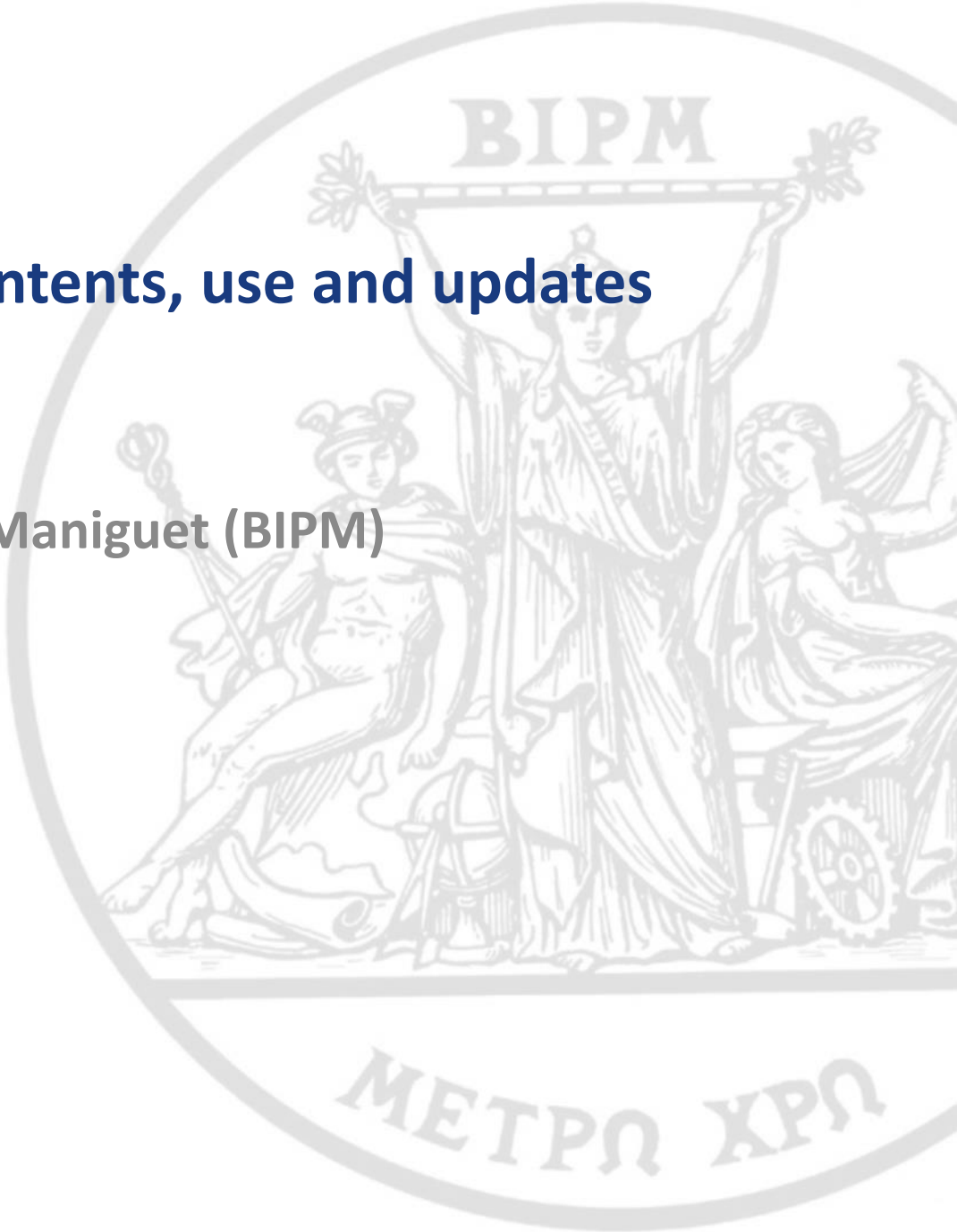
JCTLM database: Contents, use and updates

R.I. Wielgosz and S. Maniguet (BIPM)



Bureau
International des
Poids et
Mesures

Outline of Presentation

- The BIPM and the JCTLM Database
- Assuring the Quality of Products in the Database
- Who is using the database?
- Impact of ISO TC 212 WG2 activities
- What's covered and what's not?
- What's the future?

Bureau International des Poids et Mesures (BIPM)

The International Bureau of Weights and Measures

- Intergovernmental organization with 56 Member States and 41 Associate States/economies, Established in 1875 to:

  … ensure and promote the global comparability of measurements, including providing a coherent international system of units for:

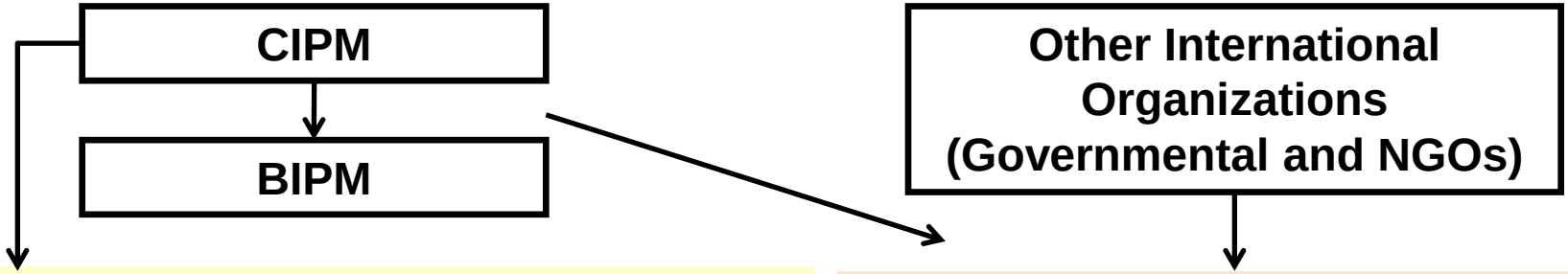
  - ***Scientific discovery and innovation,***
  - ***Industrial manufacturing and international trade,***
  - ***Sustaining the quality of life and the global environment.***

5 scientific departments:

- **Chemistry**
- Electricity
- Ionizing Radiation
- Mass
- Time

Bureau International des Poids et Mesures

BIPM Committees



- CCAUV Acoustics, Ultrasound and Vibration
- CCEM Electricity and Magnetism
- CCL Length
- CCM Mass and Related Quantities
- CCPR Photometry and Radiometry
- **CCQM Amount of Substance (Chemistry and Biology)**
- CCRI Ionizing Radiation
- CCT Thermometry
- CCTF Time and Frequency
- CCU Units

- JCGM: Guides in Metrology
- JCRB: CIPM-MRA
- JCTLM: Traceability in Laboratory Medicine
- DCMAS Network: Developing Economies

JCTLM

Metrology for Healthcare: *In vitro* diagnostics, Reference Measurement Systems Database

- BIPM provides the Secretariat for JCTLM
- Maintains the **JCTLM IVD Reference Measurement Systems Database**
- Coordinates the nomination and review process for database entries
- Contributes to ISO TC 212 WG2: revisions of ISO 17511 and ISO 15195

JCTLM database developed to help IVD industry meet metrological traceability requirements of the EU IVD Directive

Database Contains:

- **295 Certified Reference Materials**
- **170 Reference Methods**
- **130 Reference Measurement Services**

JCTLM Chair: Dr G. Myers (AACC)

JCTLM Executive Secretary: Dr R.I. Wielgosz (BIPM)
Dr S. Maniguet (BIPM)

