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Weqas | GLOBAL PROVIDER OF QUALITY IN DIAGNOSTIC MEDICINE

EXTERNAL QUALITY ASSESSMENT

INTERNAL QUALITY CONTROL

REFERENCE MEASUREMENT SERVICES

EDUCATION & TRAINING

Understanding Measurement Traceability and Uncertainty

David Ducroq

Summary of Presentation

- Introduction to Metrology
- Why Do We Need Measurement Traceability
- Introduction to Traceability and Measurement systems
- Introduction to Measurement Uncertainty

Traceability

English Dictionary Definition

- **TRACE**:

Origin

Middle English (first recorded as a noun in the sense **'path that someone or something takes**'): from Old French *trace* (noun), *tracier* (verb), based on Latin *tractus*

- **TRACEABLE:**

(to somebody/something) if something is **traceable**, you can find out where it came from, where it has gone, when it began or what its cause was

The Science of Metrology: the 4 Ms

Metrology:

'The science of measurement and its application'

Measurand:

'Quantity *intended* to be measured'

> ***Analyte:*** The term "analyte", or the name of a substance or compound, is sometimes (for example in chemistry) used for measurands. This usage is not consistent with the present Vocabulary because these terms do not refer to quantities.

Measurement:

'Process of experimentally obtaining one or more **values** that can reasonably be attributed to a **quantity** together with any other available relevant information**'**

Measurement procedure:

'Detailed description of a **measurement** according to one or more **measurement principles** and to a given **measurement method,** based on a **measurement model** and including any calculation to obtain a **measurement result'**

VIM 4 2021 (International Vocabulary of Metrology)

Measurement in Clinical Chemistry as Metrologists

Creatinine as an example

System	Component (Analyte)	Kind of Quantity
Blood/Serum/Urine etc	e.g. Creatinine	Amount of substance concentration

Analyte: Creatinine

Measurand:. e.g. Creatinine (mmol/L) in serum

Metrological History

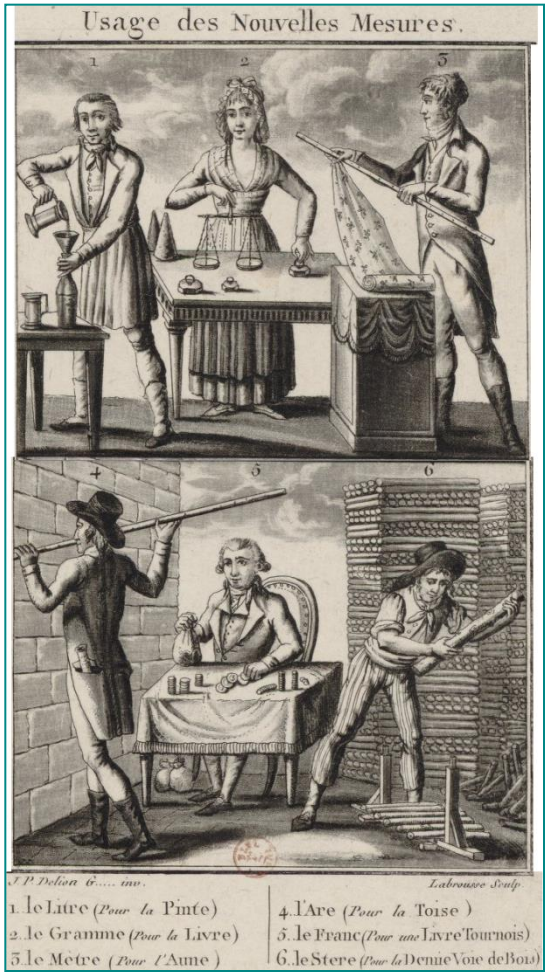
Royal Egyptian Cubit, approx. 2900 B.C

Museum of the Ancient Agora, Athens (5^{th}-2^{nd} Century BC)

24-30	Commercial lead weights 5^{th}-2^{nd} cent. B.C.
	Clay tokens
31-33	Presumably used as identity c

Lead commercial weights

2 staters = wheel (1792.5 grams)
stater = knucklebone (841.5 grams)
mna = dolphin (455 grams)
third (stater) = amphora (301 grams)
quarter (stater) = tortoise (231 grams)
sixth (stater) = half amphora (156.5 grams)
eighth (stater) = half tortoise (105 grams)

