CIRME

UNIVERSITÀ DEGLI STUDI DI MILANO

Centre for Metrological Traceability in Laboratory Medicine (CIRME)

site: http://users.unimi.it/cirme

CIRME CELEBRATING 10 Years

ISO Standards for IVD Traceability

Updating and Revision of Standards

R.I. Wielgosz (BIPM)

The BIPM

"The BIPM is an intergovernmental organization established by the Metre Convention, through which Member States act together on matters related to measurement science and measurement standards".

- **Founded in Paris in 1875 by 17 Member States and based at the *Pavillon de Breteuil* in Parc St Cloud, Sèvres, France**
- **Now involving about 100 states and economies as Members or Associates.**

The Metre Convention

THE METRE CONVENTION
established in 1875 by 17 States, now with 57 Member States in 2016.

CGPM – Conférence Générale des Poids et Mesures

Composed of Member State representatives.
Typically meets every 4 years to decide on matters relating to the Metre Convention and the SI

CIPM – Comité International des Poids et Mesures

18 individuals of different nationalities appointed by CGPM.

BIPM – Bureau International des Poids and Mesures

International Coordination:
•Infrastructure for committees
•Technical coordination

104th meeting of the CIPM (March 2015)

Consultative Committees (CCs)

CCAUV – Acoustics, US & Vibration
CCEM – Electricity & Magnetism
CCL – Length
CCM – Mass and related
CCPR – Photometry & Radiometry
CCQM – Amount of substance
CCRI – Ionizing Radiation
CCT – Thermometry
CCTF – Time & Frequency
CCU - Units