Bureau International des Poids et Mesures

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

http://www.bipm.org/jctlm/

For use by (primarily)

a) IVD industry
b) Regulators

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JCTLM

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

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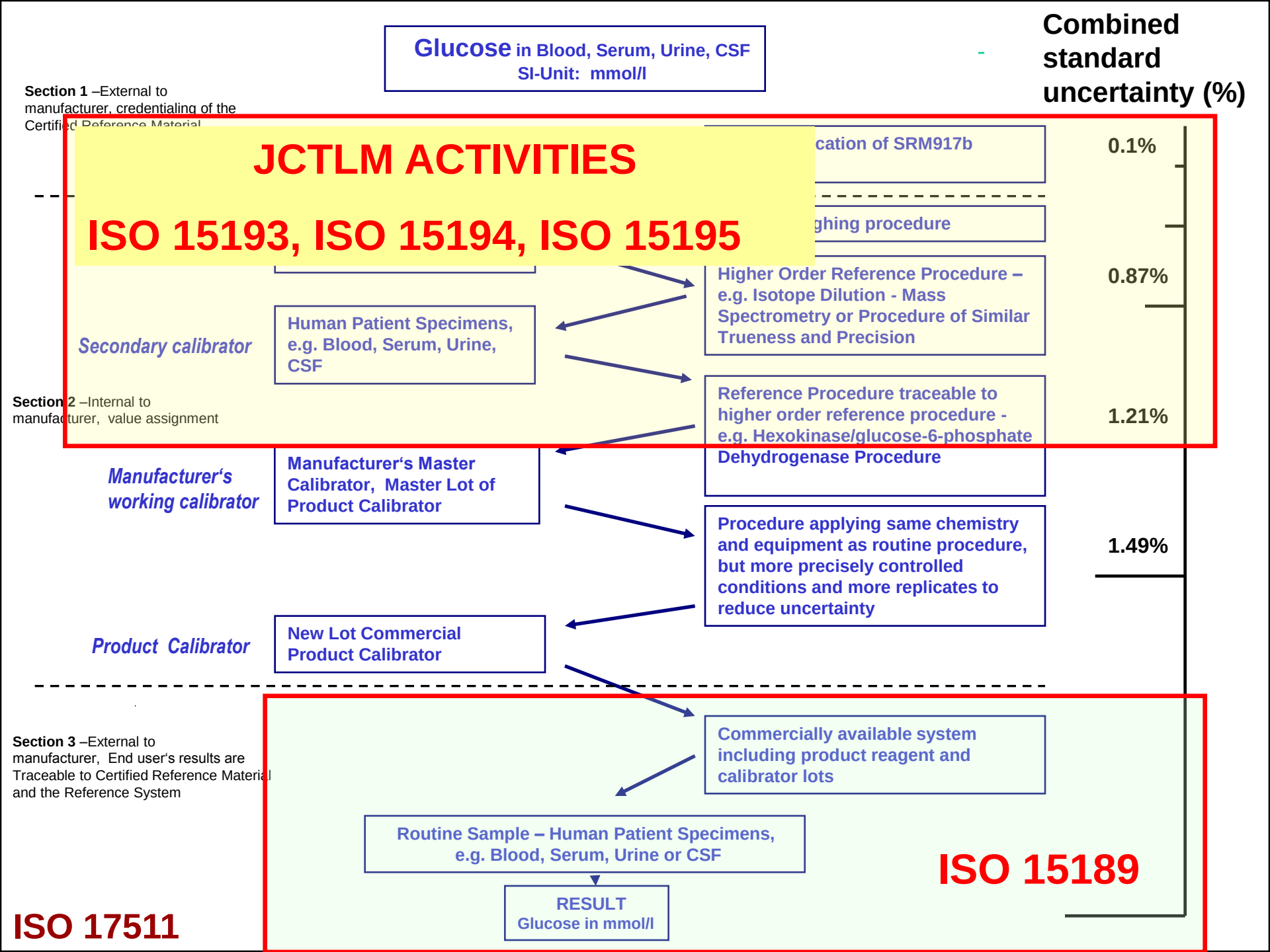
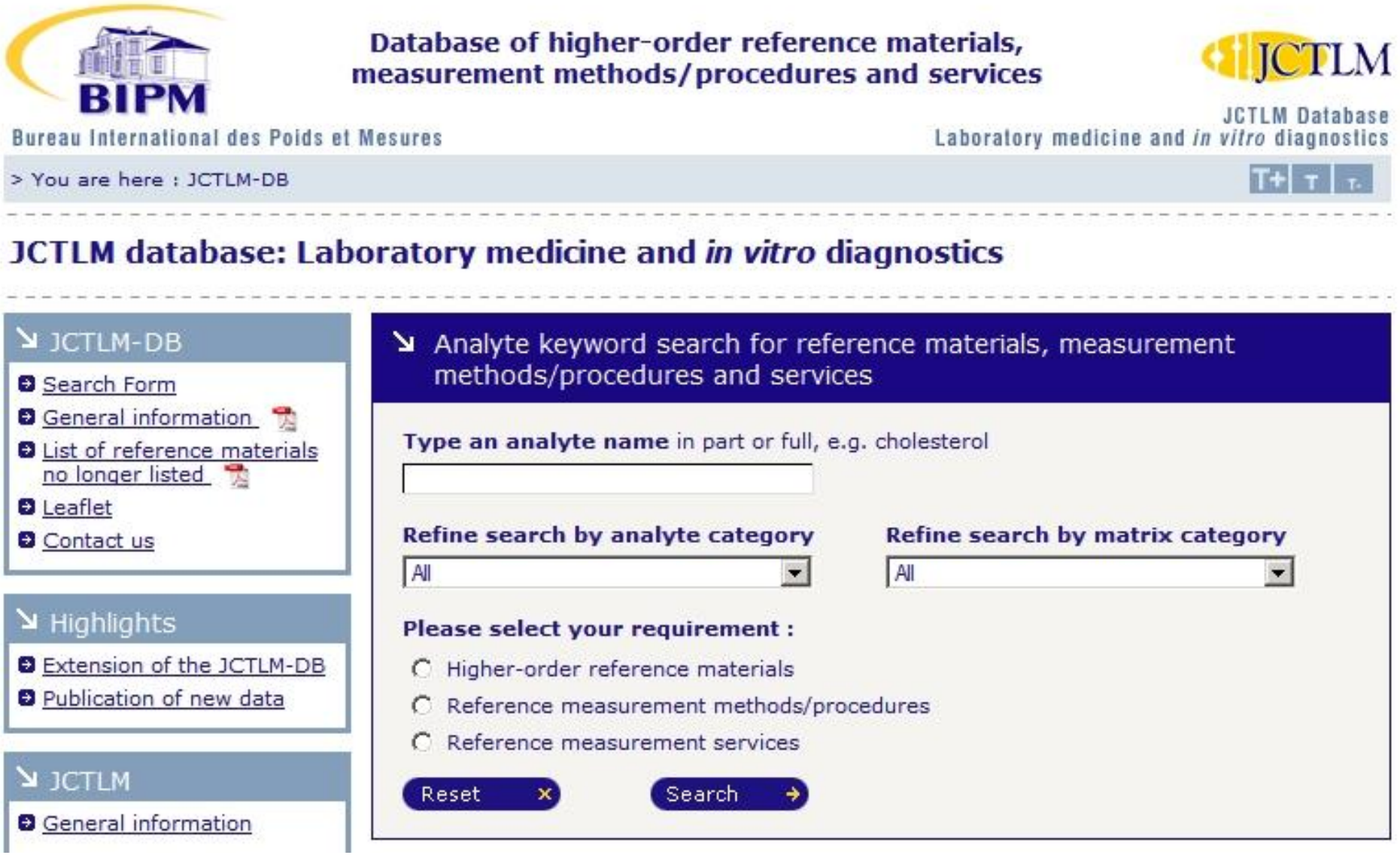
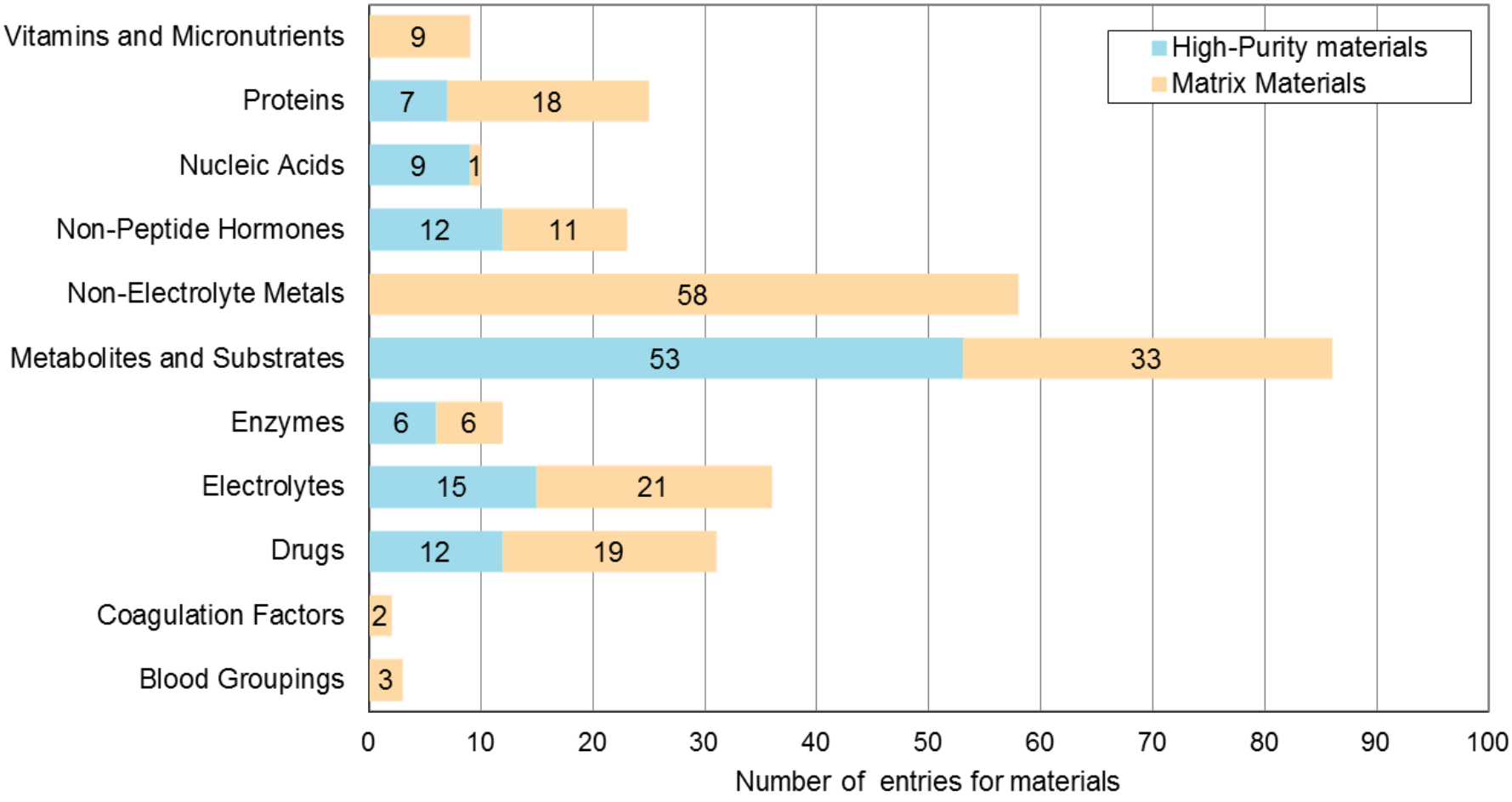