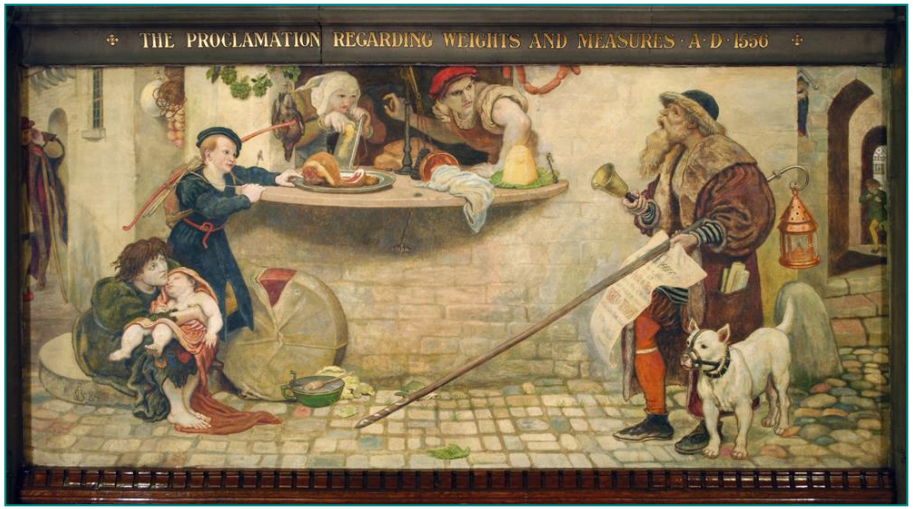


French metric system 1800

↓

Le Système International d'Unités

We ordain and command that the weights and measures, throughout our realm, be as our worthy predecessors have established.
11^{th} Century Act of the Royal Council



s and Measures, 1556

BIPM - Centre of Global Metrology

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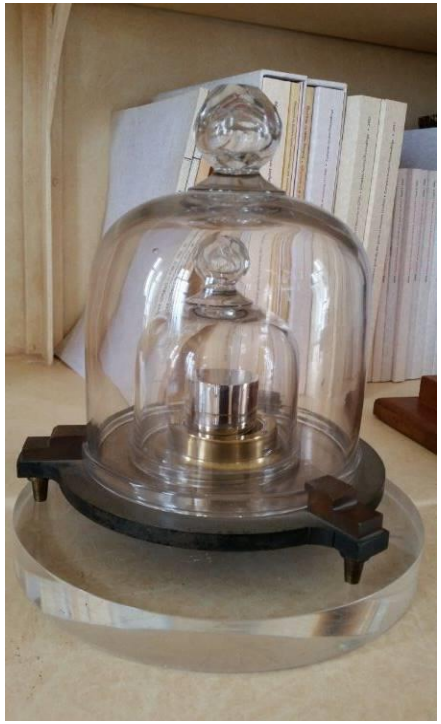
BIPM

Bureau International des Poids et Mesures

Metre

The metre is now the length of the path travelled by light in vacuum during a time interval of 1/299 792 458 of a second

Kilogram



The kilogram is now defined in terms of the Planck constant, h

150 Years of the Metre Convention

Why Do We Need Measurement Traceability?

Considerations when measuring patient samples

Geographic Location – Country, City, 1°/2°

- P
- P
ass
- M
pa

Lab results - correct interpretation relies on:

- A Clinical decision limit
  – Local or National guidelines, assumes same method used in the lab as the publication/study
- Long-term Patient monitoring
  – The method used for all previous results