Bureau International des Poids et Mesures

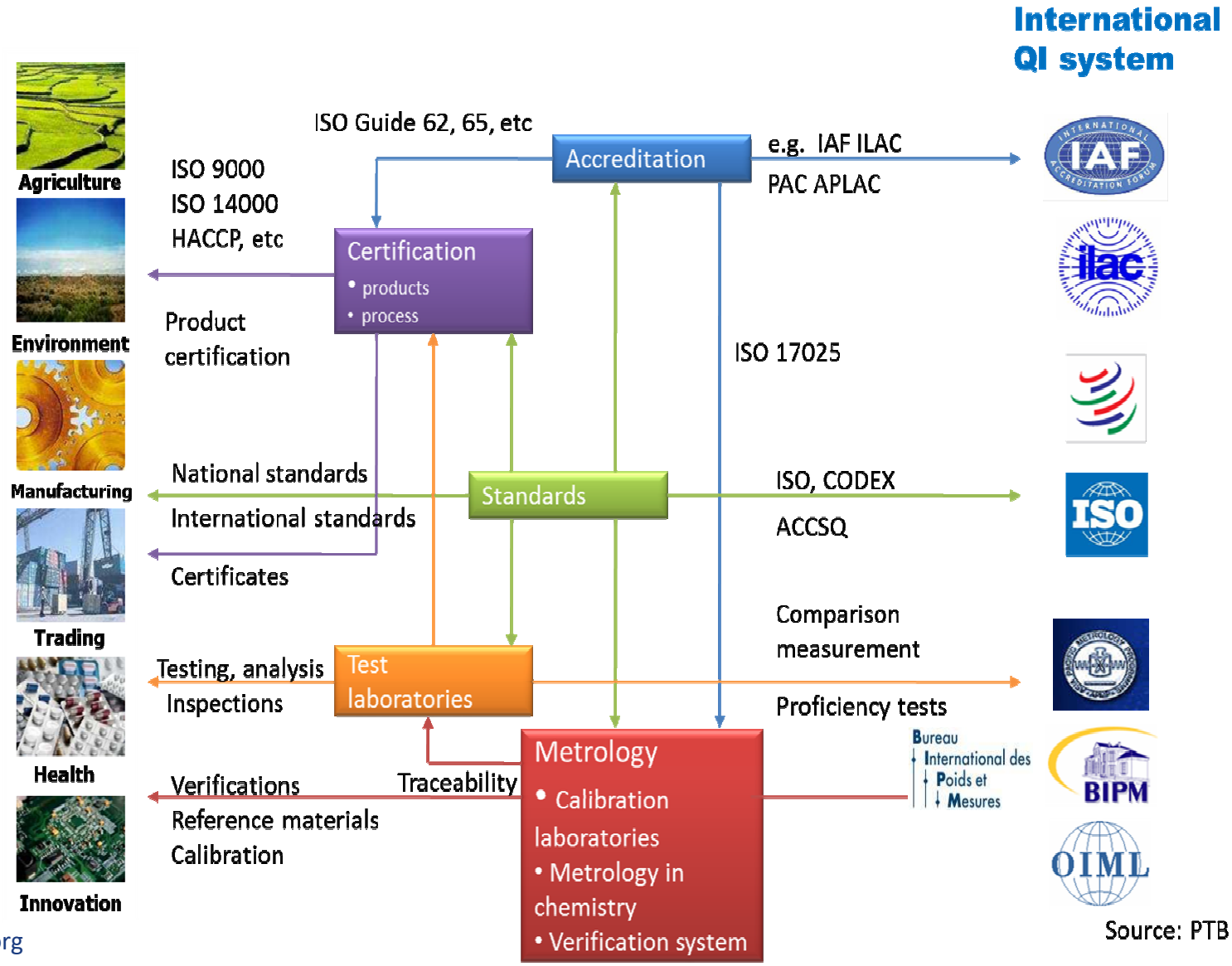
The CIPM Mutual Recognition Arrangement

- Metrology is a key part of the global “quality infrastructure” that underpins world trade.
- The work of the NMIs is made visible and transparent through the CIPM-MRA signed in 1999.
- The aim of the MRA is to provide the technical basis for the **worldwide acceptance** of national measurement standards and calibration and measurement certificates from NMIs.
- The work of the CIPM-MRA now goes far beyond matters of trade to cover climate change, healthcare etc.

CIPM MRA

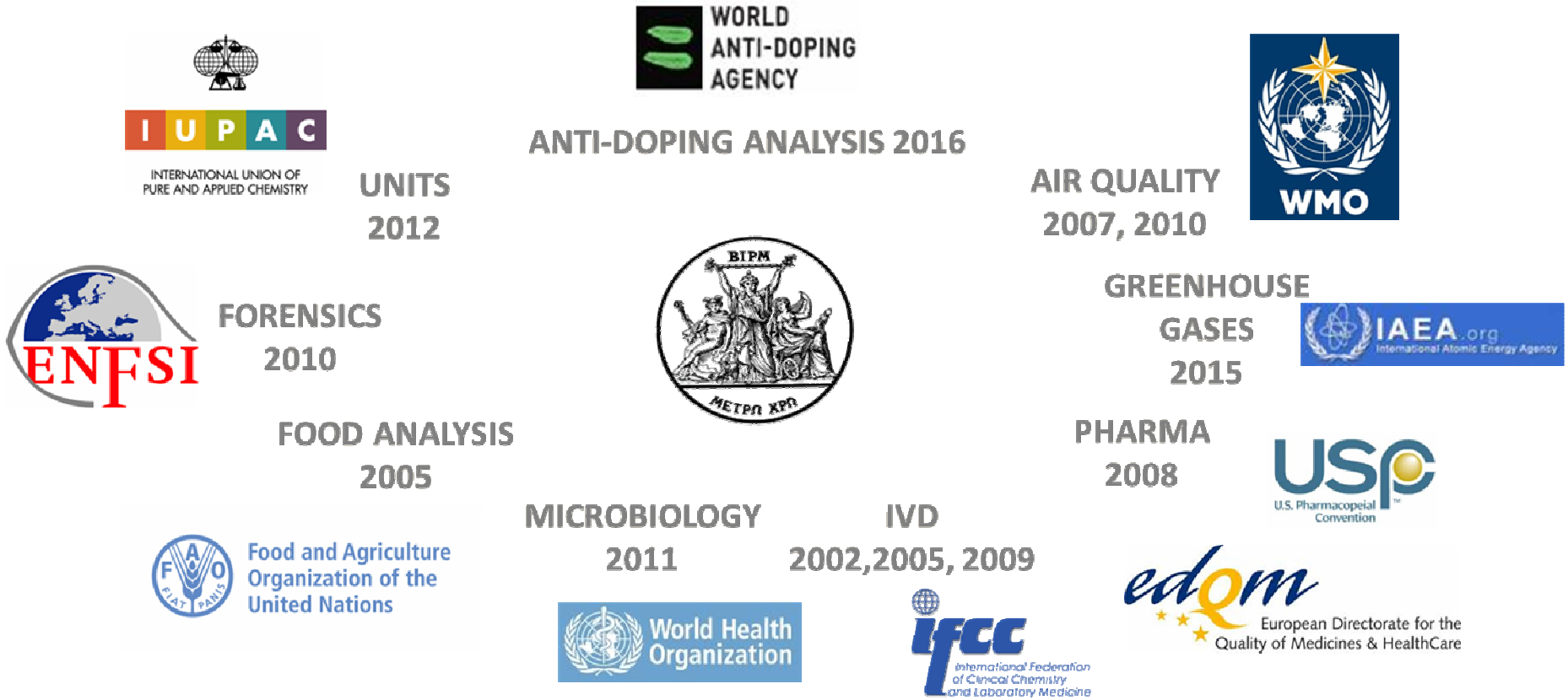
Bureau International des Poids et Mesures

