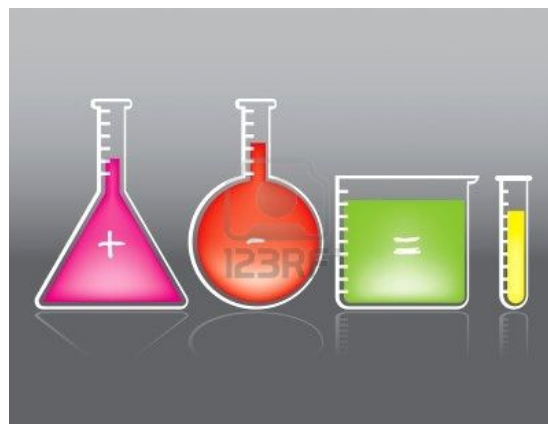
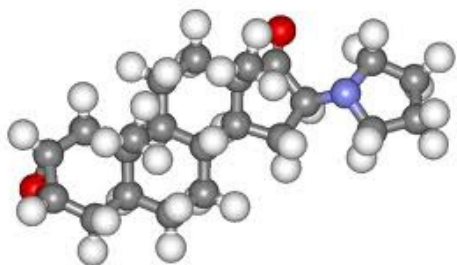


Assay	Reference Method/Material Traceability	Calibrator/Control	Target Value Common Units	Total Uncertainty Common Units	Common Units	Conversion Factor	Target Value SI Units	Total Uncertainty SI Units	SI Units	% Uncertainty
Calcium_CPC (CA, CA_c)	Atomic Absorption Method NIST SRM 915, NIST SRM 909b	Siemens Chemistry Calibrator	10.4	0.12	mg/dL	0.25	2.59	0.03	mmol/L	1.16
Calcium_2, Arsenazo III (CA_2, CA_2c)	Inductively Coupled Atomic Emission Method, NIST SRM 915, NIST SRM 909b	Siemens Chemistry Calibrator	10.3	0.19	mg/dL	0.25	2.57	0.05	mmol/L	1.79
Carbon Dioxide Liquid (CO2_L, CO2_c)	Corning 965 Reference Method, NIST SRM 192	CO2 Calibrator/Diluent	29.8	0.80	mEq/L	1	29.80	0.80	mmol/L	2.68
Cholesterol_2 (CHOL_2, CHOL_c)	CDC Reference Method (modified Abell-Kendall) NIST SRM 909b	Siemens Chemistry Calibrator	198.0	2.57	mg/dL	0.0259	5.12	0.07	mmol/L	1.34
Cholinesterase (CHE)	Molar extinction coefficient of reaction product	ADVIA Chemistry Enzyme 1 Calibrator	14200.0	432.4	U/L	1	14200.0	432.4	U/L	3.30
Creatinine_2, Jaffe, sample rate blanked, intercept corrected (CREA_2, CREA_2c)	IDMS Reference Method NIST SRM 967	Siemens Chemistry Calibrator	8.2	0.13	mg/dL	88.4	724.9	11.6	µmol/L	1.61
Creatinine Kinase (CKNAC)	IFCC-Reference Method IRMM/IFCC-455	Chemistry Control 1 <sup>a</sup>	62.0	1.18	U/L	1	62.0	1.18	U/L	1.88
		Chemistry Control 2 <sup>a</sup>	250.0	2.50		1	250.0	2.50		0.98
Creatine Kinase (CK_L)	IFCC Reference Method at 37°C	ADVIA Chemistry Enzyme 3 Calibrator	650	27.6	U/L	1	650	27.6	U/L	4.25
Direct Bilirubin_2 (DBIL_2)	AACC Reference Method NIST SRM 916	Siemens Chemistry Calibrator	3.03	0.03	mg/dL	17.1	51.8	0.47	µmol/L	0.89
Direct HDL Cholesterol (D-HDL)	NCEP Designated Comparison Method	HDL/LDL Cholesterol Calibrator	80.0	0.80	mg/dL	0.0259	2.07	0.02	mmol/L	0.98
Enzymatic Creatinine_2 (ECRE_2)	IDMS Reference Method NIST SRM 914a, NIST SRM 967	Siemens Chemistry Calibrator	8.9	0.04	mg/dL	88.4	786.8	3.5	µmol/L	0.45
Gamma-Glutamyl Transferase (GGT)	IFCC Reference Method at 37°C IRMM/IFCC-452	ADVIA Chemistry Enzyme 1 Calibrator	840.0	50.80	U/L	1	840.0	50.80	U/L	5.90