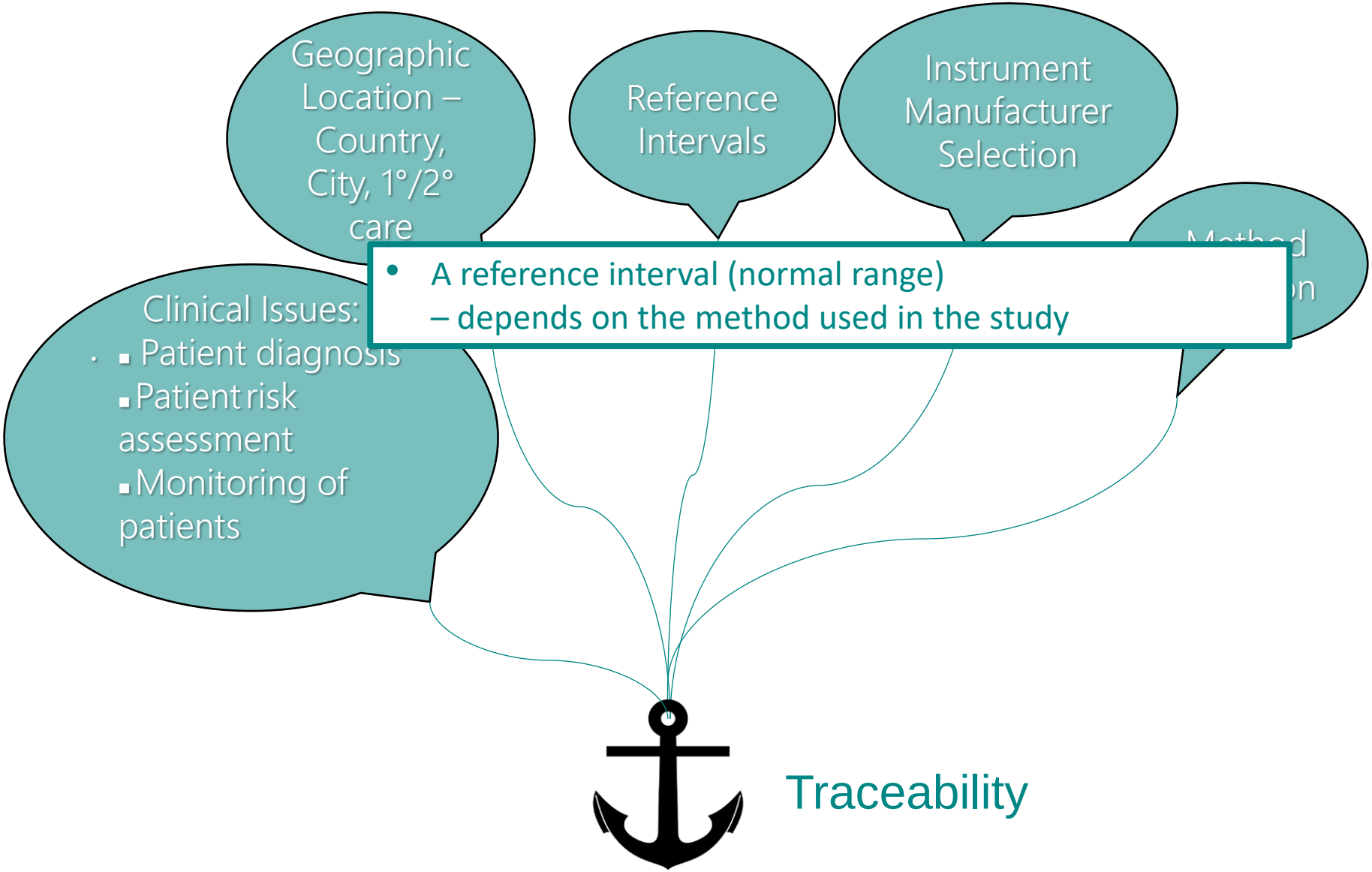
Patient Journey in the Modern World

- GP to hospital / specialist (e.g. PoCT to Lab method)
- Using a different laboratory
- Travelling to a different city
- Travelling to a different country (holiday, work etc)
- To manage your health, you need your pathology results from different labs to be comparable

All labs results

- Wrong diagnosis
- Wrong management
- Incorrect monitoring

Considerations when measuring patient samples



Measurement Traceability

'Traceability' means that the measurement results can be related to a stated reference by an unbroken chain of accredited comparisons
(NPL)

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
(source: VIM 4, JCGM, 2021)

Traceability concept – metre measurement

The SI unit of length is the metre (m):

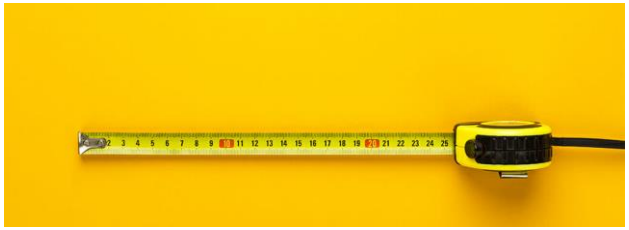
The metre is the length of the path travelled by light in vacuum during a time interval of 1/299 792 458 of a second.

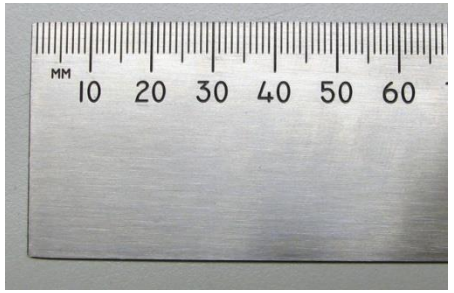
Measuring means comparing

Prototype Metre bar, made of an alloy of platinum and iridium, that was the standard from 1889 to 1960 (stored in BIPM).

Standardised meter rule in e.g. NPL lab, London

Commercially available calibrated measure





Calibrated ruler, accredited organisation

Traceability in Clinical Measurement

Reference Measurement Systems
- Traceability concept and standardisation of methods

Pillars of Traceability

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Measurement Traceability

- Reference measurement procedures (RMP)
- Traceable Reference materials (RM)
- Network of reference measurement laboratories (RMS)
- Universal reference intervals/ Medical decision limits
- Trueness-based proficiency testing schemes

JCTLM Accurate results for patient care

IFCC International Federation of Clinical Chemistry and Laboratory Medicine

Mauro Pantegini

Measurand Categories

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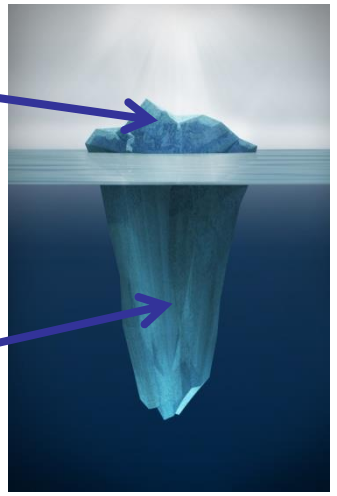
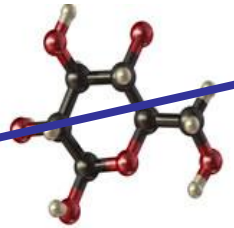
Type A Measurands (SI traceable)

- 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).





