BIPM
Bureau international des poids et mesures

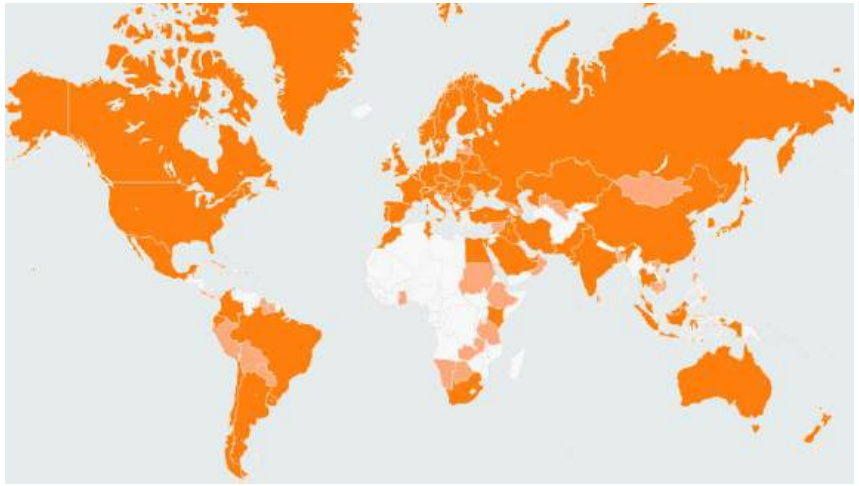
JCTLM
Accurate results for patient care

Metrological traceability as a unique tool to improve the quality of laboratory tests

Robert Wielgosz, Director Chemistry Department (BIPM)

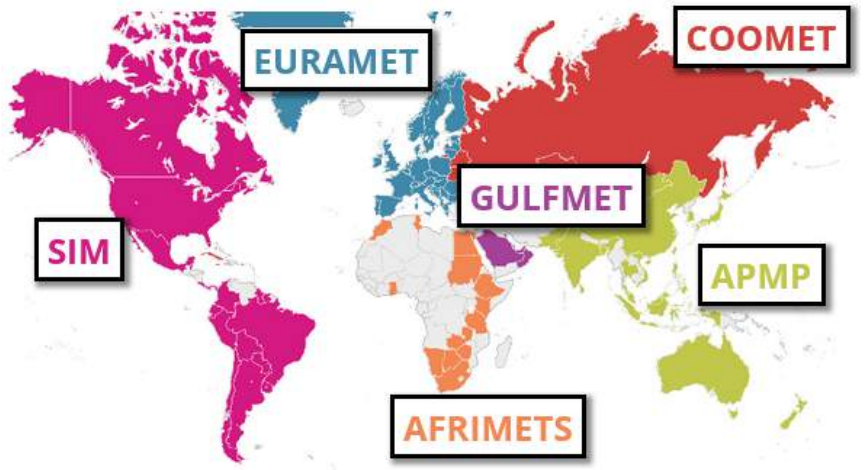
JCTLM Executive Secretary

Bureau International des Poids et Mesures (BIPM)



- 64 Member States* and
- 36 Associates of the CGPM
(States and Economies)

- 6 Regional Metrology Organizations



A global network to compare measurement standards and ensure their equivalence worldwide enabling SI traceable measurements

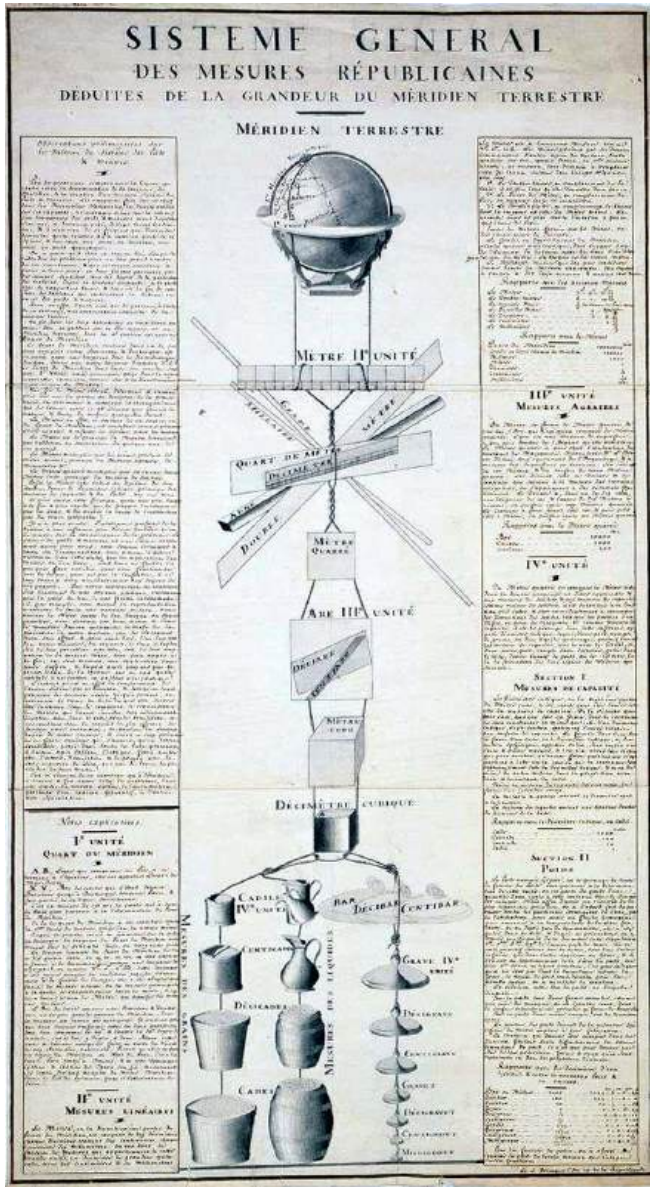
Organized via 10 Committees, areas covered include: Chemistry & Biology, Ionizing Radiation, Thermometry, Photometry & Radiometry, Mass, etc.

www.bipm.org

Currently in the KCDB there are

Intergovernmental Organization Headquarters with Offices and Laboratories: Sèvres, France, 70 Staff

From the metre to the International System of Units (SI)



17 April 1795 Metric System in France established - law of 18 Germinal Year III (Republican calendar)

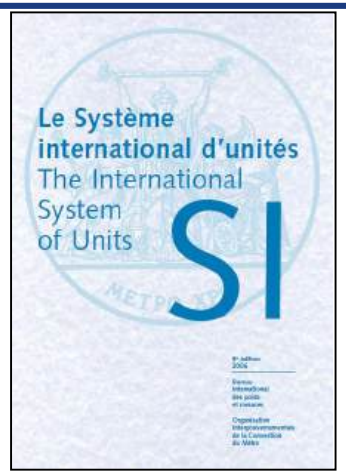
> "Never has anything grander and simpler and more coherent in all its parts come from the hands of men." – Lavoisier

20 May 1875 Metre Convention signed establishing the ***Bureau international des poids et mesures (BIPM)***

20 May 2019 **SI** in terms of fixed values of **fundamental constants**

From definitions to dissemination of standards

Definition →



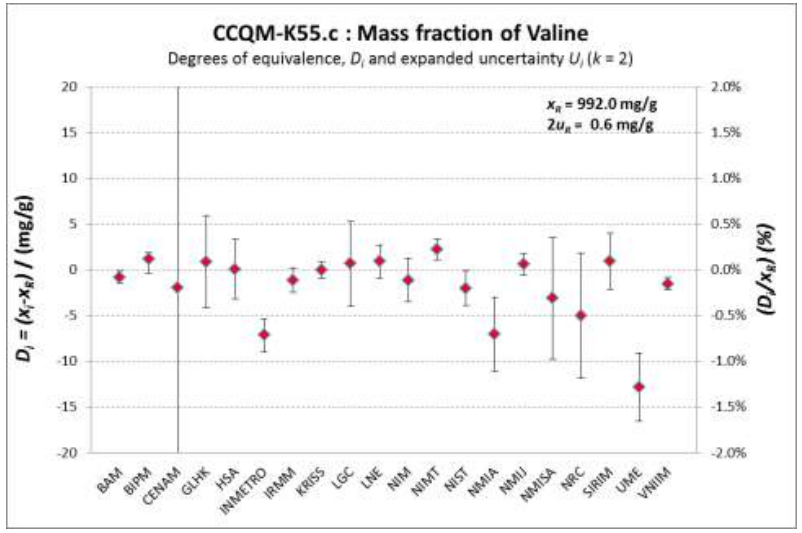
SI Unit of amount of substance: mole

↓

Realization

↓

Comparisons →



↓

Key comparison performance

⇨ open-access http://kcdb.bipm.org/appendixB/KCDB_ApB_search.asp

⇨ basis for: individual NMI CMC claim
peer review and approval of CMC

Dissemination →

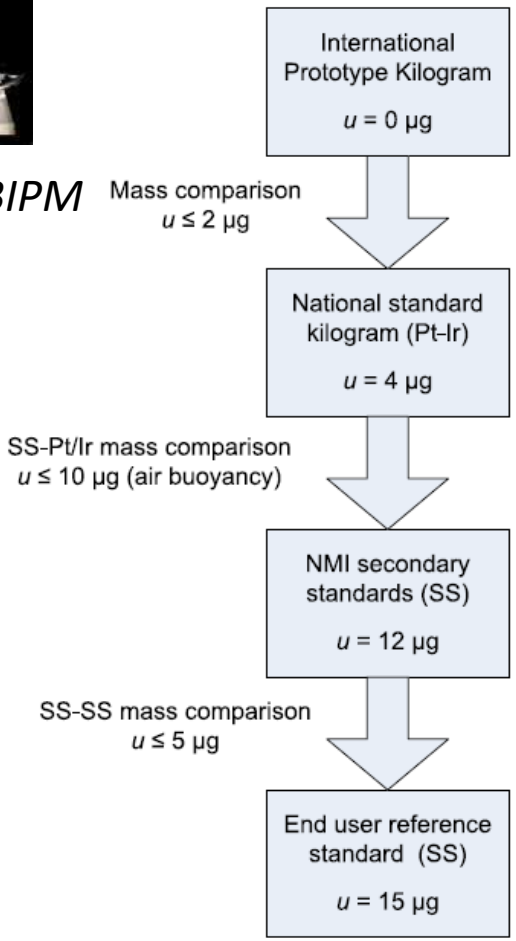
- Certified Reference Material (CRM)
- Calibration service
- EQAS material assignment