Example of Manufacturer Traceability

# What Constitutes a Reference Method

- Reference Methods are used to assign values to Reference Materials (calibrator or accuracy check)
- Defined measurand
- Reference methods generally will have an end point detection that looks at the molecular species



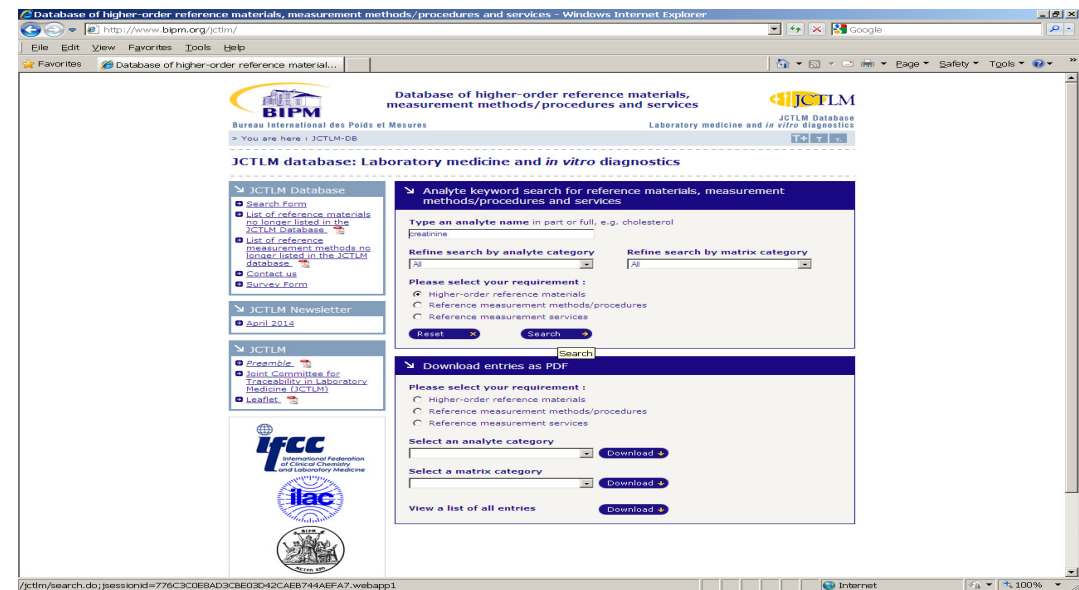
# Reference materials

Reference Material	Usage
<b>Primary Reference Standard</b>	Certified Standard with the highest metrological order. A calibrator with certified purity traceable to the SI unit with associated uncertainty.
<b>Primary Reference Material</b>	Material used for verification of a primary reference method, traceable to the primary reference standard. This material may also be used for verification of a routine method if shown to be commutable.
<b>Secondary Reference Material</b>	Material used for verification of a secondary reference method, traceable to the primary reference standard. This material may also be used for verification of a routine method if shown to be commutable.

It is important to confirm the certification for each certified reference material to ensure it is fit for purpose in the method of choice

# Sources of Certified Reference Material and 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 Methods

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

Various Reference Materials for Creatinine

The screenshot shows the JCTLM website interface. The header includes the BIPM logo and the text "Database of higher-order reference materials, measurement methods/procedures and services". The main content area displays the search results for "higher-order reference materials" with the analyte "creatinine". A table lists 8 results with columns for "Select", "Analyte", "Analyte category", "Matrix/Material", and "Organization".