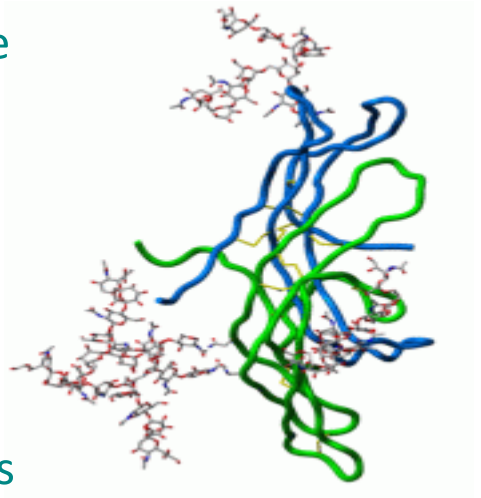
Type B Measurands (Not SI traceable)

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



Material	Procedure	Responsibility
m1 Certified Primary Reference Material	**p1** Measurement procedure for purity assessment e.g qNMR	BIPM, NML
	p2 Primary reference procedure for calibrator e.g. gravimetric prep	BIPM, NML, ARML
m2 Primary Calibrator (solution)	**p3** Reference Measurement Procedure	NML, ARML
m3 Secondary Calibrator/ CRM (commutable)	**p4** Manufacturer selected Measurement Procedure	ML
m4 Manufacturers Working Calibrator		
	p5 Manufacturers Standing Measurement Procedure	ML
m5 End-user IVD MD calibrator (various lots)		
	p6 End-user's routine procedure	ML, End user
m6 Routine sample		

SI Unit

Result

Type A Measurands

Weqas Ref Lab involvement

Adapted from ISO 17511:2020

Reference Materials

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Certified Primary Reference Material (m1)

Certified purity

Primary Reference Calibrator (m2)

Calibration of Primary Reference Method

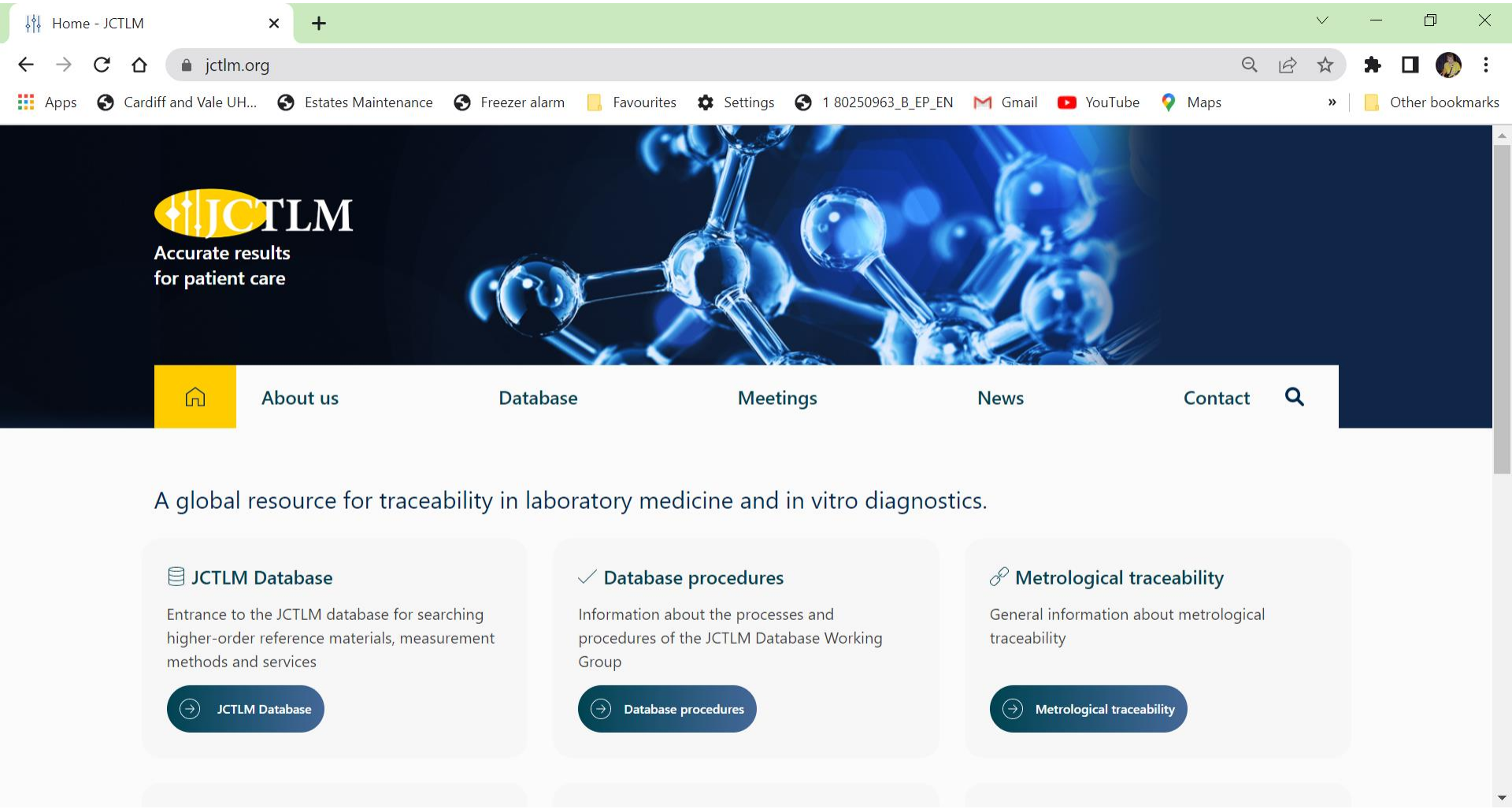
Secondary (commutable) Reference Material (calibrator / CRM; m3)