National Institute of Advanced Industrial Science and Technology
National Metrology Institute of Japan
NMIJ
Reference Material Certificate
NMIJ CRM 4601-a
No. 100
3,5-Bis(trifluoromethyl)benzoic Acid for Quantitative NMR (^{1}H, ^{19}F)
AIST

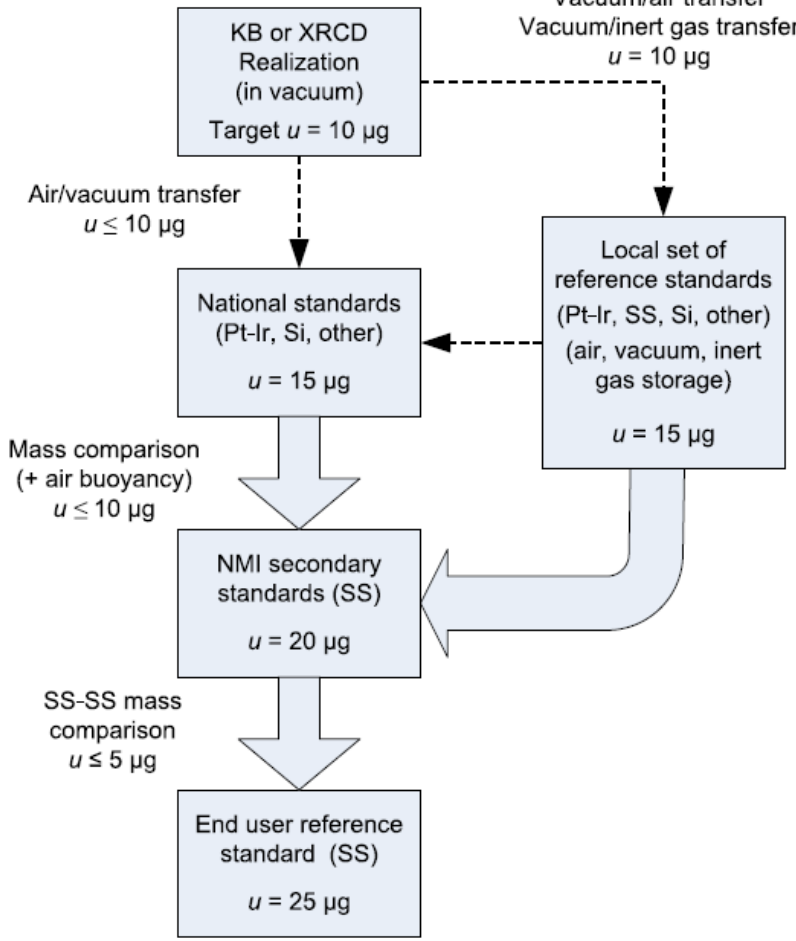

National Institute of Standards & Technology
Certificate of Analysis
Standard Reference Material® 350b
Benzoic Acid (Acidimetric)
C_6H_5COOH

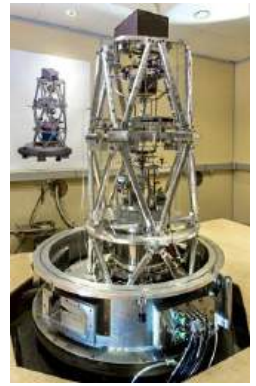
The IPK, at the BIPM

Pre-2019 Traceability Chain

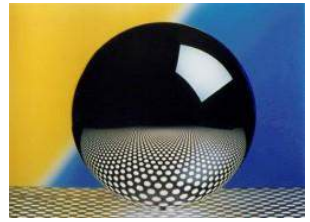


Post-2019 Traceability Chain





Kibble Balance



XRCD

Metrological Traceability chains for mass measurements

Traceable measurement results are compatible

National Metrology Institutes and Designated Institutes

The Republic of Poland became a Member State on **12 May 1925**.

CIPM MRA

Signatory/NMI

Central Office of Measures ROR
→ GUM
Warsaw

Participating in the CIPM MRA since: 14 October 1999
Signed by: Krzysztof Andrzej MORDZINSKI (then Director, GUM)

Designated institute(s)

Institute of Low Temperature and Structure Research/Instytut Niskich Temperatur i Badañ Strukturalnych ROR
For temperature measurements from 13.8033 K to 273.16 K
→ INTiBS
Wroclaw

National Centre for Nuclear Research, Radioisotope Centre ROR
For ionizing radiation
→ POLATOM
Swierk

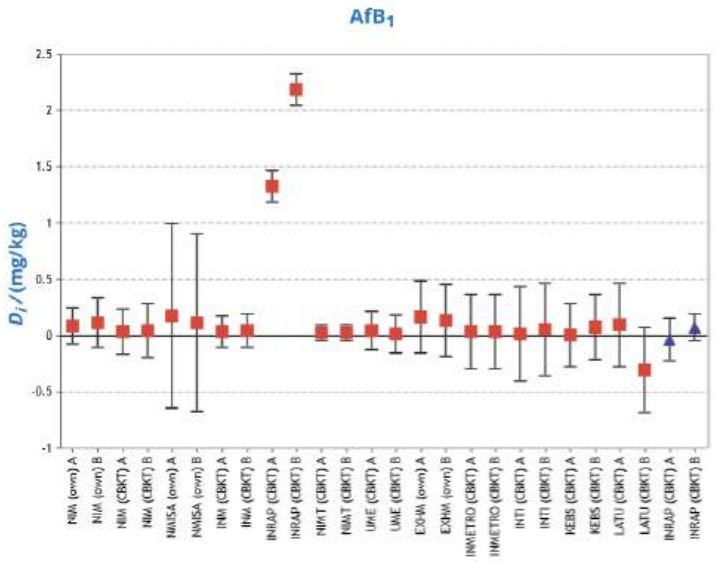
Główny Urząd Miar

Chemical and Biological Measurement Standards

> 50 participating institutes

> 6500 Calibration and RM services

> 500 inter-laboratory comparisons



CCQM: Metrology in Chemistry and Biology

CCQM-AH-WG-MOLE
CCQM *AD HOC* WORKING GROUP ON THE MOLE

CCQM-EAWG
CCQM WORKING GROUP ON ELECTROCHEMICAL ANALYSIS

CCQM-IAWG
CCQM WORKING GROUP ON INORGANIC ANALYSIS

CCQM-KCWG
CCQM WORKING GROUP ON KEY COMPARISONS AND CMC QUALITY

CCQM-OAWG
CCQM WORKING GROUP ON ORGANIC ANALYSIS

CCQM-SAWG
CCQM WORKING GROUP ON SURFACE ANALYSIS

CCQM-CAWG
CCQM WORKING GROUP ON CELL ANALYSIS

CCQM-GAWG
CCQM WORKING GROUP ON GAS ANALYSIS

CCQM-IRWG
CCQM WORKING GROUP ON ISOTOPE RATIOS

CCQM-NAWG
CCQM WORKING GROUP ON NUCLEIC ACID ANALYSIS

CCQM-PAWG
CCQM WORKING GROUP ON PROTEIN ANALYSIS

CCQM-SPWG
CCQM STRATEGIC PLANNING WORKING GROUP

https://www.bipm.org/kcdb/

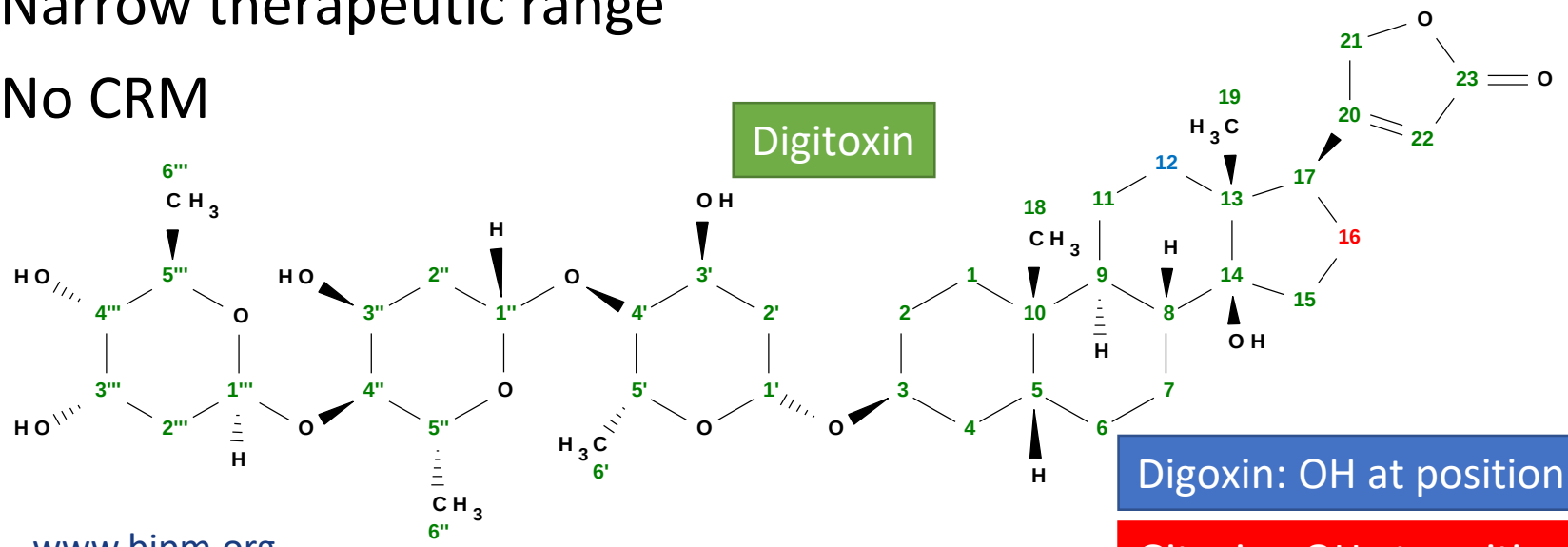
KCDB

Current BIPM HQ Laboratory Projects (1)