The Role of Metrology in National Quality Infrastructure



Source: PTB

BIPM/CCQM Workshops with Stakeholder Communities



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:

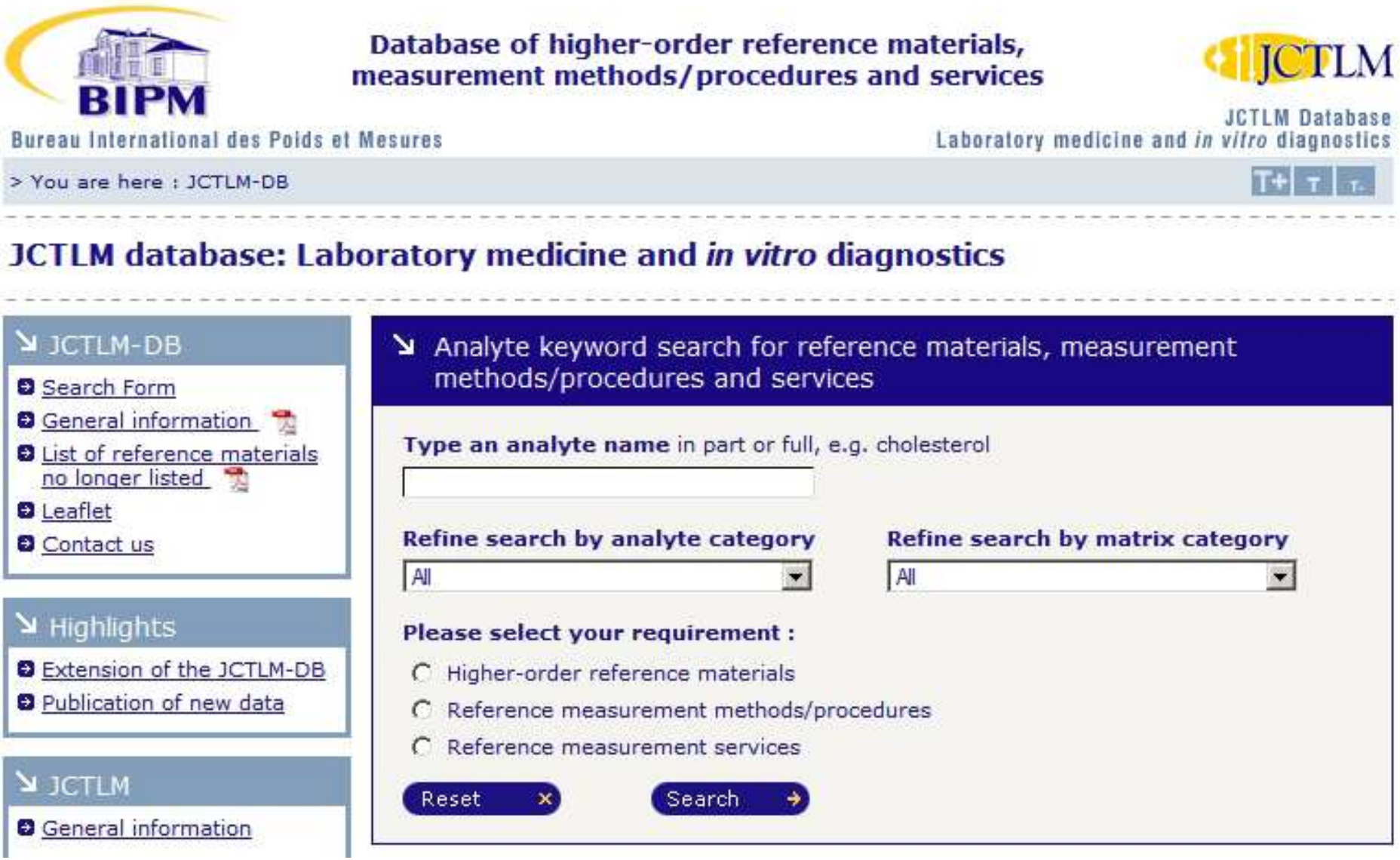
- **295 Certified Reference Materials**
- **170 Reference Methods**
- **130 Reference Measurement Services**