Glucose in Blood, Serum, Urine, CSF
SI-Unit: mmol/l
Combined standard uncertainty (%)
Section 1 –External to manufacturer, credentialing of the Certified Reference Material
JCTLM ACTIVITIES
ISO 15193, ISO 15194, ISO 15195
cation of SRM917b
0.1%
ghing procedure
Higher Order Reference Procedure – e.g. Isotope Dilution - Mass Spectrometry or Procedure of Similar Trueness and Precision
0.87%
Secondary calibrator
Human Patient Specimens, e.g. Blood, Serum, Urine, CSF
Section 2 –Internal to manufacturer, value assignment
Reference Procedure traceable to higher order reference procedure - e.g. Hexokinase/glucose-6-phosphate Dehydrogenase Procedure
1.21%
Manufacturer's working calibrator
Manufacturer's Master Calibrator, Master Lot of Product Calibrator
Procedure applying same chemistry and equipment as routine procedure, but more precisely controlled conditions and more replicates to reduce uncertainty
1.49%
Product Calibrator
New Lot Commercial Product Calibrator
Section 3 –External to manufacturer, End user's results are Traceable to Certified Reference Material and the Reference System
Commercially available system including product reagent and calibrator lots
Routine Sample – Human Patient Specimens, e.g. Blood, Serum, Urine or CSF
RESULT
Glucose in mmol/l
ISO 15189
ISO 17511