Select	Analyte	Analyte category	Matrix/Material	Organization
<input type="checkbox"/>	creatinine	metabolites and substrates	creatinine crystalline material	NIST
<input type="checkbox"/>	creatinine	metabolites and substrates	creatinine crystalline material	NMIJ
<input type="checkbox"/>	creatinine	metabolites and substrates	frozen human serum	CENAM
<input type="checkbox"/>	creatinine	metabolites and substrates	frozen human serum	NIST
<input type="checkbox"/>	creatinine	metabolites and substrates	human serum	IRMM
<input type="checkbox"/>	creatinine	metabolites and substrates	human serum	LGC
<input type="checkbox"/>	creatinine	metabolites and substrates	human serum	NIST
<input type="checkbox"/>	creatinine	metabolites and substrates	frozen human serum	HSA



# Creatinine: reference standard material

Information specific to each material: quantity, purity, uncertainty etc

The screenshot shows a web browser window displaying the BIPM JCTLM database. The page title is "Database of higher-order reference materials, measurement methods/procedures and services". The search results are for "creatinine in creatinine crystalline material" from the National Institute of Standards and Technology (NIST), United States. The results table includes the following information:

Name of the reference material	Quantity
SRM 914a, creatinine	Mass fraction
Analyte certified/assigned value	99.7 %
Expanded uncertainty (level of confidence 95 %)	0.3 %
Reference(s) on commutability	Not applicable: A high-purity material used as a primary calibrator for higher order reference methods
Traceability	SI
CRM listing	List I

Additional information provided includes contact details for NIST: Phone: +1 301 975 6776, Fax: +1 301 948 3730, Email: srinfo@nist.gov, and Web: http://www.nist.gov/srm. A note states: "This (Certified) Reference Material has been reviewed for compliance with ISO 15194:2003 but not been reviewed against ISO 15194:2009".

# Creatinine: reference measurement services

Information specific  
to each accredited  
Reference  
Laboratory: matrix,  
uncertainty etc

The screenshot shows a web browser window displaying the search results for creatinine reference measurement services. The page header includes the BIPM logo and the JCTLM Database logo. The search criteria are: Reference measurement services; Analyte: creatinine; Analyte category: -; Matrix category: -. The results are sorted by Analyte, Matrix or Material, and Service provider. A table lists 12 results with columns for Select, Analyte, Matrix or Material, Country, and Service provider.

Select	Analyte	Matrix or Material	Country	Service provider
<input type="checkbox"/>	creatinine	blood plasma	Germany	DGKL
<input type="checkbox"/>	creatinine	blood plasma	Germany	Instand e.V.
<input type="checkbox"/>	creatinine	blood plasma	Belgium	UGent
<input type="checkbox"/>	creatinine	blood serum	Germany	DGKL
<input type="checkbox"/>	creatinine	blood serum	Germany	Instand e.V.
<input type="checkbox"/>	creatinine	blood serum	France	LNE
<input type="checkbox"/>	creatinine	blood serum	Belgium	UGent
<input type="checkbox"/>	creatinine	blood serum	United Kingdom	WEQAS
<input type="checkbox"/>	creatinine	calibration solution	Germany	DGKL
<input type="checkbox"/>	creatinine	calibration solution	France	LNE
<input type="checkbox"/>	creatinine	urine	Germany	DGKL
<input type="checkbox"/>	creatinine	urine	Belgium	UGent

# Suppliers of Reference Materials



Reference  
Material  
Producers



Producer and  
distributor

LGC Standards



Material distributors  
from NIST, ERM,  
NMIJ etc.

# Reference Material Requirements

- Measurand clearly defined
- Readily available
- Known purity with associated uncertainty (for 1° reference standards)
- A stated measurement result, demonstrated traceability with associated uncertainty (CRM)
- Stable under defined storage conditions
- Homogeneous
- Commutable
- Detailed Certificate outlining usage restrictions, reference methods as appropriate etc.
- Meet the requirements of ISO 15194 (required for JCTLM database listing)



Accurate results  
for patient care