JCTLM Chair: Dr G. Myers (AACC)

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

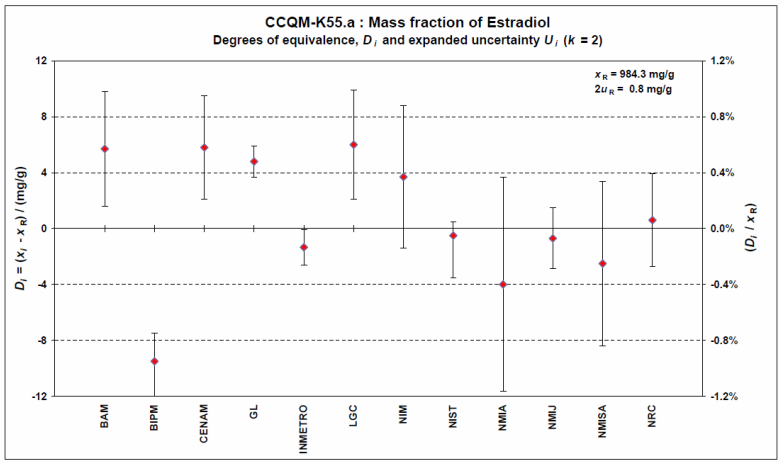
Bureau International des Poids et Mesures

JCTLM Database : www.bipm.org/jctlm/

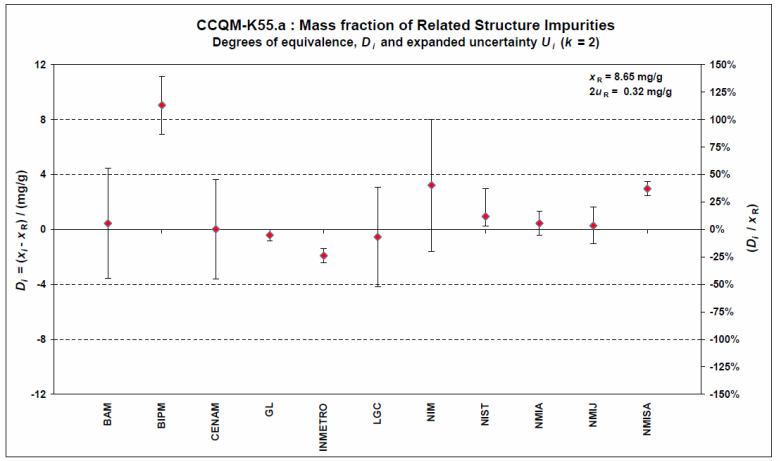


Assuring the Quality of JCTLM Listed Products: Key Comparisons (Estradiol, Primary Calibrator, CCQM-K55.a)