JCTLM Database : www.bipm.org/jctlm/



JCTLM DB: CRMs by analyte group



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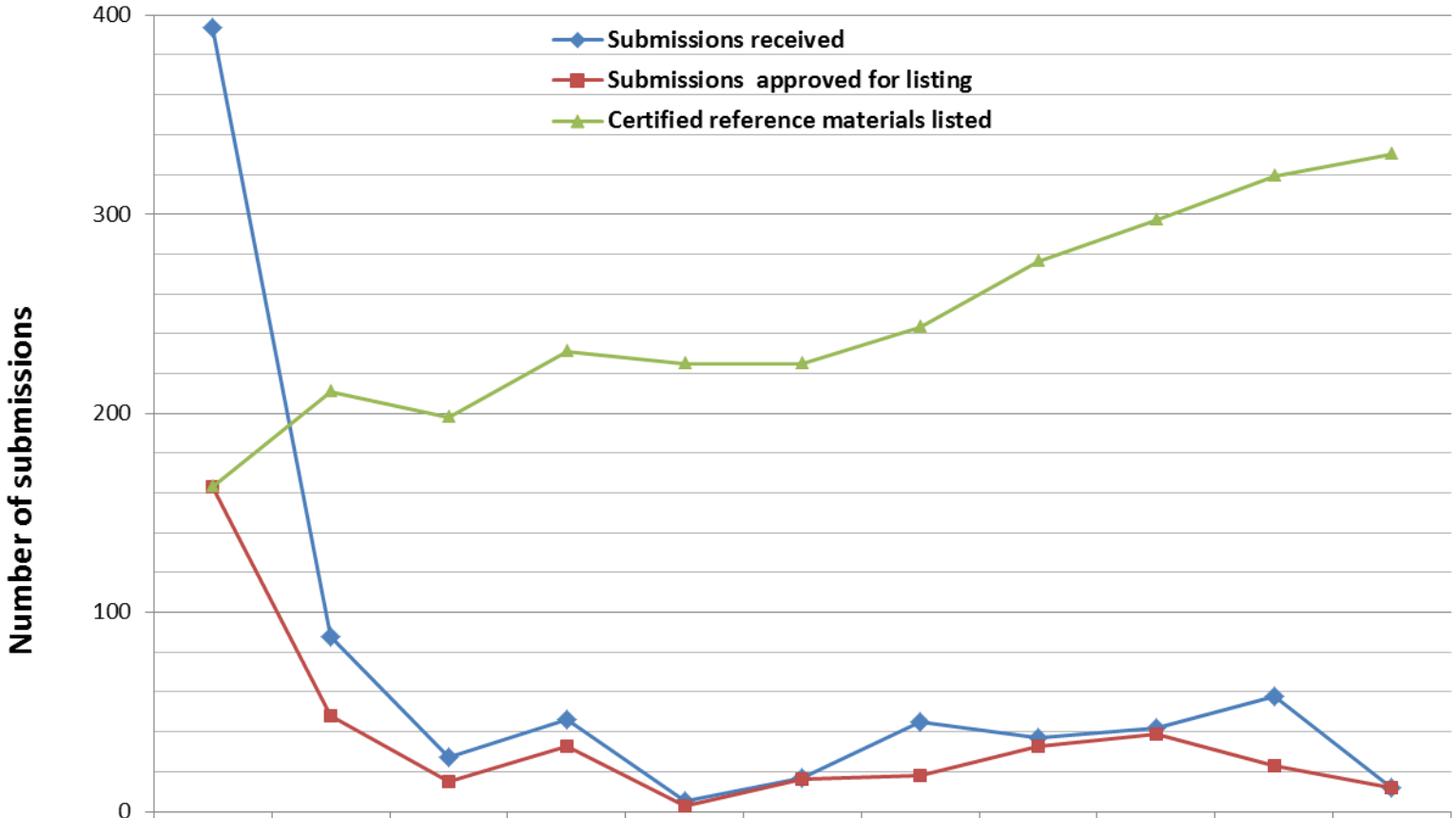
295 entries = **175** pure materials (calibration solution included) + **120** Matrix materials (June 2015)

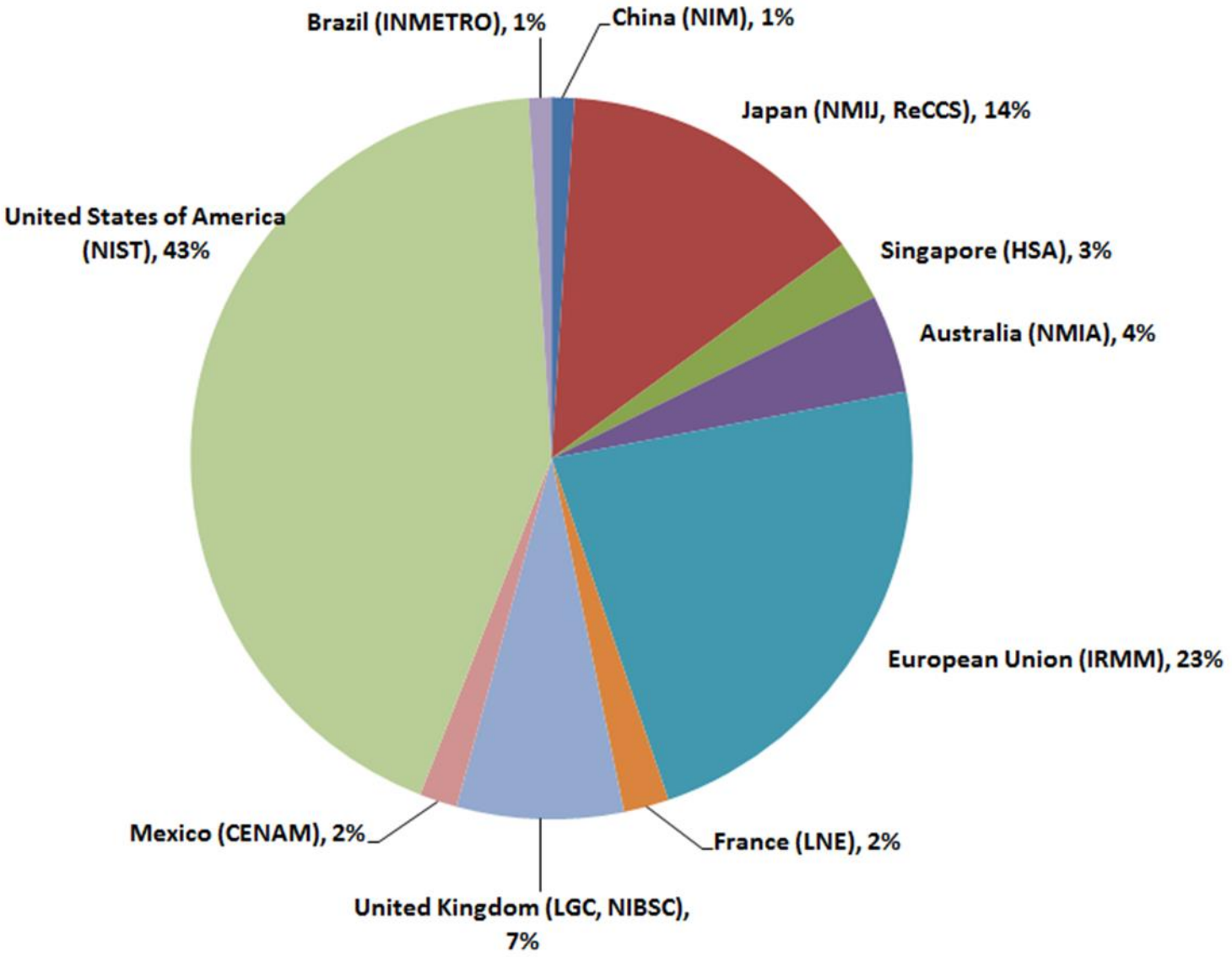
JCTLM Database Submissions – December 2014

Certified Reference Materials



	2004 (Cycle 1)	2005 (Cycle 2)	2006 (Cycle 3)	2007 (Cycle 4)	2008 (Cycle 5)	2009 (Cycle 6)	2010 (Cycle 7)	2011 (Cycle 8)	2012 (Cycle 9)	2013 (Cycle 10)	2014 (Cycle 11)
Submissions received	394	88	27	46	5	17	45	37	42	58	12
Submissions approved for listing	163	48	15	33	3	16	18	33	39	23	12
Certified reference materials listed	163	211	198	231	225	225	243	276	297	319	330