CCQM-K148.c Digitoxin purity comparison

- Organic purity assessment of a cardiac glycoside (CG) - digitoxin
- Treatment of heart failure and potential cancer therapeutic
- Narrow therapeutic range
- No CRM

TÜBİTAK BIPM UME



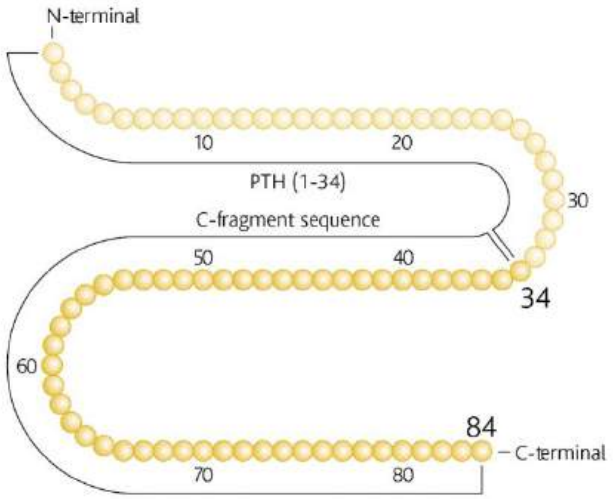
Digitalis Purpurea (Foxglove)

Digitalis Lanata

Current BIPM HQ Laboratory Projects (2)

CCQM-K115.d Parathyroid hormone, PTH 1-84 in solution

- PTH is a 84 amino acid peptide hormone.
- Calcium/phosphate metabolism
- Monitoring of chronic kidney disease (CKD)
- Assessment of hypo- or hyperparathyroidisms.



Solid materials

Frozen liquid solutions

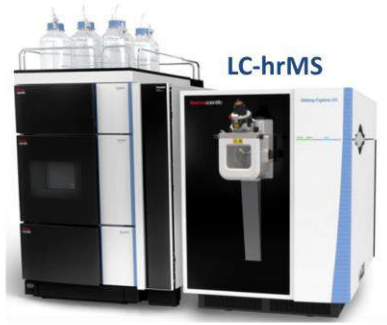
Mass balance
KFT, IC, GC-MS, LC-hrMS

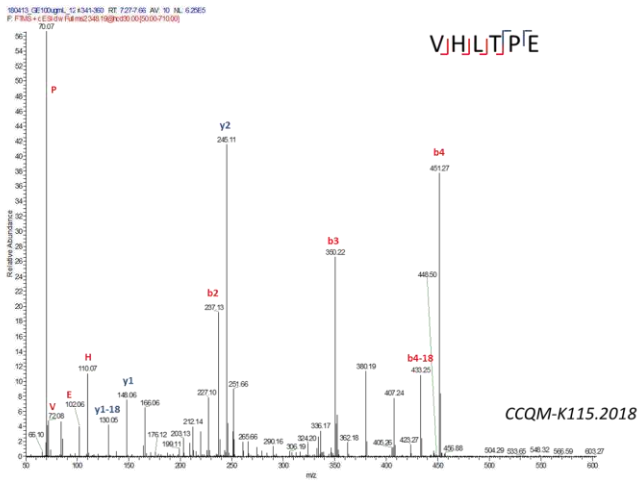
qNMR
+ LC-hrMS

AAA
+ LC-hrMS

Prot. Pept. Analysis
+ LC-hrMS

MS¹ High resolution, accurate mass
MS² fragmentation data





Joint Committee for Traceability in Laboratory Medicine

Established in 2002. 4 Executive Committee Organizations

Regulations and Metrological Traceability for IVDs
Essential Requirements of the IVD Directive

98/79/EC of 27 October 1998 on in vitro diagnostic medical devices

"The traceability of values assigned to calibrators and/or control materials must be assured through available reference measurement procedures and/or available reference materials of a higher order.. "

Annex I - Essential Requirements
Part A. General Requirements, Clause 3

JCTLM Accurate results for patient care

BIPM

Equivalent measurement results through metrological traceability

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 2 Metrological traceability requires an established **calibration hierarchy**.

Metrological Traceability in Laboratory Medicine

The concept of reference measurement systems is well developed in Laboratory Medicine:

- **Reference Methods**
- **Reference Materials**
- **Reference Measurement Services**

JCTLM
Accurate results for patient care

BIPM

Achieving Accurate Results: Metrology and Quality Infrastructure

Physician requesting laboratory test

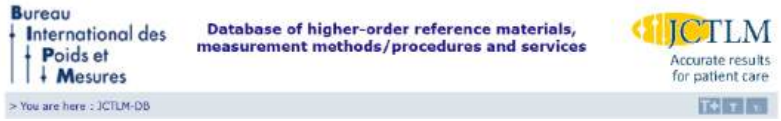
Medical Laboratory (Hospital)

ISO 15189

ISO 17511

IVD Manufacturers

Calibration (Reference) Laboratory



A database of reference resources to **help the IVD industry** meet traceability requirements of the **EC IVD Directive.**

A quality assured database:
All data examined with respect to conformity with appropriate international documentary standards.

Certified Reference Materials
ISO 15194 **(National Metrology Institutes)**

ISO 17025
ISO 15195
ISO 15193

ISO standards for compliance with Traceability Requirements

ISO 17511: 2020 **In vitro diagnostic medical devices - Requirements for establishing metrological traceability of values assigned to calibrators, trueness control materials and human**

ISO 15193:2009 **Requirements for content and presentation of reference measurement procedures** (under revision)

ISO 15194:2009 **Requirements for certified reference materials and the content of supporting** (under revision)

ISO 15195: 2018 **Laboratory medicine — Requirements for the competence of calibration laboratories using reference measurement procedures**

JCTLM Accurate results for patient care

BIPM

ISO 17511: Establishing Metrological Traceability for IVD MDs


INTERNATIONAL STANDARD

ISO 17511

Second edition
2020-04

In vitro diagnostic medical devices — Requirements for establishing metrological traceability of values assigned to calibrators, trueness control materials and human samples

Dispositifs médicaux de diagnostic in vitro — Exigences pour l'établissement d'une traçabilité métrologique des valeurs attribuées aux étalons, aux matériaux de contrôle de la justesse et aux échantillons humains

ISO

Reference number
ISO 17511:2020(E)

© ISO 2020

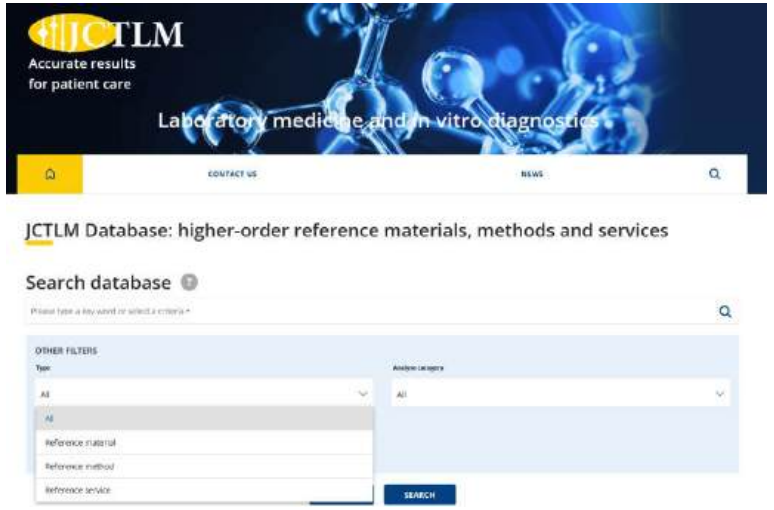
6 model calibration hierarchies described:

1) **Cases with RMPs and primary RMs**
2) **Cases with a primary RMP that defines the measurand**
3) **Cases for measurands defined by a RMP calibrated with a particular primary calibrator**
4) **Cases with an international conventional calibrator that defines the measurand**
5) **Cases with metrological traceability supported by an international harmonization protocol**
6) **Cases for measurands with metrological traceability only to manufacturer's internal arbitrarily defined RM(s)**

What has JCTLM delivered?

A Quality assured database, for *in vitro* diagnostics, of:

a) Higher Order Reference Materials
b) Reference Measurement Procedures
c) Laboratory Reference Measurement Services



www.jctlmdb.org

An education resource for traceability in laboratory medicine:

www.jctlm.org

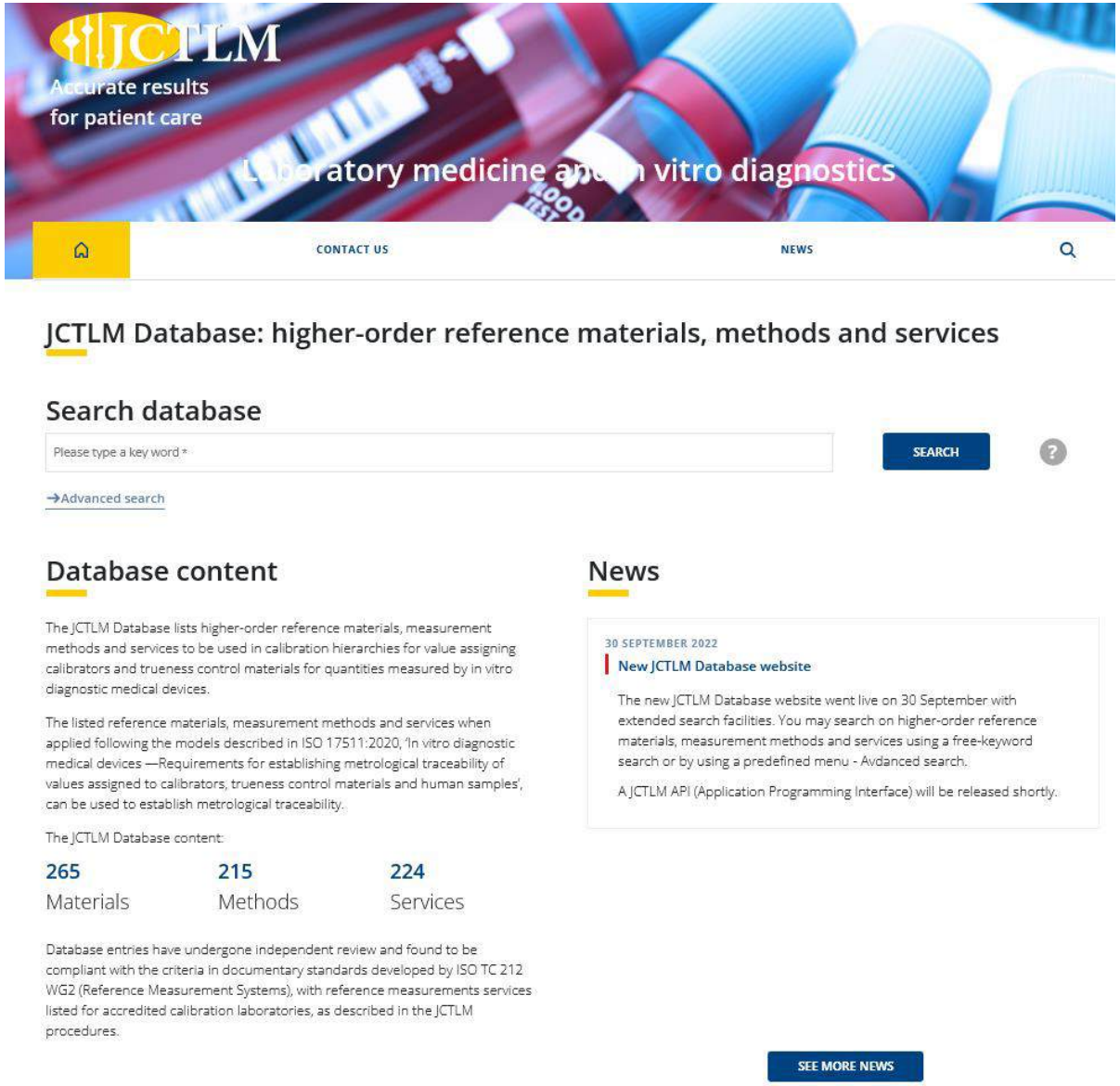
Vision for the JCTLM

JCTLM
Accurate results for patient care

Our Objective

To have all IVD MD manufacturers, regulators and laboratory medicine professionals worldwide use and refer to our database when claiming accuracy of diagnostic results.

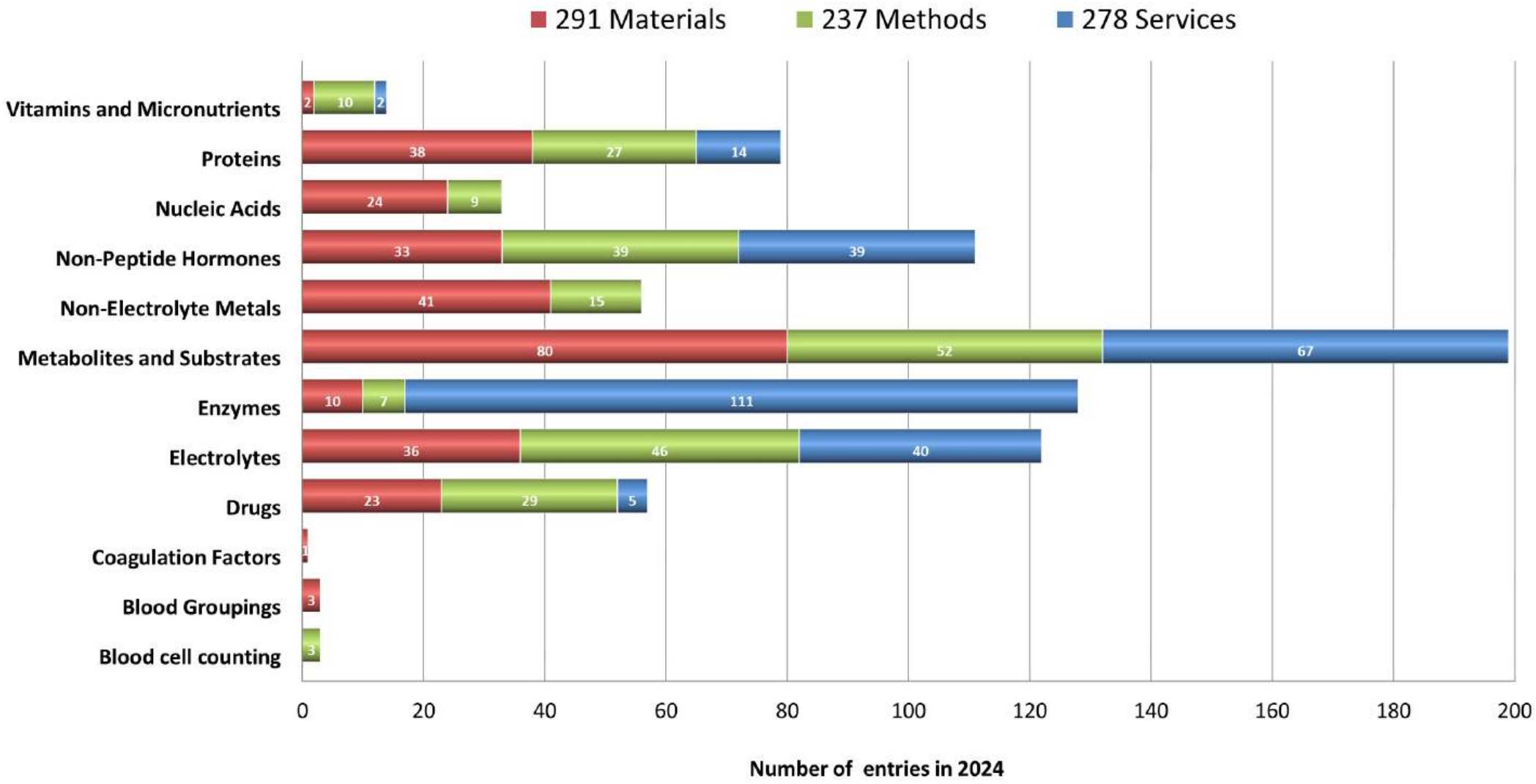
www.jctlmdb.org



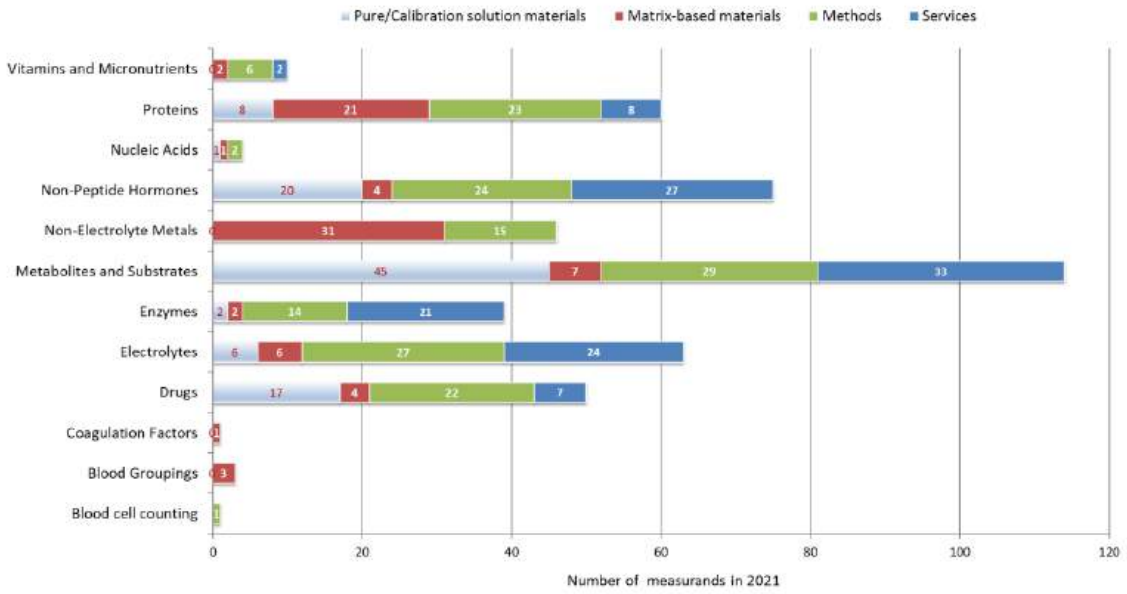
Version 2.0
Went Live:
3 October 2022

JCTLM Database Contents (April 2024)

JCTLM
Accurate results for patient care



JCTLM Database (www.jctlmdb.org): Contents

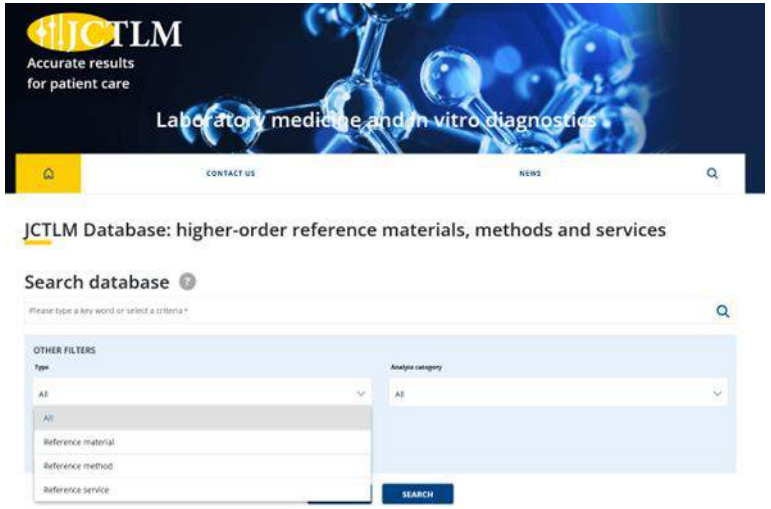


The JCTLM Database content:

265 Materials

215 Methods

224 Services



- Annual nomination and review cycle
- Around 100 nominations treated each year
- 11 review teams with expert reviewers
- New entries published each year that meet ISO standard requirements

Standardizing Chemical Measurements Worldwide Example: Diabetes Care

- **Over 420 million people worldwide have diabetes****
- **Diabetes is a major cause of blindness, kidney failure, heart attacks, stroke and lower limb amputation**
- **Diabetes affects 34.2 million people In the US (10.5% of the US population)***
- **$ 327 billion – estimated diabetes costs in the U.S. in 2017 (direct and indirect for diagnosed cases)***
- **3.9 million people diagnosed with diabetes in the UK †**
- **90% of diagnoses are for Type 2 Diabetes**
- **Biomarkers of interest include: Glucose, HbA1c, C-peptide**

**WHO, 13 April 2021

†Diabetes in the UK 2019 : key statistics on diabetes (Diabetes UK)

*Centers for Disease Control and Prevention. National diabetes statistics report 2020

measurement procedure (ms.)