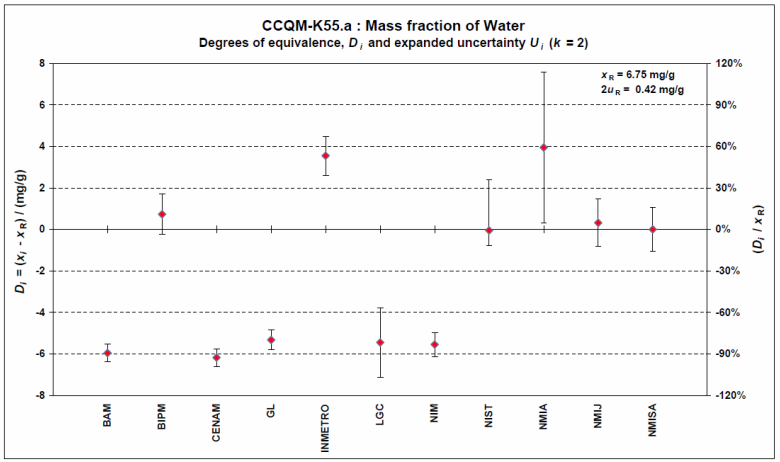
Mass fraction: Estradiol



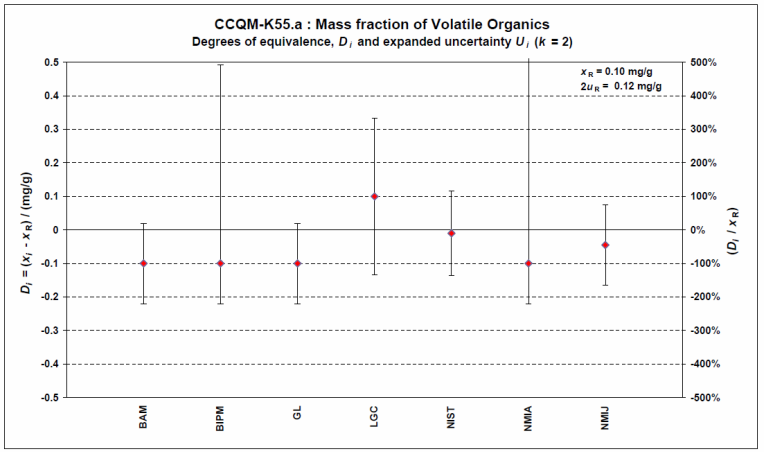
Mass fraction: Related Substances



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

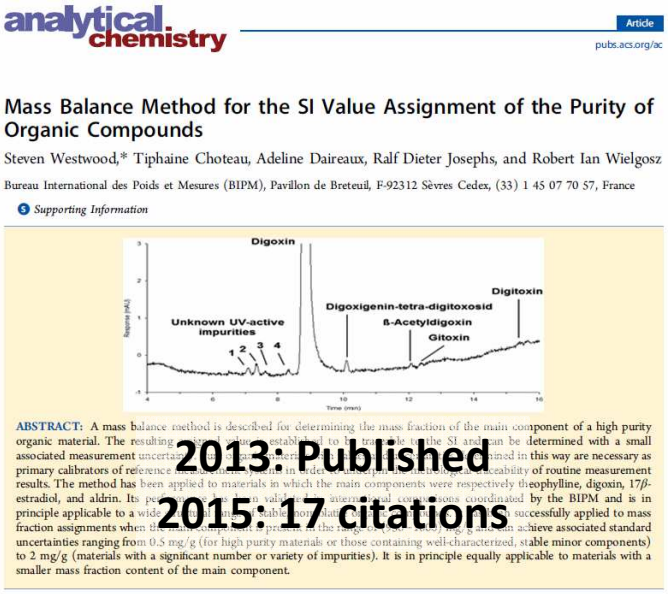
List of higher-order reference materials

JCTLM

Available CRMs

BIPM/CCQM Small Organic 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 ... can be determined with a small associated measurement uncertainty ... primary calibrators of reference ... 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 ... successfully applied to mass fraction assignments when ... 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

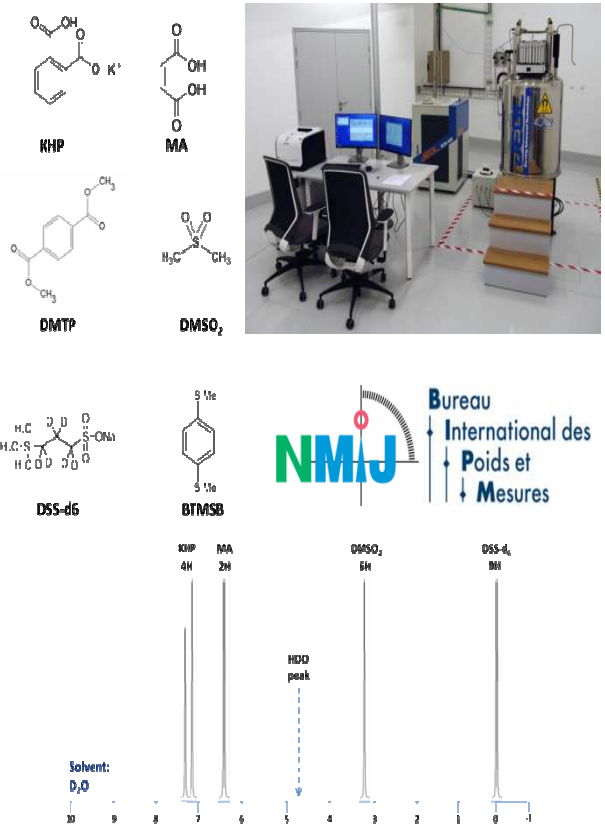
IUPAC

FUNDED

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

Bureau International des Poids et Mesures

Universal Calibrators for qNMR



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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