Source (country of origin) of CRMs in JCTLM Database



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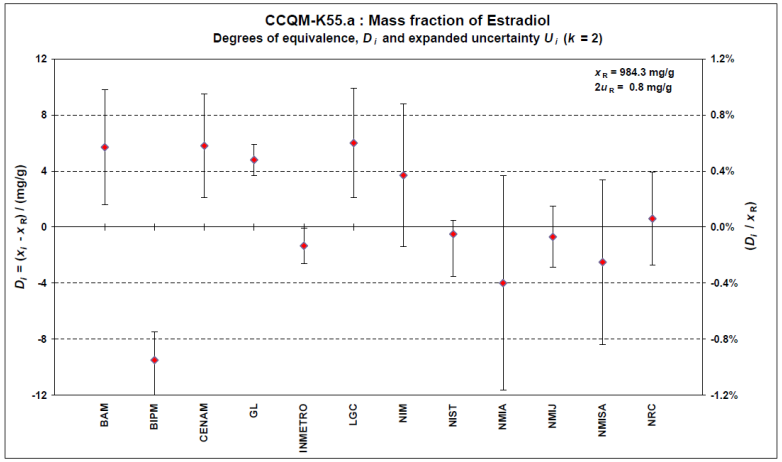
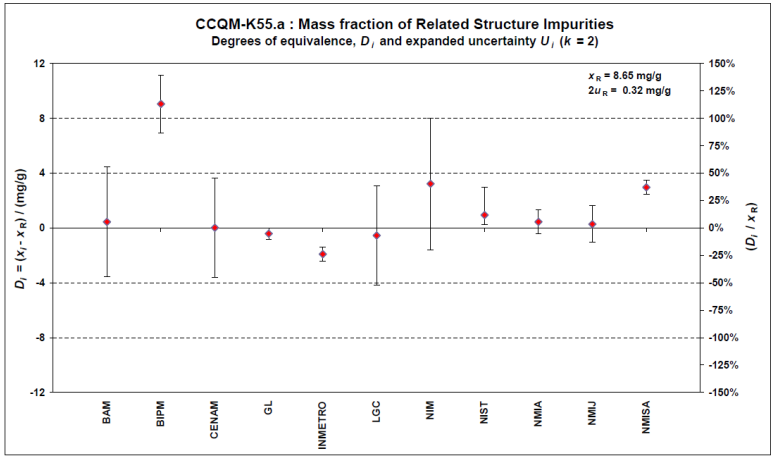
Assuring the Quality of JCTLM Listed Products: Key Comparisons (Estradiol, Primary Calibrator, CCQM-K55.a)

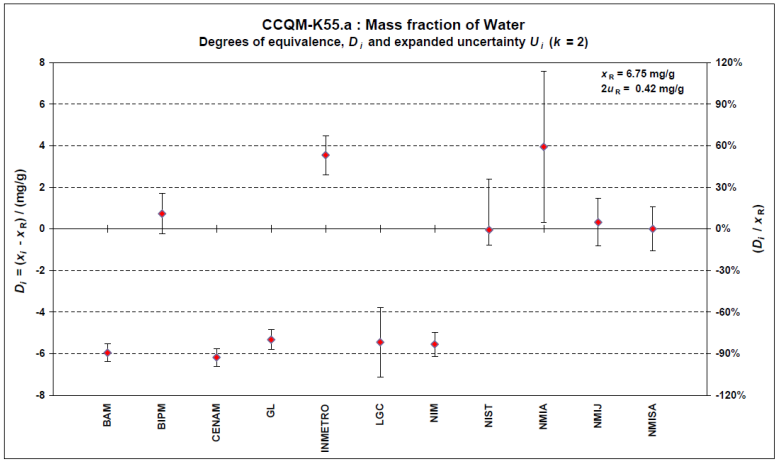
Mass fraction: Estradiol



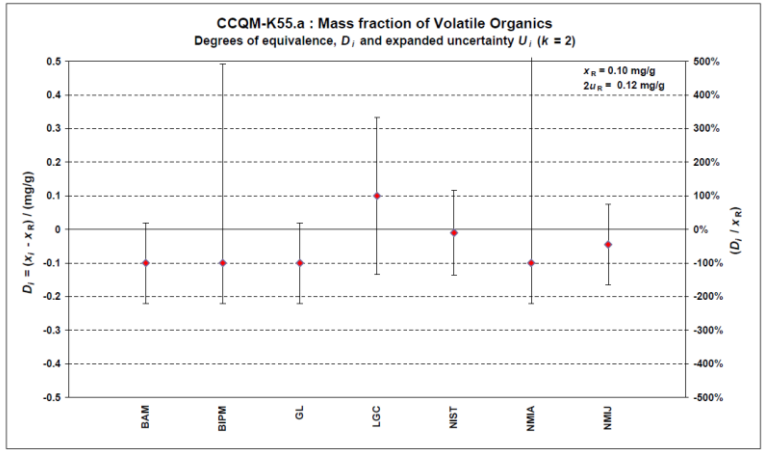
Mass fraction: Related Substances



Mass fraction: Water



Mass fraction: VOCs



Assuring the Quality of JCTLM Listed Products

Biological fluids and materials, Blood serum

United Kingdom, LGC (Laboratory of the Government Chemist)

Complete CMCs in Chemistry for Biological fluids and materials for United Kingdom (.pdf file)

Matrix or material	Analyte or component	Dissemination range of measurement capability		Range of certified values in reference materials	
		Mass fraction in mg/kg	Relative expanded uncertainty in %	Mass fraction in mg/kg	Absolute expanded uncertainty in mg/kg
serum	creatinine	3 to 50	0.3 to 0.5	3.1 to 50	0.5 to 3

Mechanism(s) for measurement service delivery: Calibration and ERM-DA250 to DA253
Expanded uncertainty for certified values estimated with k = ~ 2 (level of confidence 95%)
Uncertainty convention 1.
Approved on 06 December 2011
Internal NMI service identifier: LGC/Org-019

Calibration and Measurement Capabilities
Chemistry (not including pH and electrolytic conductivity)
Service details

KCDB

CMC – 'Capability'

creatinine in human serum

LGC Limited (LGC), United Kingdom

Phone : +44 (0)20 8943 8480
Fax : +44 (0)20 8943 7554
Email : uksales@lgcstandards.com
Web : http://www.lgc.co.uk

Name of the reference material	ERM-DA252a
Quantity	Mass concentration
Analyte certified/assigned value	3.1 mg/kg
Expanded uncertainty (level of confidence 95 %)	0.2 mg/kg
Other relevant publication(s)	Stokes P and O Connor G, *Journal of Chromatography B*, 2003,1,125-136
Traceability	SI
CRM listing	List I

This (Certified) Reference Material has been reviewed for compliance with ISO 15194:2003 but not been reviewed against ISO 15194:2009

List of higher-order reference materials

JCTLM

Available CRMs

CCQM Small Organic Primary Calibrator Comparison Program

Higher profile for Metrology and Traceability in Organic Analysis

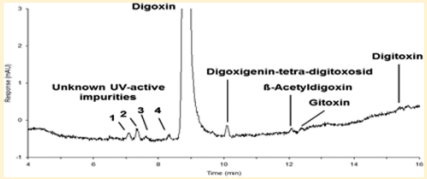
analytical chemistry — Article — pubs.acs.org/ac

Mass Balance Method for the SI Value Assignment of the Purity of Organic Compounds

Steven Westwood,* Tiphaine Choteau, Adeline Daireaux, Ralf Dieter Josephs, and Robert Ian Wielgosz

Bureau International des Poids et Mesures (BIPM), Pavillon de Breteuil, F-92312 Sèvres Cedex, (33) 1 45 07 70 57, France

Supporting Information



ABSTRACT: A mass balance method is described for determining the mass fraction of the main component of a high purity organic material. The resulting ... established to ... the SI and can be determined with a small associated measurement uncertainty. ... determined in this way are necessary as primary calibrators of reference measurement systems in order to underpin the metrological traceability of routine measurement results. The method has been applied to materials in which the main components were respectively theophylline, digoxin, 17β-estradiol, and aldrin. Its performance ... in validation ... international comparisons coordinated by the BIPM and is in principle applicable to a wide ... successfully applied to mass fraction assignments when the ... the results ... can achieve associated standard uncertainties ranging from 0.5 mg/g (for high purity materials or those containing well-characterized, stable minor components) to 2 mg/g (materials with a significant number or variety of impurities). It is in principle equally applicable to materials with a smaller mass fraction content of the main component.