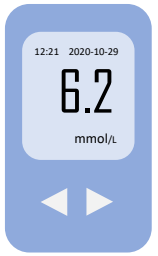
ms. 1
Quantitative Nuclear Magnetic Resonance (qNMR) procedure for purity and identity assessment

ms. 2
Primary reference measurement procedure for calibrator. Weighing of the certified primary reference material m. 1

ms. 3
Reference measurement procedure for the measurand. Isotope dilution mass spectrometry of the diluted certified primary reference material m. 2 conforming to ISO 15193

ms. 4
Manufacturers selected measurement procedure

ms. 5
Manufacturers standing measurement procedure



ms. 5
End-users measurement device

Refernce material (m.)

m. 1
Certified primary reference material conforming to ISO 15194

m. 2
Primary calibrator - prepared as solution of m. 1 in water

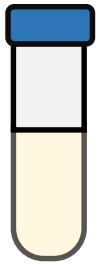
m. 3
Secondary, commutable certified reference materiial conforming to ISO 15194. Matrix is pooled human plasma

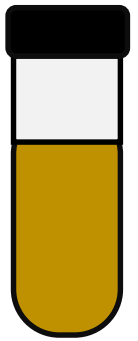
m. 4
Manufacturers working calibrator

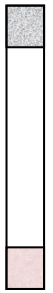
m. 5
Calibrator for the end-user measurement device

m. 6
Human sample with result


National Institute of Standards & Technology
Certificate of Analysis
Standard Reference Material® 917c
D-Glucose (Dextrose)







End users

Metrology Institutes and Reference Labs

Manufacturers

JCTLM
Accurate results for patient care

Glucose in Serum: Primary Reference Material

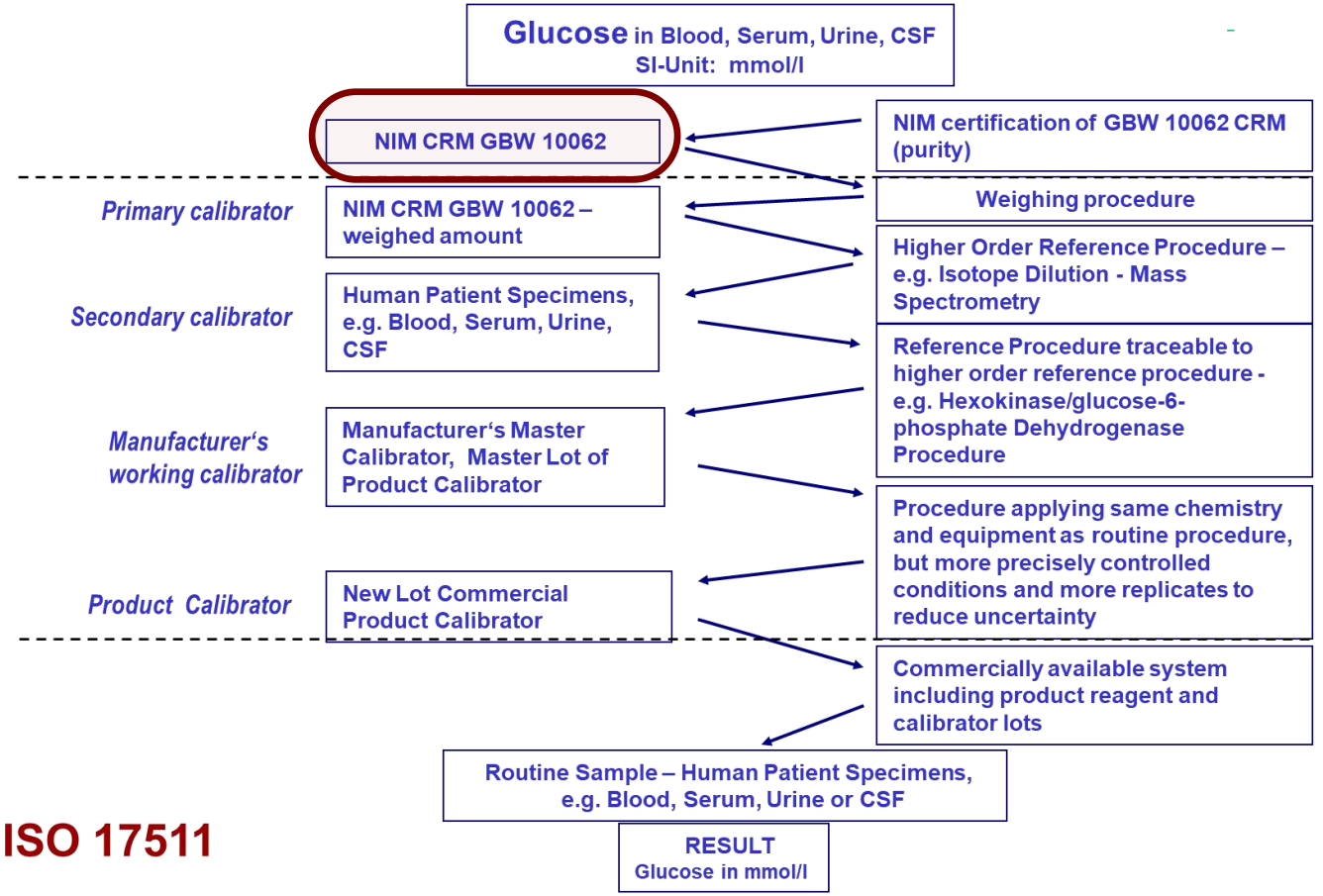
glucose in glucose crystalline material

National Institute of Metrology (NIM), China

Phone: +86 10 6422 1811 **Email:** crmservice@nim.ac.cn

Fax: +86 10 6421 3149 **Web:** http://www.nim.ac.cn/

Name of the reference material	NIM CRM GBW 10062, Purity of Glucose
Quantity	Mass fraction
Analyte certified/assigned value	0.996 g/g
Expanded uncertainty (level of confidence 95 %)	0.003 g/g
Reference(s) on commutability	Not applicable: a high-purity material used as a primary calibrator for higher order reference methods
Other relevant publication(s)	Establishment of the purity values of carbohydrate certified reference materials using quantitative nuclear magnetic resonance and mass balance approach, C. Quan, *Food Chemistry*, 2014, **153**, 378-386
Traceability	traceable to SI
CRM listing	List I