BIPM/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

LNE

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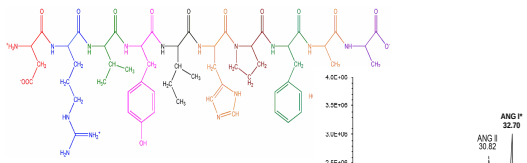
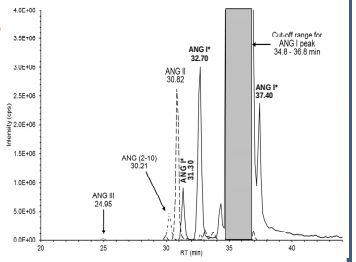
Development of methods for cross-linked peptides and future comparison (Hepcidin)(2015)



Angiotensin (2010)

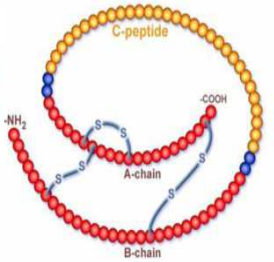
NIST Bureau International des Poids et Mesures



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 Bureau International des Poids et Mesures



Liquid chromatography mass spectrometry method for C-peptide in blood serum

JCTLM

UMC DDL reference method for serum C-peptide

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)

Bureau International des Poids et Mesures

Council Directives related to medical devices

- **90/385/EEC of 20 June 1990 relating to active implantablemedical devices**
- **93/42/EEC of 14 June 1993 concerning medical devices**
- **98/79/EC of 27 October 1998 on in vitro diagnostic medical devices**
- **2000/70 EC of 16 December 2000 on stable derivates of human bloodor human plasma as amended by 2001/104/EC**

(K. Howes, DG Enterprise: JCTLM Workshop 2002)

The IVD Directive of the EU requires that:

"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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Aim of the IVD Directive

“to ensure that IVDs do not compromise the health and safety of patients, users and third parties and attain the performance levels attributed to them by their manufacturer. ”

MHRA, UK Guidance 2006

ISO TC 212 WG2 standards for IVD Metrological Traceability

ISO 17511:2003 In **Revised version under development** **nent of quantities in bi** **f values assigned to calibrators and control materials**