2013: Published

2015: 17 citations

IUPAC

FUNDED

IUPAC Technical Report on *SI Value Assignment of the Purity of Organic Compounds for use as Reference Materials and Calibrators*

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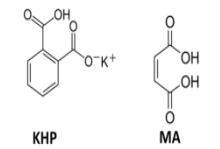
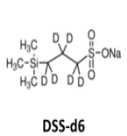
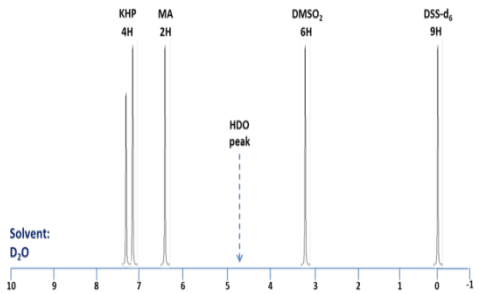
Universal Calibrators for qNMR





NMIJ — Bureau International des Poids et Mesures



Wider adoption of new technologies for purity assignment and increased availability of primary and secondary calibrator CRMs

Increase in availability of pure material CRMs for IVDs

JCTLM

	2012	2015
Number of CRMs	68	93
NMIs with CRMs	7	7

Reference Materials

USP U.S. Pharmacopeial Convention

BRITISH PHARMACOPOEIA

edqm European Directorate for the Quality of Medicines & HealthCare

FEUM FARMACOPEA de los Estados Unidos Mexicanos

CCQM Peptide Primary Calibrator Comparison Program

Enabling the adoption of SI traceable reference measurements systems

Body fluid		Method	‡Mean ALL sample
Urine	**	I	#2.9
		II	44.4
		III	13.4
		IV	35.1
		V	427.1
		VI	7.9
	*		
Plasma		I	#11.4
		II	13.0
		0	27.4
		IV	16.4
		V	124.6
		VI	17.3
		VII	12.4
		VIII	41.5

*nmol/L **nmol/mmol Creatinine

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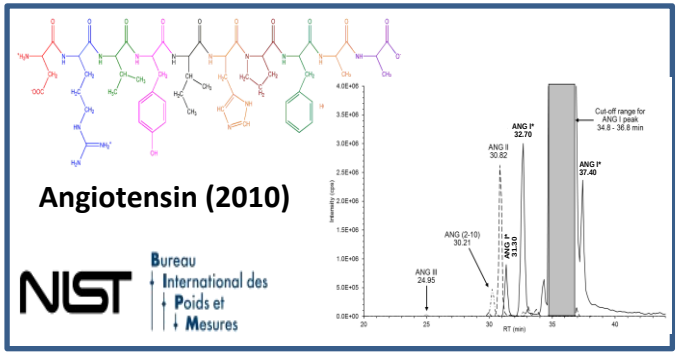
LNE — Le progrès, une passion à partager

Bureau International des Poids et Mesures

Development of methods for cross-linked peptides and future comparison (Hepcidin)(2015)



Angiotensin (2010)

NIST

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Higher profile for Metrology and SI Traceability for Diagnostics and Therapeutics

CCQM-K115: 1st key comparison on peptide purity (2015): C-peptide (Diabetes diagnosis)

NIM

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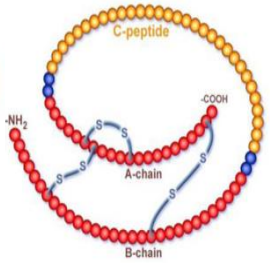


Liquid chromatography mass spectrometry method for C-peptide in blood serum ▸ UMC DDL reference method for serum C-peptide	JCTLM
Applicable matrice(s)	lyophilized, fresh, or frozen human serum or urine
Full description of technique(s)	Liquid chromatography mass spectrometry (LC/MS)
Quantity	Amount-of-substance concentration
Applicable range	0.01 nmol/L to unlimited after appropriate dilution
Expected uncertainty (level of confidence 95%)	0.036 nmol/L to 0.09 nmol/L
Reference(s)	Use of cation exchange chromatography for human C-peptide isotope dilution - Mass spectrometric assay, Stoyanov AV et al., *J. Chromatogr. A*, 2011, **1218**, 9244-9249;
Comparability assessment study(ies)	Human C-peptide Quantitation by LC-MS Isotope-Dilution Assay in Serum or Urine Samples, Stoyanov AV et al., *J. Chromat. Separation Techniq.*, 2013, **4**, 172
Comment(s)	University of Missouri-Columbia Diabetes Diagnostic Laboratory (UMC DDL)
JCTLM DB identification number	C10RMP12_C-Peptide

Realizing SI traceability for Therapeutic Peptide Characterization: Meeting Industry and Regulator needs as production methods move to chemical synthesis and away from recombinant technologies (Oxytocin and Calcitonin with NIM: 2016-2019)