Verification of Reference Method / Manufacturer procedure

EQA / QCRM

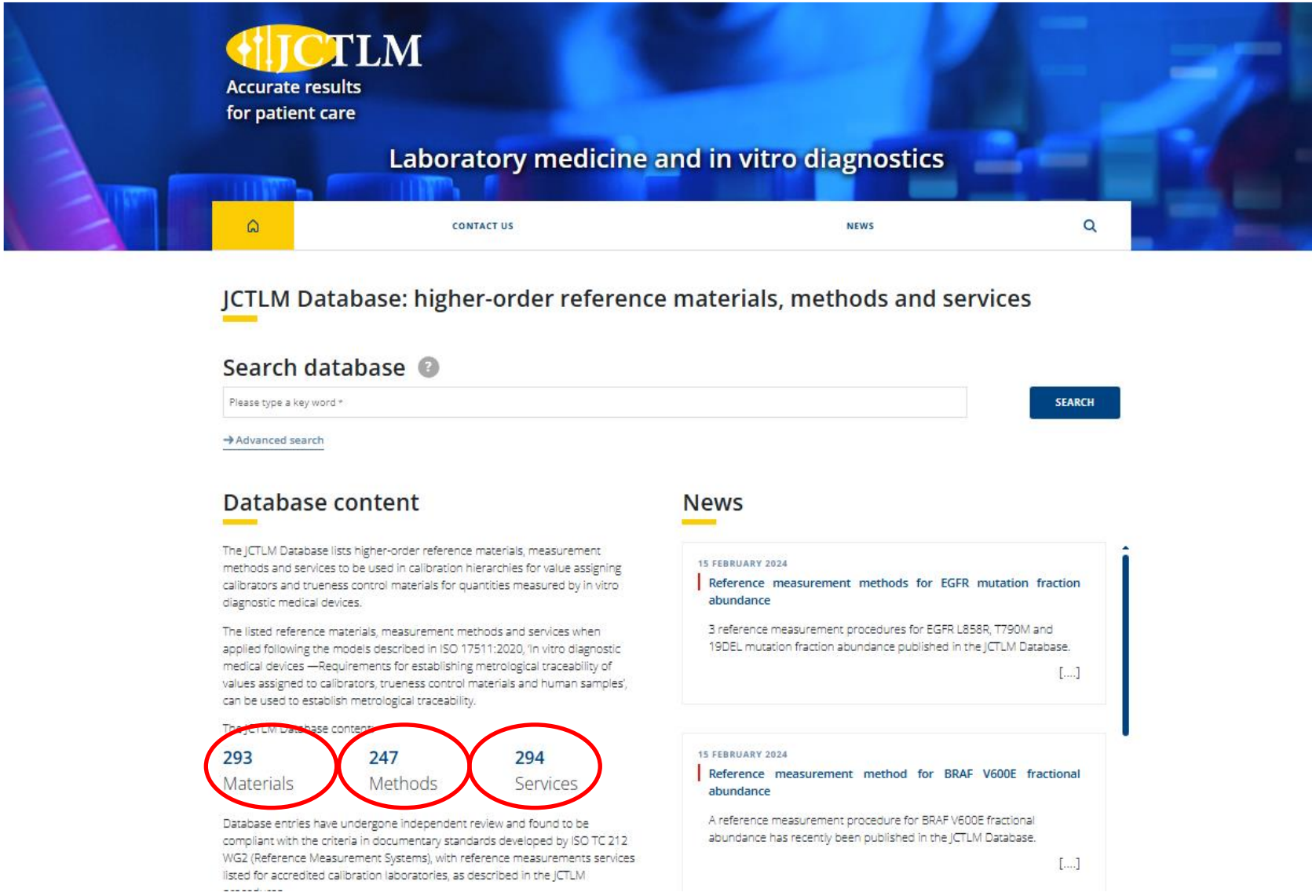
Check certificate for appropriate usage (commutability)

Joint Committee for Traceability in Laboratory Medicine Website (JCTLM)



www.jctlm.org

JCTLM Database Homepage



Generation of Reference Measurement Values

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Specialist Laboratories Required:

- Extensive method development and validation with traceability to the SI unit

Accredited to ISO17025 and ISO15195

Limited number of laboratories worldwide

Bureau International des Poids et Mesures

Database of higher-order reference materials, measurement methods/procedures and services