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

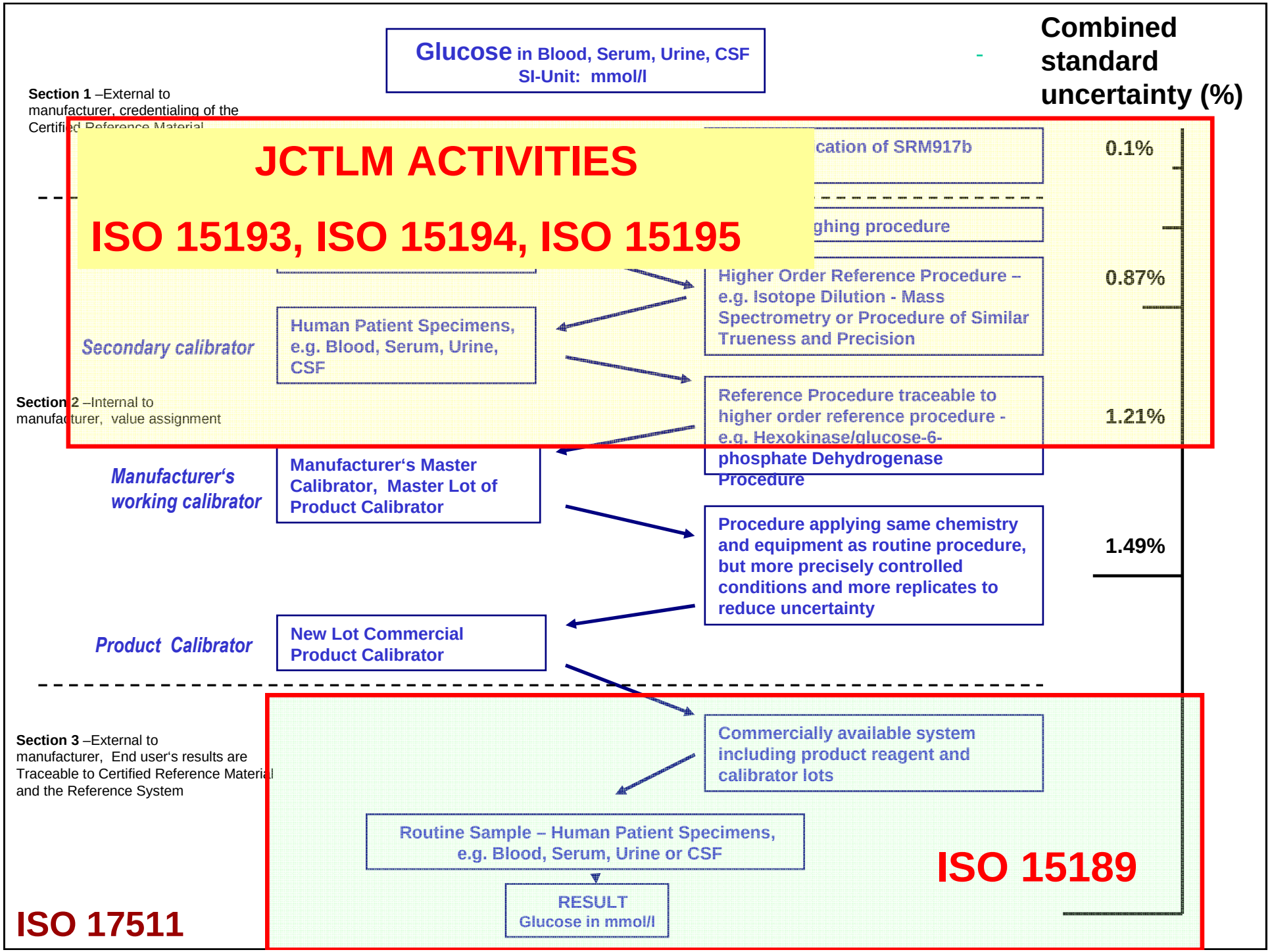
ISO 15194:2009 Requirements for certified reference materials and the content of supporting documentation

ISO 18153: 2003 M **Revised version to be incorporated into revised ISO 17511** **concentration** **ol materials**

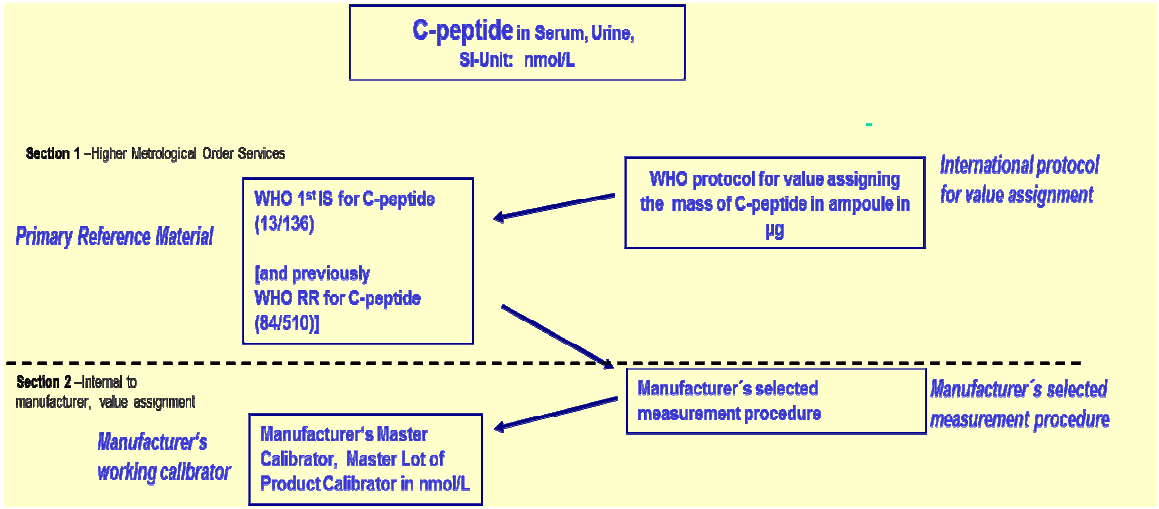
ISO 15195: 2003 R **Revised version at CD in ISO TC 212**