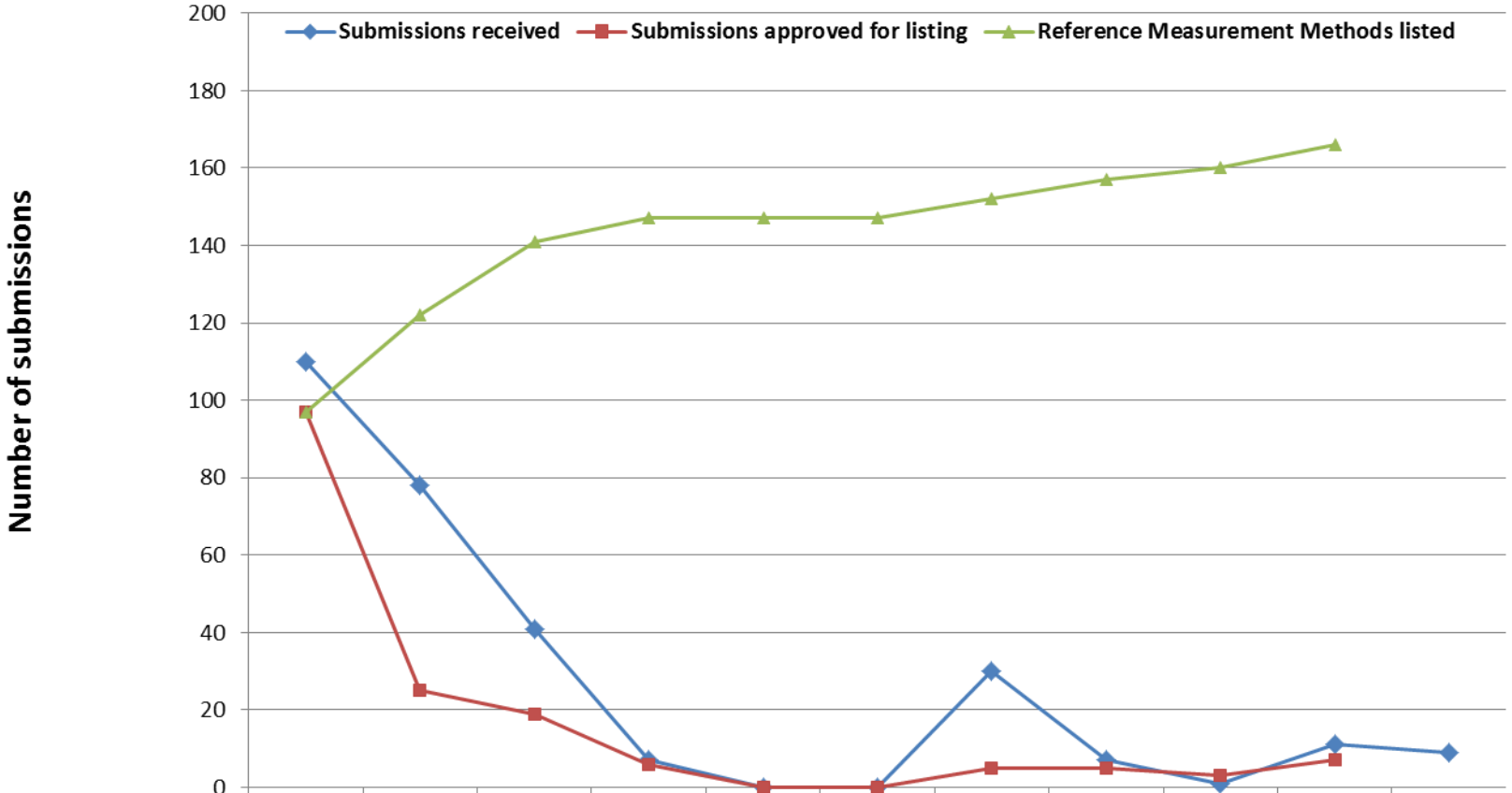
JCTLM Database Update – June 2015

Reference measurement methods/procedures

Analyte Category	Number of submissions listed	Number of Matrix – Analyte	Number of Analytes
Blood cell counting	2	1	1
Blood gases	-	-	-
Blood groupings	-	-	-
Coagulation factors	-	-	-
Drugs (2015)	13(+2)	14(+2)	9(+2)
Electrolytes	30	16	7
Enzymes	7	13	7
Metabolites and Substrates	46	34	13
Microbial serology	-	-	-
Non Electroyte Metals	15	14	7
Non-peptide Hormones	30	18	13
Nucleic acids	-	-	-
Proteins (2015)	20 (+1)	18 (+1)	18 (+1)
Vitamins	7	4	5
Total : 9	170	131	79

JCTLM Database Status – December 2014

Reference measurement methods/procedures



	2004 (Cycle 1)	2005 (Cycle 2)	2006 (Cycle 3)	2007 (Cycle 4)	2008 (Cycle 5)	2009 (Cycle 6)	2010 (Cycle 7)	2011 (Cycle 8)	2012 (Cycle 9)	2013 (Cycle 10)	2014 (Cycle 11)
Submissions received	110	78	41	7	0	0	30	7	1	11	9
Submissions approved for listing	97	25	19	6	0	0	5	5	3	7	
Reference Measurement Methods listed	97	122	141	147	147	147	152	157	160	166	

In 2012 publication of two outstanding Blood Cell Counting Methods, and
in 2013 Total protein measurement method placed in the list of no longer listed methods.

JCTLM Database Status – June 2015

Reference measurement services

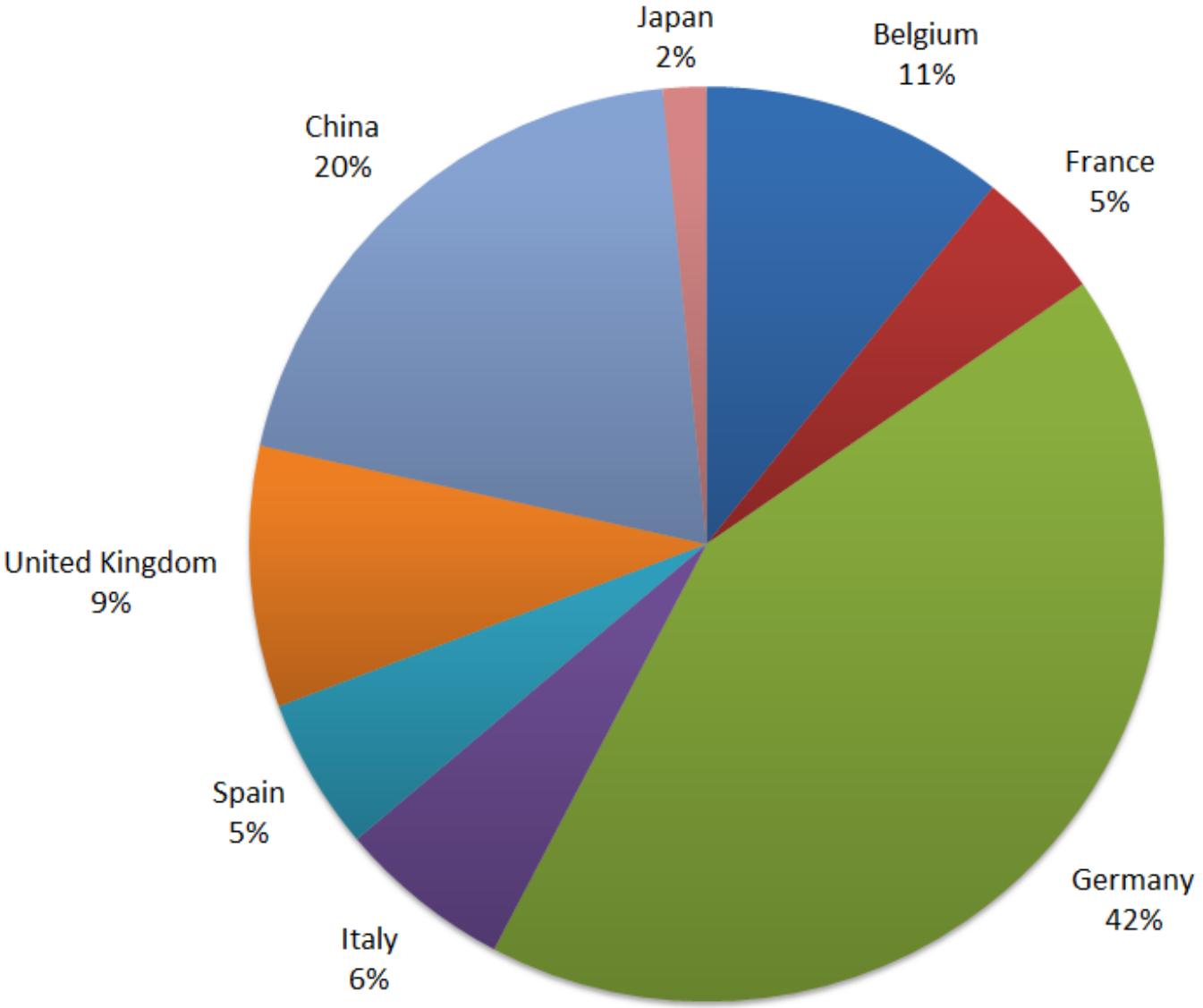
- 130 reference measurement services listed
- 12 Reference Laboratories accredited for compliance with ISO 15195 +ISO/IEC 17025 and 2 NMIs;