JCTLM
Accurate results for patient care

RELA: EQA for Reference Measurement Laboratories

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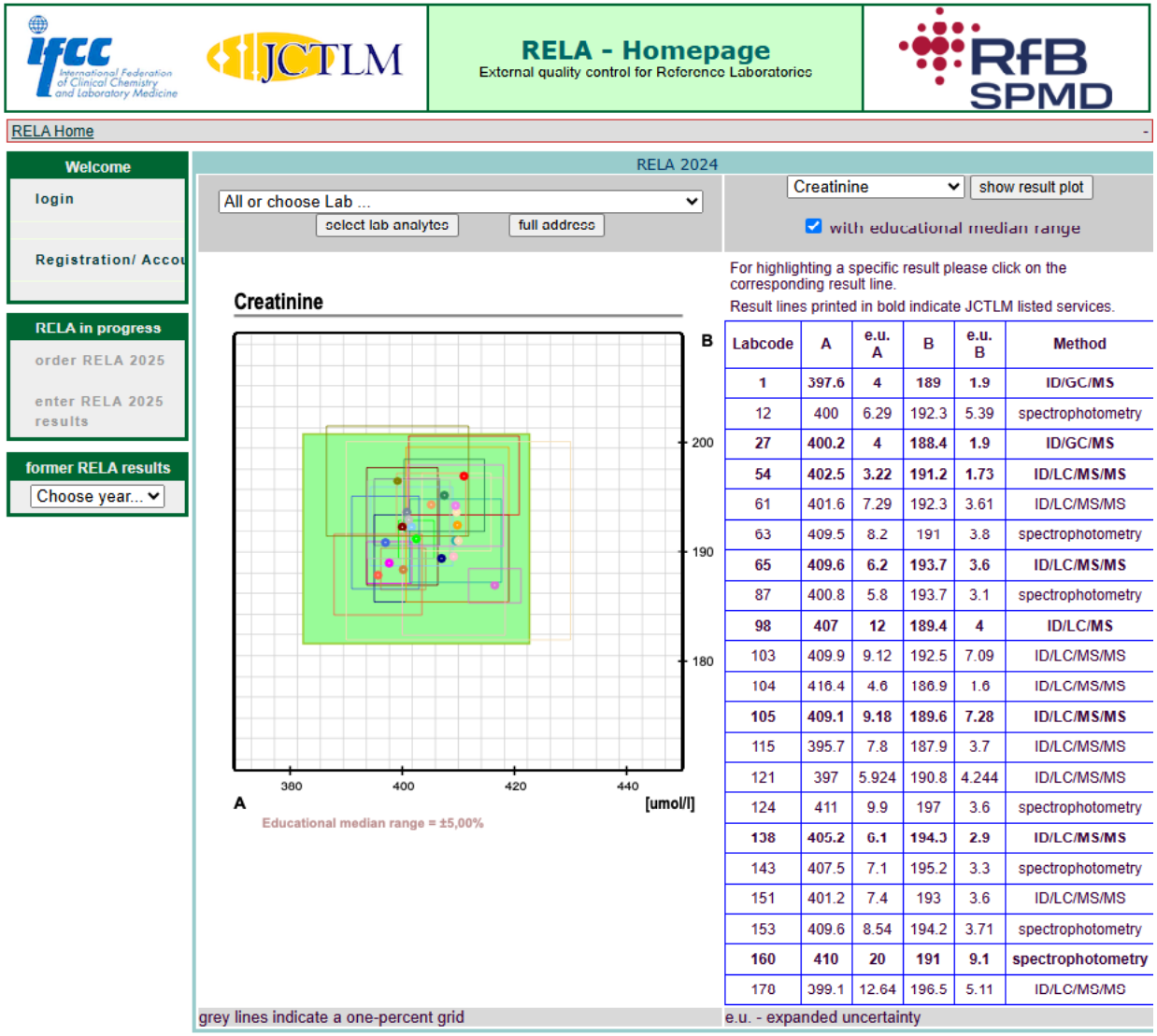


Labcode	A	e.u. A	B	e.u. B	Method
1	**397.6**	**4**	**189**	**1.9**	**ID/GC/MS**
12	400	6.29	192.3	5.39	spectrophotometry
27	**400.2**	**4**	**188.4**	**1.9**	**ID/GC/MS**
54	**402.5**	**3.22**	**191.2**	**1.73**	**ID/LC/MS/MS**
61	401.6	7.29	192.3	3.61	ID/LC/MS/MS
63	409.5	8.2	191	3.8	spectrophotometry
65	**409.6**	**6.2**	**193.7**	**3.6**	**ID/LC/MS/MS**
87	400.8	5.8	193.7	3.1	spectrophotometry
98	**407**	**12**	**189.4**	**4**	**ID/LC/MS**
103	409.9	9.12	192.5	7.09	ID/LC/MS/MS
104	416.4	4.6	186.9	1.6	ID/LC/MS/MS
105	**409.1**	**9.18**	**189.6**	**7.28**	**ID/LC/MS/MS**
115	395.7	7.8	187.9	3.7	ID/LC/MS/MS
121	397	5.924	190.8	4.244	ID/LC/MS/MS
124	411	9.9	197	3.6	spectrophotometry
138	**405.2**	**6.1**	**194.3**	**2.9**	**ID/LC/MS/MS**
143	407.5	7.1	195.2	3.3	spectrophotometry
151	401.2	7.4	193	3.6	ID/LC/MS/MS
153	409.6	8.54	194.2	3.71	spectrophotometry
160	**410**	**20**	**191**	**9.1**	**spectrophotometry**
170	399.1	12.64	196.5	5.11	ID/LC/MS/MS

Suppliers of Reference Materials

National Institute of Advanced Industrial Science and Technology
National Metrology Institute of Japan

Australian Government
National Measurement Institute

LABORATOIRE NATIONAL DE MÉTROLOGIE ET D'ESSAIS

National Institute of Standards and Technology
U.S. Department of Commerce

ERM
European Reference Materials

中国计量科学研究院
National Institute of Metrology, China

World Health Organization

HSA
Health Sciences Authority

Reference Material Producers

LGC

LGC Standards

Producer and distributor

SIGMA-ALDRICH

Material distributors from NIST, ERM, NMIJ etc.