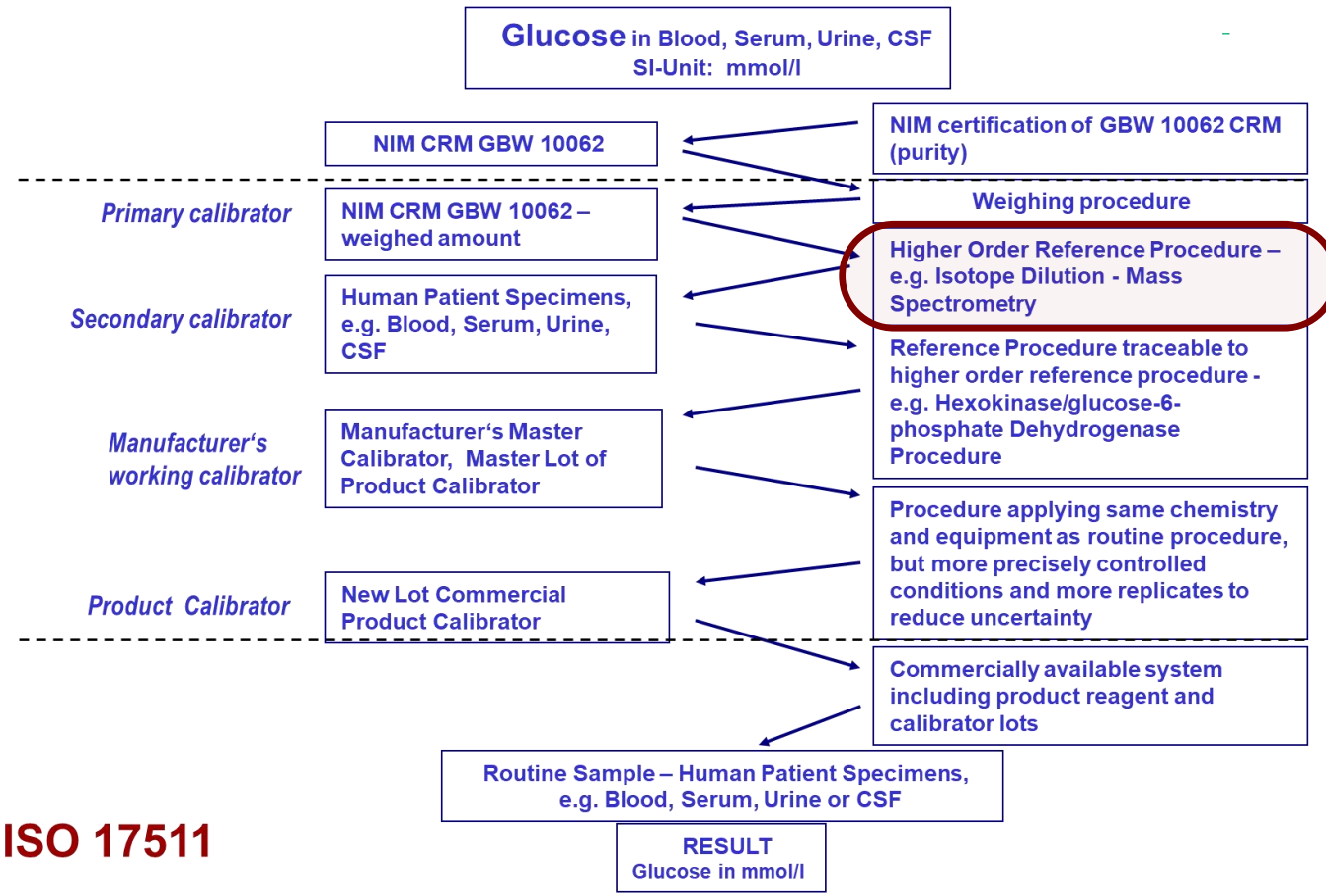
ISO 17511

JCTLM
Accurate results for patient care

Glucose in Serum: Reference Measurement Procedure

University of Ghent reference method for glucose	
Applicable matrice(s)	lyophilized, fresh, or frozen human serum
Full description of technique(s)	ID/GC/MS
Quantity	Amount-of-substance concentration
Applicable range	1 mmol/l to 20 mmol/l
Expected uncertainty (level of confidence 95%)	1 % to 2 %
Reference(s)	*Clin. Chem.*, 1993, **39**, 1001-1006 *Clin. Chem.*, 1993, **39**, 993-1000 *Eur. J. Clin. Chem. Clin. Biochem.*, 1996, **34**, 853-860
Comparability assessment study(ies)	EUROMET 563
JCTLM DB identification number	NRMeth 4

Liquid chromatography mass spectrometry method for glucose in blood serum NCCL ID LC-MS/MS reference measurement procedure for glucose	
Applicable matrice(s)	human serum; fresh, frozen or lyophilized
Full description of technique(s)	Isotope Dilution Mass Spectrometry (IDMS), Liquid Chromatography Mass Spectrometry (LCMS)
Quantity	Amount-of-substance fraction
Applicable range	1.5 mmol/L to 25 mmol/L
Expected uncertainty (level of confidence 95%)	0.5 % to 1.5 %
Reference(s)	Determination of serum glucose by isotope dilution liquid chromatography-tandem mass spectrometry: a candidate reference measurement procedure, Zhang T, et al., *Analytical Bioanalytical Chemistry*, 2016, **408**(26), 7403-7411
Comparability assessment study(ies)	Agreement between the ID LC-MS/MS and the ID GC-MS reference measurement procedures for Glucose, Electronic Supplement Material of Analytical Bioanalytical Chemistry 2016 publication. IFCC External Quality assessment scheme for Reference Laboratories in Laboratory Medicine (RELA), lab code 18, Results year 2012 and 2014
JCTLM DB identification number	C14RMP11



ISO 17511

Glucose in Serum: Measurement Services from Reference Laboratories

Instand e.V., Germany

Phone: +49 211 1592 1337
Fax: +49 211 1592 1356
Web: http://www.instand-ev.de

Contact person: Dr. Patricia Kaiser
Email: Kaiser@instand-ev.de

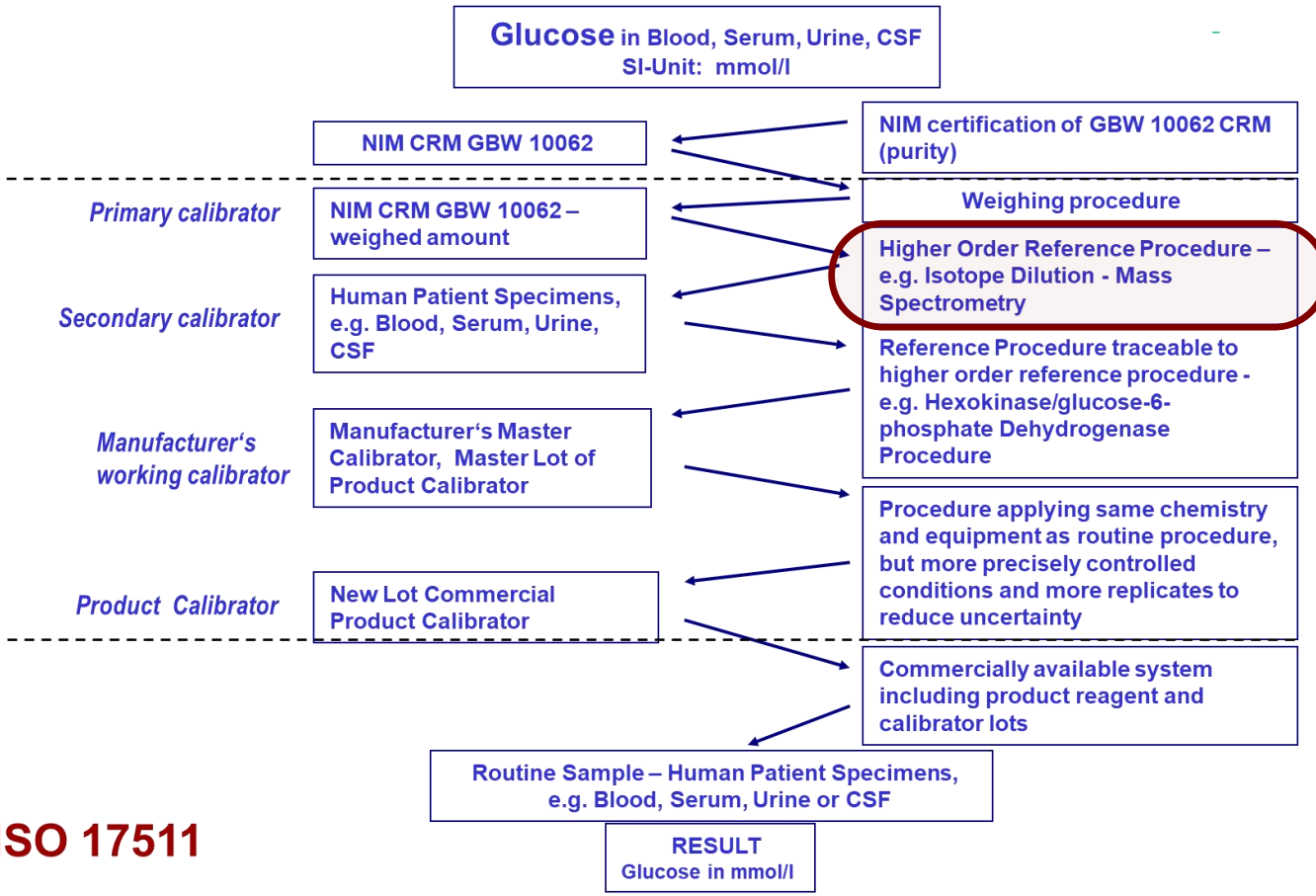
Analyte	glucose
Material or matrix	blood serum, blood plasma
Applicable material or matrix	fresh, frozen or lyophilized blood serum or plasma
Quantity	Amount-of-substance concentration
Service measurement range	1 mmol/L to 60 mmol/L
Expanded uncertainty (level of confidence 95%)	1.0 % The stated expanded uncertainty value corresponds to the best measurement capability.
Interlaboratory comparison results	RELA - IFCC External Quality assessment scheme for Reference Laboratories in Laboratory Medicine at http://www.dgkl-rfb.de:81/index.shtml
Measurement principle	GC-ID/MS
JCTLM reference measurement method/procedure	University of Ghent reference method for glucose

LNE, France

Phone: +33 (0) 140 434 075
Fax: +33 (0) 140 433 737
Web: http://www.lne.fr

Contact person: Dr Vincent DELATOUR
Email: vincent.delatour@lne.fr

Analyte	glucose
Material or matrix	blood serum, calibration solution
Applicable material or matrix	lyophilized, fresh, or frozen human serum, calibration solution
Quantity	Amount-of-substance concentration
Service measurement range	1.6 mmol/L to 20 mmol/L
Expanded uncertainty (level of confidence 95%)	2 % to 1 % The expanded uncertainty is relative.
Interlaboratory comparison results	RELA - IFCC External Quality assessment scheme for Reference Laboratories in Laboratory Medicine at http://www.dgkl-rfb.de:81/index.shtml
Measurement principle	ID-GC/MS
JCTLM reference measurement method/procedure	University of Ghent reference method for glucose



Glucose in Serum: Performance of Reference Laboratories in Comparisons

Laboratory performance in IFCC RELA scheme

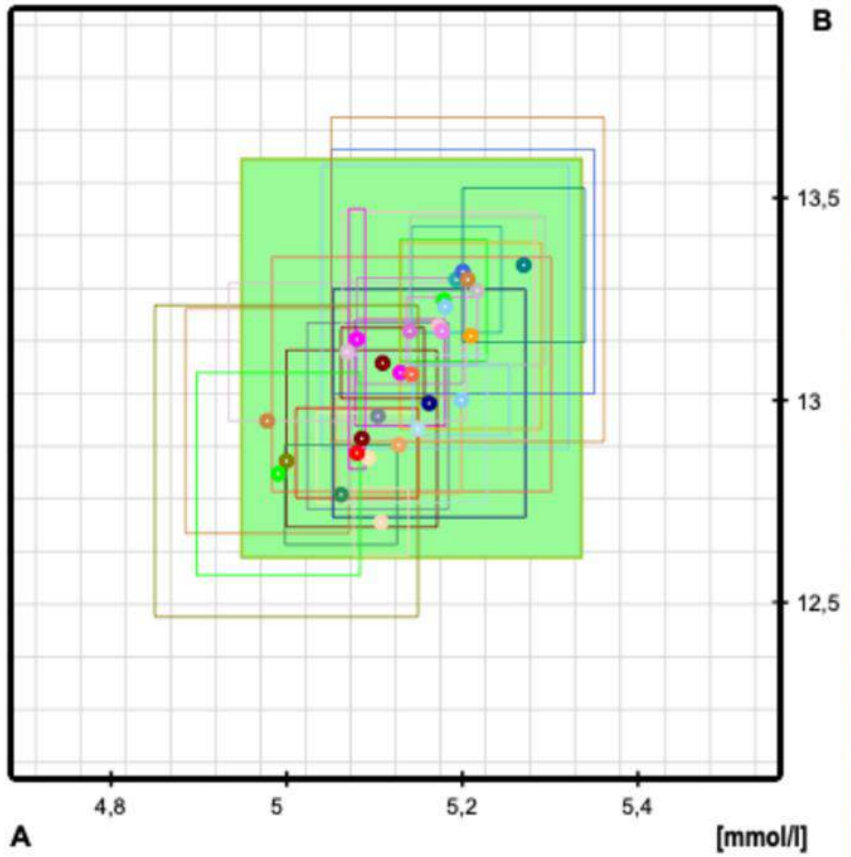
RELA 2020

All or choose Lab ...

select lab analytes | full address

Glucose | show result plot

with limits of equivalence



For highlighting a specific result please click on the corresponding result line.