Analyte Categories	Number of Services listed	Number of Analytes	Analytes	Number of Reference Laboratories	Country
Drugs	3	3	digitoxin, digoxin, theophylline	2	Germany
Electrolytes	15	6	Li, K, Na, Cl, Mg, Ca	4	Germany, United Kingdom
Enzymes	45	7	ALP, ALT, AST, CK, GGT, alpha-amylase, LDH	7	Germany, Italy, Spain, United Kingdom, China
Metabolites and Substrates	38	9	creatinine, glucose, cholesterol (total), glycerides (total), urea, uric acid, bilirubin, HDL-Cholesterol, LDL-Cholesterol	10	Belgium, France, Germany, Italy, Japan, United Kingdom, China
Non-peptide Hormones	21	10	17 beta-estradiol, 17-hydroxyprogesterone, aldosterone, cortisol, estriol (non conjugated), progesterone, testosterone, free thyroxine, total thyroxine (TT4), total triiodothyronine (TT3)	4	Belgium, Germany, United Kingdom
Proteins	6	2	HbA1c, total protein	6	France, Germany, Italy, Japan, China
Vitamins	2	2	Hydroxyvitamins D2 & D3	1	Belgium
Total	130	39			

JCTLM Database Status – June 2015

Reference measurement services

Distribution of service providers by country of origin



JCTLM Database Update – December 2014

JCTLM Database User Feedback

*** 1. Please tick the one box below that most accurately describes your organization:**

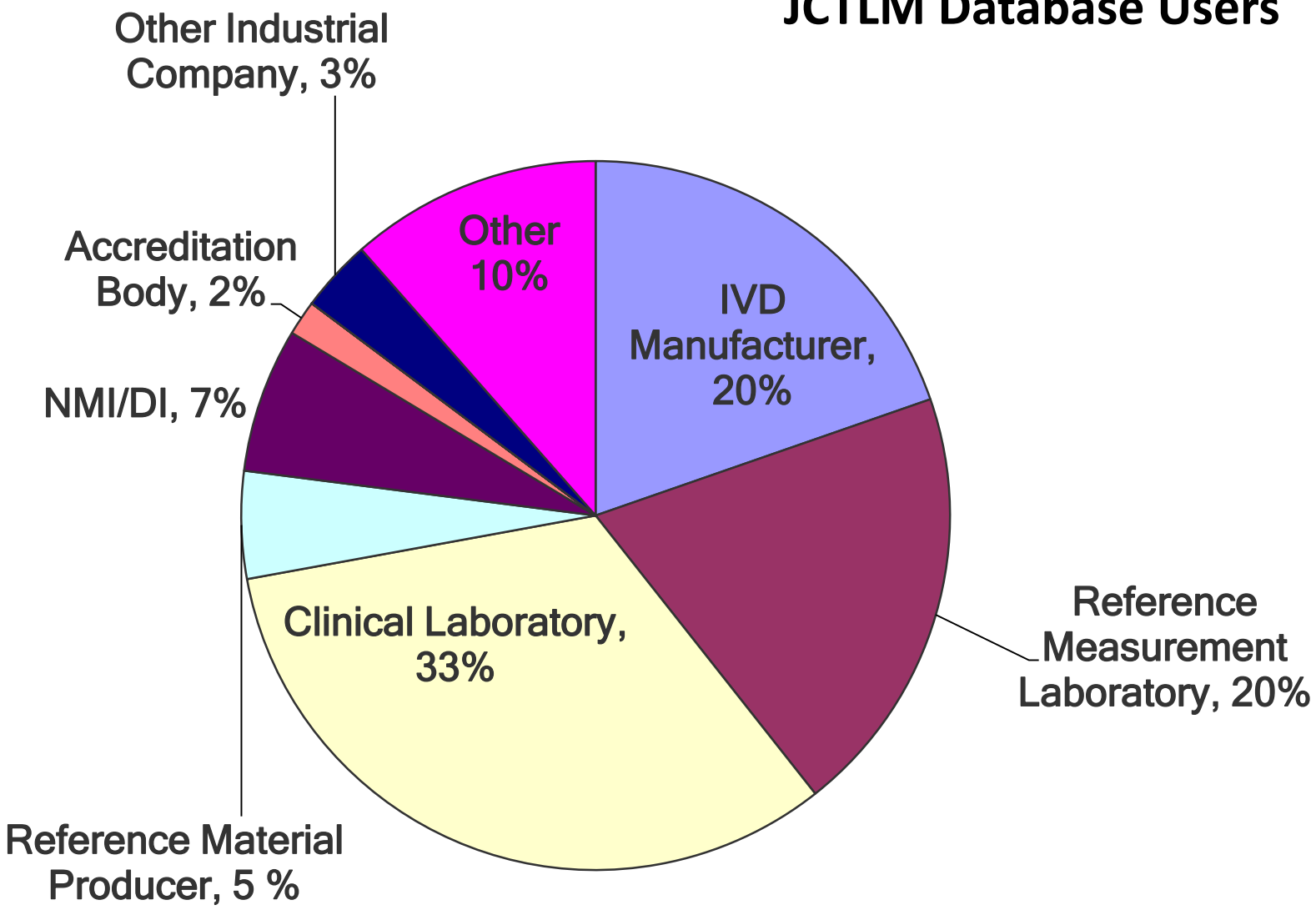
- ○ IVD Manufacturer
- ○ Reference Measurement Laboratory
- ○ Clinical Laboratory
- ○ Reference Material Producer
- ○ National Metrology Institute/ Designated Institute
- ○ Accreditation Body
- ○ Standardization body
- ○ Regulator
- ○ Other Industrial Company
- ○ Other (please specify)

2. What is the initial purpose of your visit to the website today?

- ○ for information on available certified reference materials
- ○ for information on published reference measurement methods
- ○ for information on providers of reference measurement services
- ○ Other (please specify)

Submit

JCTLM Database Users



JCTLM Review for compliance with ISO standards

ISO 17511:2003 In[illegible]nent of quantities in bi[illegible]f values assigned to calibrators and control materials

Revised version under development

ISO 15193:2009 Requirements for content and presentation of reference measurement procedures

ISO 15194:2009 Requirements for certified reference materials and the content of supporting documentation

ISO 18153: 2003 M[illegible] concentration [illegible]ol materials

Revised version to be incorporated into revised ISO 17511

ISO 15195: 2003 R[illegible]

Revised version at CD in ISO TC 212

Bureau International des Poids et Mesures

JCTLM

JCTLM Coverage of Clinical Laboratory tests

Routine tests in the Medical Laboratory			JCTLM Database Entries			
Laboratory test (Analyte)	Material	Relative number of tests	Pure Material CRM	Matrix CRM	Reference Measurement Services	Reference Measurement Methods
Red cell count	blood	1000				
Glucose	serum	558	3	1	4	5
Potassium	serum	556	4	4	4	5
Sodium	serum	555	4	4	4	5
Calcium	serum	550	3	4	2	7
Magnesium	serum	509	4	4	2	4
Digoxin	serum	290	1	2	1	2
Iron	serum	245				
HbA1c	blood	242	1	1		3
Transferrin	serum	202		1		1
Lithium	serum	191	1	5	2	3
C-peptide	serum	41	2			1
Ceruloplasmin	serum	37				1
Zinc	serum					
Lead - blood	blood					
Selenium	serum					

Session IV: Identifying future priorities in traceability in laboratory medicine

JCTLM 2015-2016 Strategy

- Raise awareness of JCTLM IVD Reference Measurement Systems Database
- Establishment of ad-hoc WG on JCTLM Governance
  - JCTLM Executive Committee Organizations
  - JCTLM Member Organizations
  - JCTLM Structure and Processes
- Establishment of WG on Traceability Education and Promotion (TEP)
- Member and Stakeholder meeting December 2015
- Focus on Gap analysis and New Challenges