Uncertainty

Uncertainty Definition

Uncertain:

Not completely confident or sure of something
Not able to be accurately known or predicted

Uncertainty:

Also called: uncertainness. The state or condition of being uncertain

GUM definition:
The word “uncertainty” means doubt, and thus in its broadest sense “uncertainty of measurement” means doubt about the validity of the result of a measurement.

Result = + / - x (%?)

Measurement Uncertainty

ISO Definition

Non-negative parameter characterising the dispersion of the quantity values being attributed to a measurand, based on the information used

GUM Definition

Parameter, associated with the result of a measurement, that characterises the dispersion of the values that could reasonably be attributed to the measurand

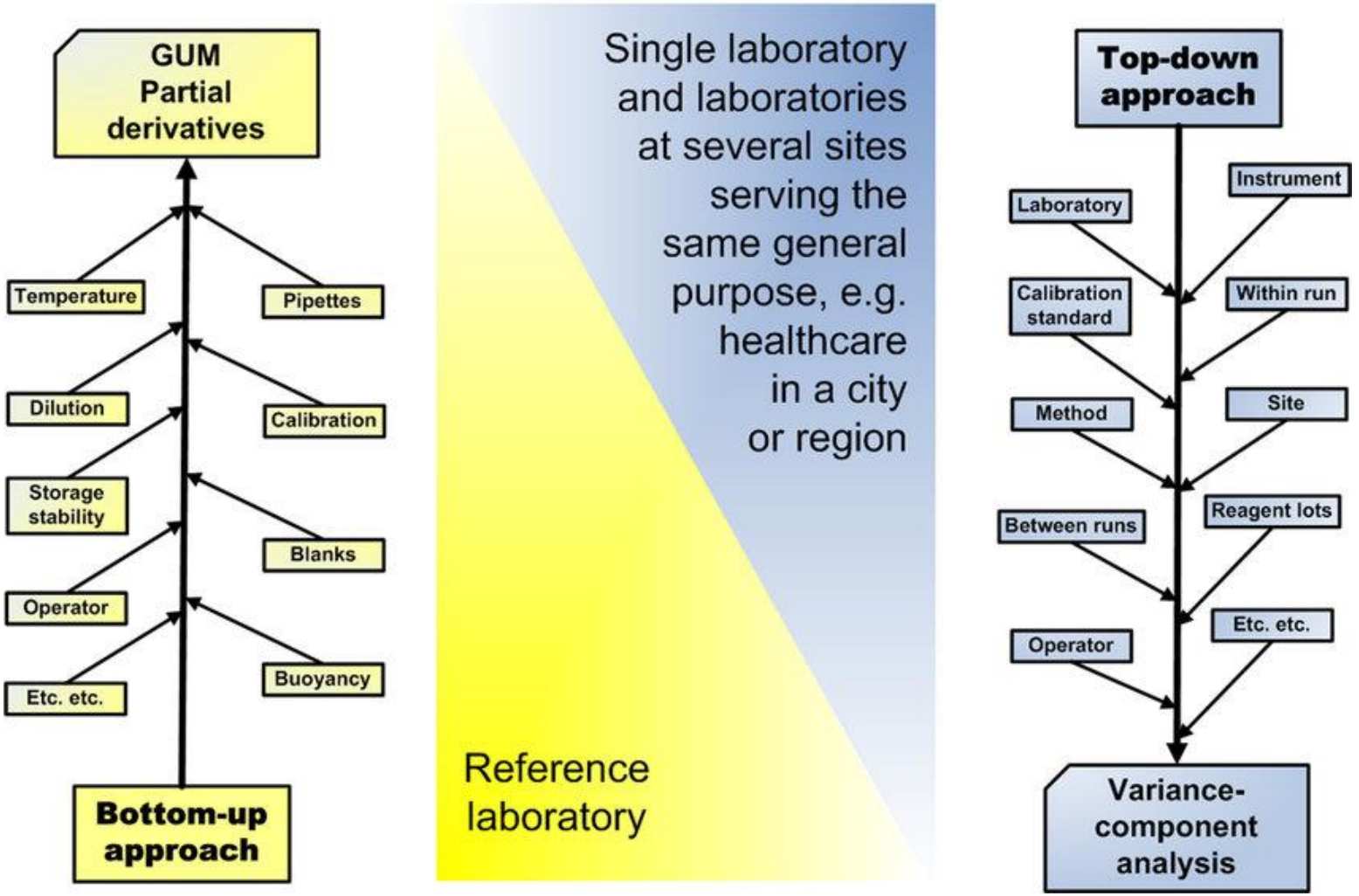
i.e. how confident you are with the provided result

Result +/- x (%?)

Why Measure Uncertainty?

- It is there, we should understand it
- Assures comparability among tests (National, International)
- Required for accreditation
- Provides an objective quality measure
- Help with method improvement
- Guide for root cause analysis and corrective action

Identifying and Combining Uncertainty



Scandinavian Journal of Clinical and Laboratory Investigation January 2012 72(3):212-20

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Type A evaluation of measurement uncertainty

Evaluation of a component of measurement uncertainty by a statistical analysis of measured quantity values obtained under defined measurement conditions.