Result lines printed in bold indicate JCTLM listed services.

Labcode	A	e.u. A	B	e.u. B	Method
3	**5.129**	**0.051**	**13.07**	**0.131**	**ID/GC/MS**
5	**5.086**	**0.087**	**12.91**	**0.219**	**ID/GC/MS**
6	**4.978**	**0.093**	**12.95**	**0.279**	**spectrophotometry**
18	**5.178**	**0.05**	**13.25**	**0.152**	**ID/LC/MS/MS**
25	**5.18**	**0.14**	**13.23**	**0.35**	**ID/GC/MS**
27	**5.193**	**0.052**	**13.3**	**0.13**	**ID/GC/MS**
30	5.093	0.058	12.86	0.111	ID/GC/MS
39	5.103	0.08	12.96	0.23	spectrophotometry
48	5.163	0.11	12.99	0.28	spectrophotometry
51	**5.21**	**0.08**	**13.16**	**0.23**	**spectrophotometry**
54	**5.14**	**0.06**	**13.17**	**0.13**	**ID/GC/MS**
61	5.174	0.11	13.18	0.28	spectrophotometry
63	5.143	0.158	13.06	0.29	spectrophotometry
65	**5.2**	**0.15**	**13.32**	**0.3**	**ID/LC/MS/MS**
87	**5.08**	**0.07**	**12.87**	**0.11**	**spectrophotometry**

JCTLM
Accurate results for patient care

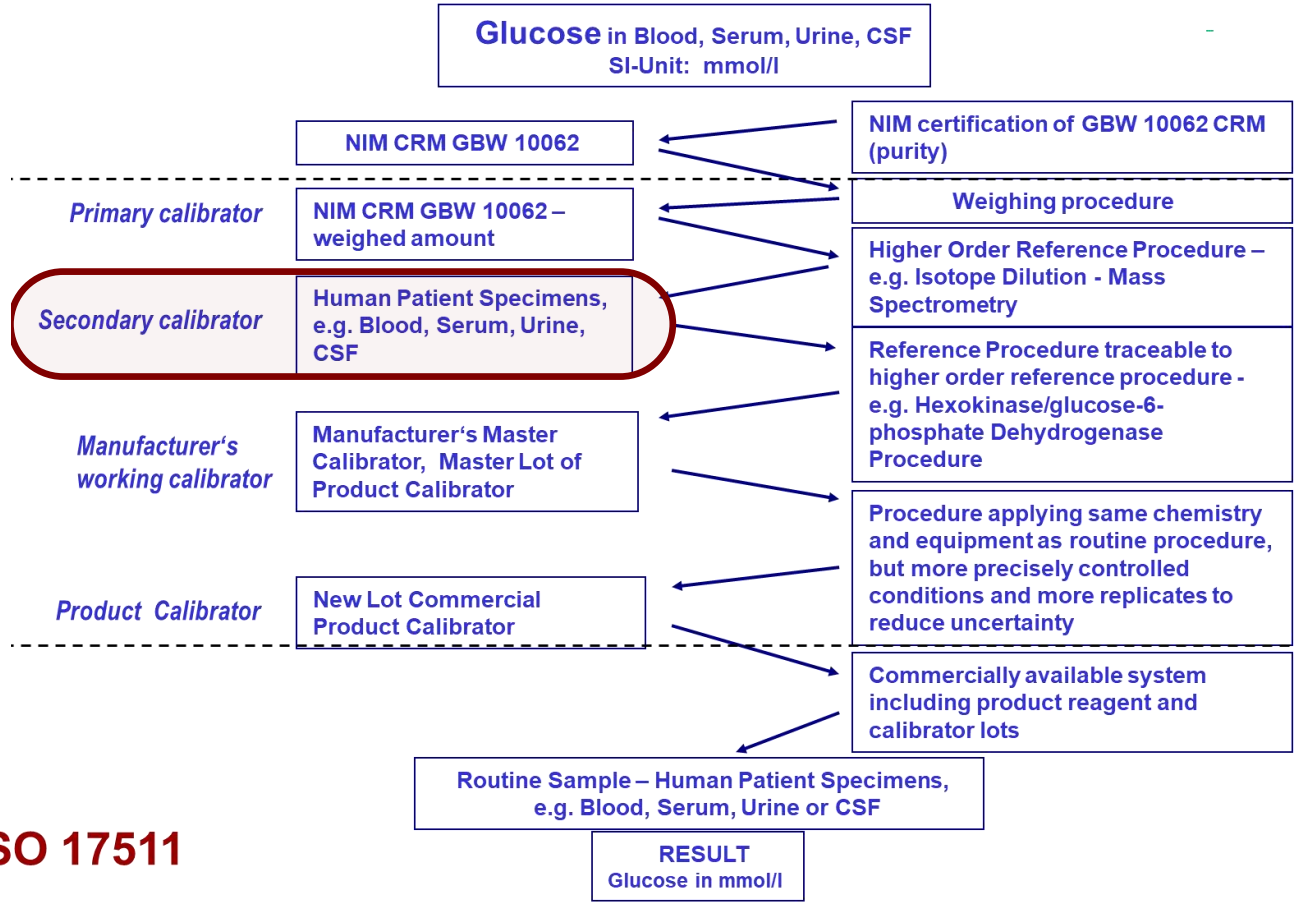
Glucose in Serum: Matrix Reference Materials

glucose in frozen human serum

Laboratoire National de Métrologie et d'Essais (LNE), France

Phone: +33 (0)1 40 43 40 75 **Email:** vincent.delatour@lne.fr
Fax: +33 (0)1 40 43 37 05 **Web:** http://www.lne.eu/

Name of the reference material	LNE CRM Bio 101a, Glucose, creatinine, total cholesterol, total glycerides, HDL-cholesterol, LDL-cholesterol in frozen human serum
Quantity	Amount-of-substance concentration
Analyte certified/assigned value	4.148 mmol/l to 11.663 mmol/l
Expanded uncertainty (level of confidence 95 %)	0.064 mmol/l to 0.165 mmol/l
Reference(s) on commutability	Commutability assessment of external quality assessment materials with the difference in bias approach: are acceptance criteria based on medical requirements too Strict? Delatour et al., *Clinical Chemistry*, 2016, **62**(12), 1670-1671
Traceability	SI
CRM listing	List I

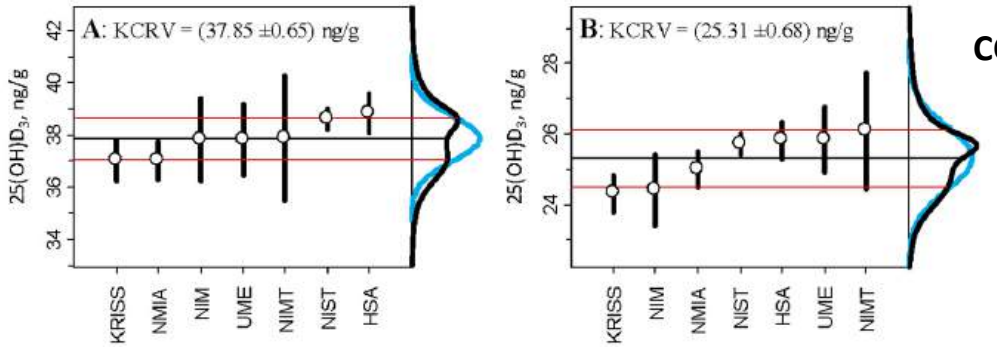


ISO 17511

JCTLM
Accurate results for patient care

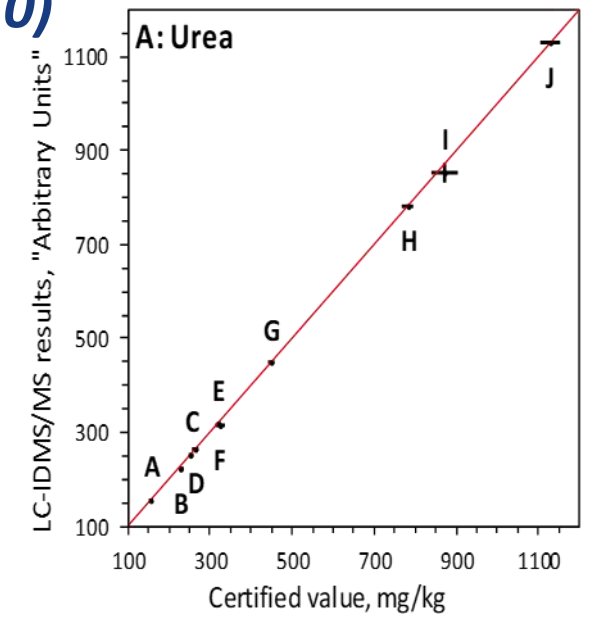
CCQM Key Comparisons for Clinical Matrix Reference Materials and Methods