Obtained during method validation:

Repeatability, Reproducibility etc

$U = SD/\sqrt{n}$ (Standard error of the mean)

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Type B evaluation of measurement uncertainty

Evaluation of a component of measurement uncertainty determined by means other than a Type A evaluation of measurement uncertainty.

These are uncertainty values generally associated with equipment and supplied by the manufacturer e.g. uncertainty associated with a balance, pH meter, thermometer

Generally assume a rectangular distribution:

$$U = a / \sqrt{3}$$

Where a = manufacturer stated uncertainty

Combining Uncertainty

Identify the components of uncertainty
Calculate all uncertainty as Standard Deviation
All uncertainty must be in the same units as the measurand
Combine Uncertainty as the square root sum of squares

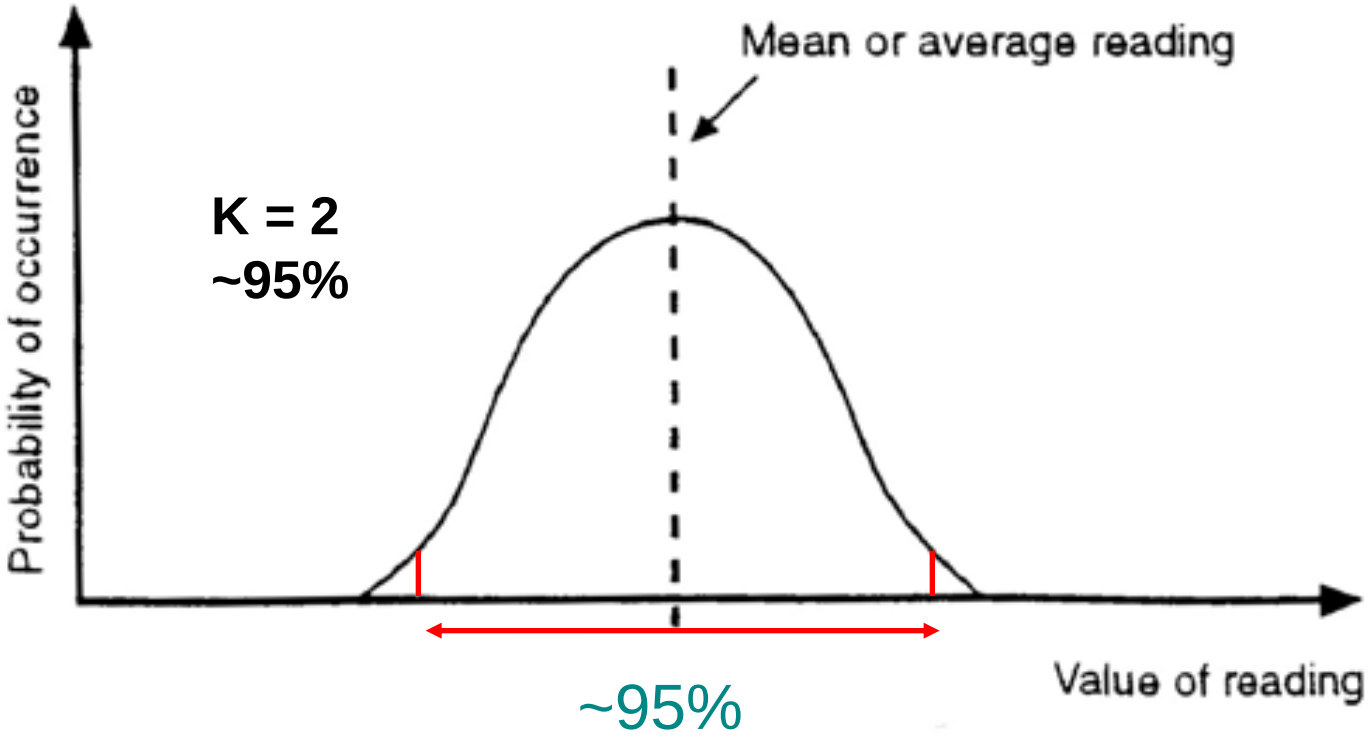
$$\text{Uncertainty} = \sqrt{(U_1^2 + U_2^2 + \ldots)}$$

Relative Standard Deviation (R_{SD}):

This is a measure of the spread of the data in comparison to the mean.

$$R_{SD} = SD / x = CV$$

Coverage Factor



Confidence Interval: a range which includes a specified (usually 95%) of the possible values

Uncertainty of target – Uncertainty Budget

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Combined uncertainty =

$$2 \times \text{result} \times \{\sqrt{(U_{sample})^2} + \sqrt{(U_{std})^2} + \sqrt{(U_{Cont})^2}\}$$

Where

U_{sample} = uncertainty associated with sample precision

U_{std} = uncertainty associated with standard preparation

U_{Cont} = uncertainty associated with the Controls

Coverage factor of 2 - 95% confidence
Uncertainty as Relative Standard Deviation (R_{SD})

Summary

- Traceability and uncertainty are essential to ensure comparability of results between different laboratories and methods
- Traceability is underpinned by Reference Materials, Reference Measurement Procedures and Reference Laboratory Networks
- Certified Reference Material is available for some measurands but not all
- Traceability and uncertainty are a requirement of ISO 15189 and ISO 17025

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Thank You