- Cholesterol in serum
  - *CCQM-K5 (1999)*
- Glucose in serum
  - *CCQM-K11 (2001, 2005)*
- Creatinine in serum
  - *CCQM-K12, K80 (2001, 2005, 2010)*
- Vitamin D in serum
  - *CCQM-K132 (2015)*
- Urea and Uric Acid
  - *CCQM-K142 (2016)*
- Selected peptides
  - *CCQM-K115 (2018-9)*
- more in the works…

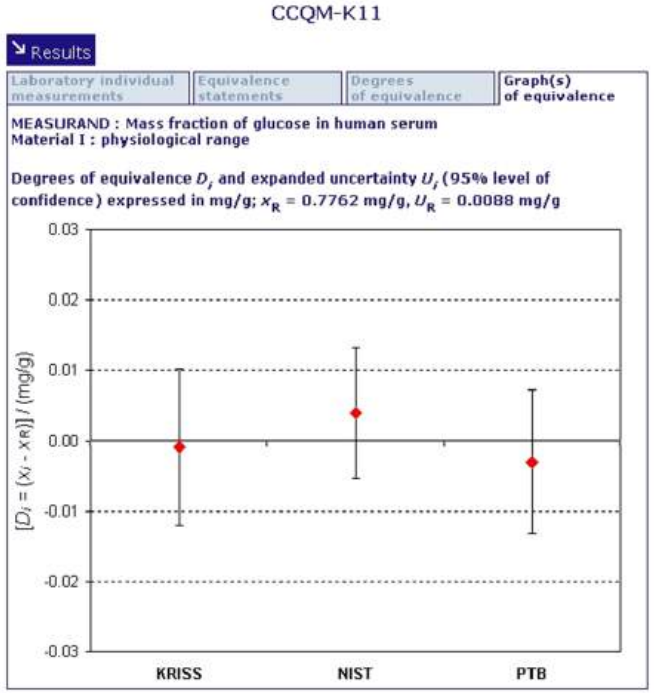


CCQM-K132 Vitamin D in Serum

CCQM
BIPM



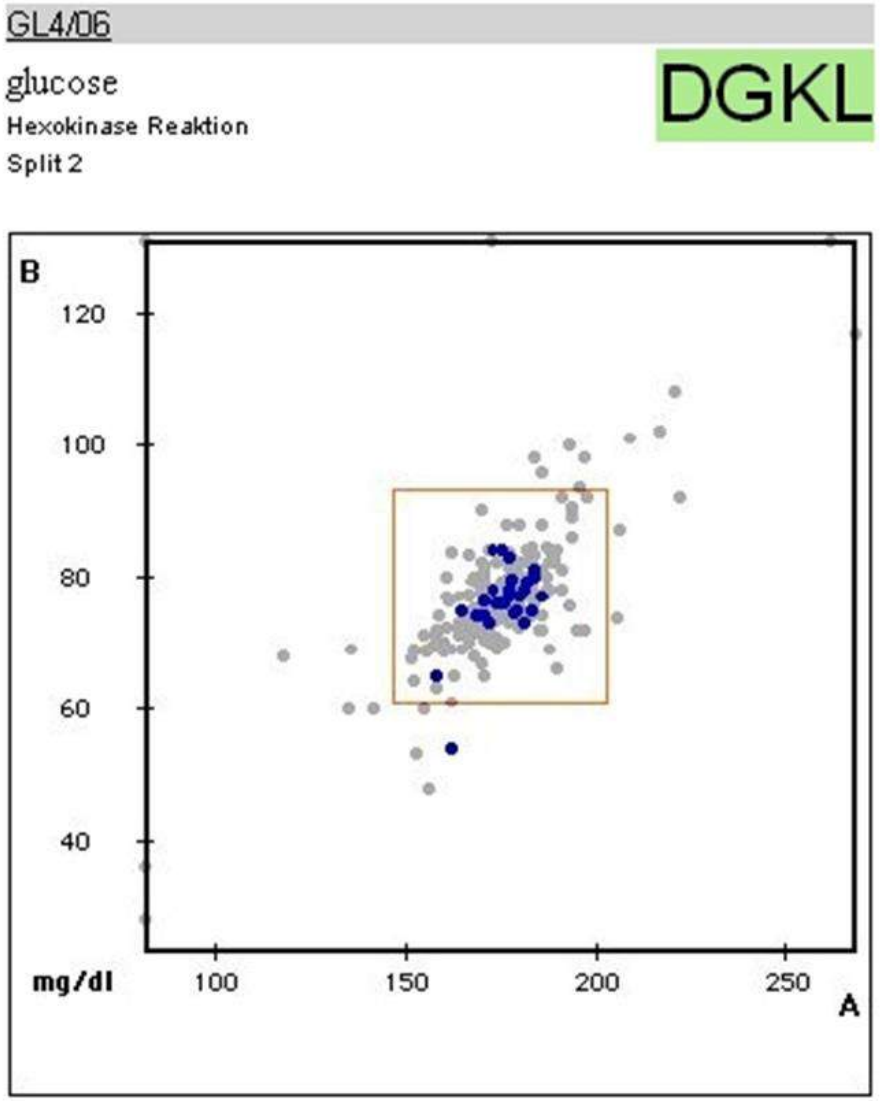
CCQM-K142 Urea and uric acid in serum and plasma materials: HSA and NIST

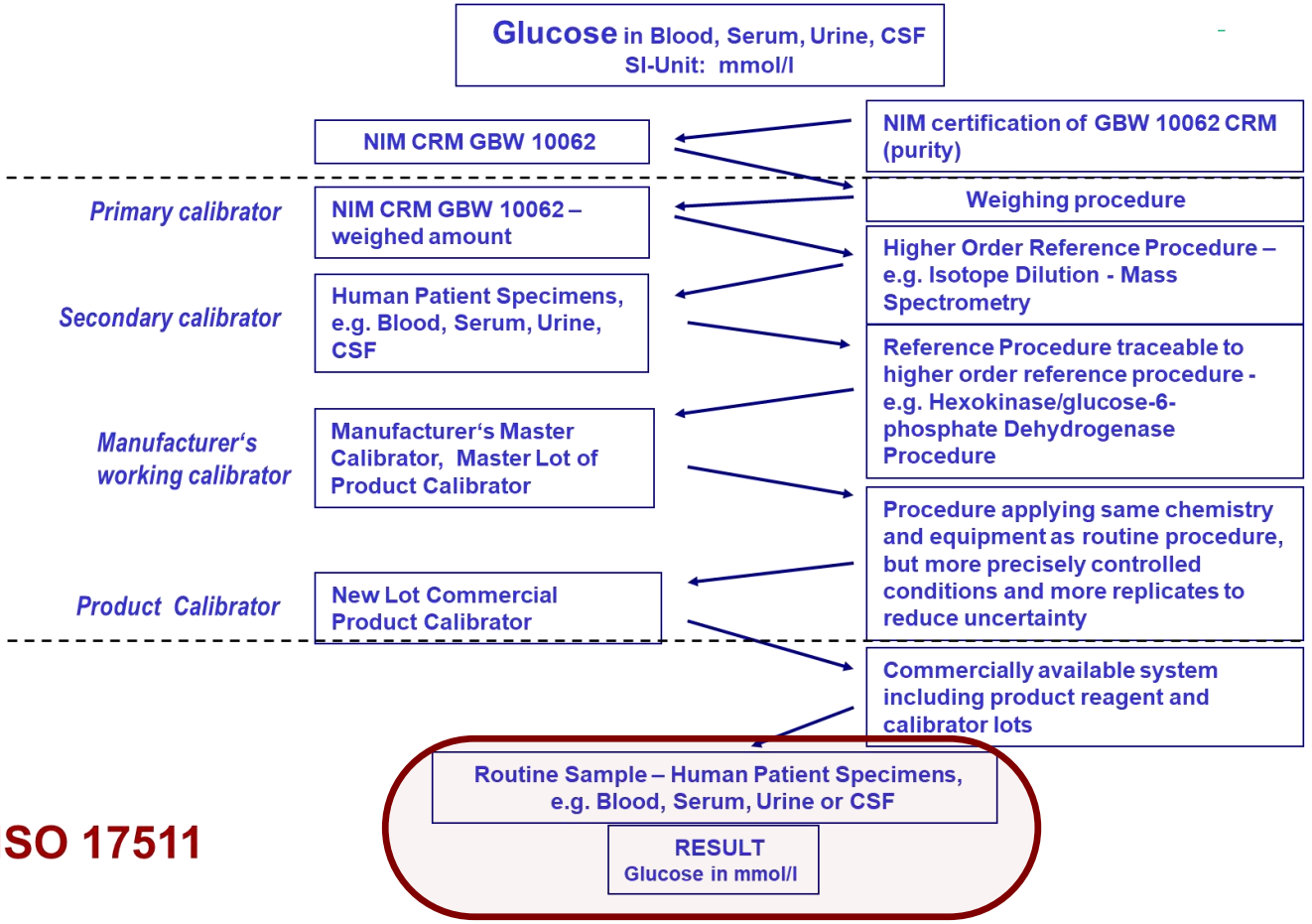


Glucose in Serum: Clinical Laboratory Performance

Proficiency Testing Scheme Results for Glucose in Serum

- Results agree with traceable reference value and within acceptance criteria





ISO 17511

JCTLM
Accurate resul
for patient ca

150 Years of the Metre Convention:
Responding to metrology challenges in ‘Health and Life Sciences’

CELEBRATING BIPM 150
1875 – 2025

Join the Celebration – 150 Years of the Metre Convention!

Open Call for posters

Deadline for abstract submission
15 December 2024

We invite you to celebrate the 150th anniversary of the Metre Convention and the BIPM with a poster on your work on a metrology challenge in one of the 9 topics listed below.

3

Health and Life Sciences

Submit

JCTLM

Accurate results
for patient care

Thank you for your attention

jctlm@bipm.org