Bureau International des Poids et Mesures

JCTLM


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

Evolving calibration hierarchies for C-peptide



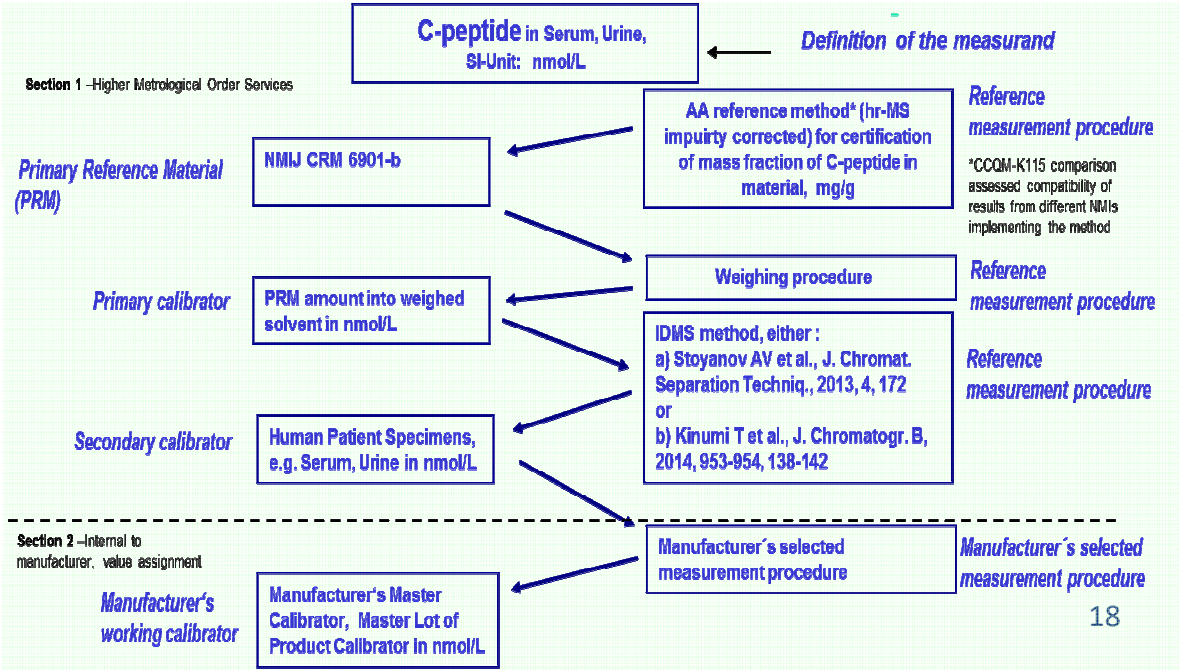
SI
Reference Measurement System

WHO
International Conventional System

Implementing a Reference Measurement System for C-peptide: Successes and Lessons Learned

Randie R. Little[1*], Robert I. Wielgosz[2], Ralf Josephs[2], Tomoya Kinumi[3], Akiko Takatsu[3], Hongmei Li[4], Chris Burns[5]

[1]University of Missouri School of Medicine, USA
[2]BIPM,
[3]NMIJ, Japan
[4]NIM, China
[5]NIBSC, UK



Revised Standards

- Stage 1: Proposal stage
- Stage 2: Preparatory stage
- Stage 3: Committee stage
- Stage 4: Enquiry stage
- Stage 5: Approval stage
- Stage 6: Publication stage

ISO 15194:2009

Oct 2007 –ISO/DIS 15194 sent to ISO Central Secretariat

Jan 2008 –FDIS status and final vote by Countries

April 2008 – Approval of new standard

1 May 2009 – Publication of new standard in all countries

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ISO 15194 Revision

ISO 15194: 2002

In vitro diagnostic medical devices – Measurement of quantities in samples of biological origin – Description of reference materials

ISO 15194:2009

In vitro diagnostic medical devices – Measurement of quantities in samples of biological origin – Requirements for certified reference materials and the content of supporting documentation

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Modified Scope

ISO 15194: 2002 (Scope)

This European Standard specifies requirements and formats for the description of reference materials. It is applicable to reference materials of higher metrological order, classifiable as primary and secondary measurement standards…..

This European Standard is not applicable to the production of the reference materials.

ISO 15194:2009 (Scope)

This International Standard specifies requirements for certified reference materials (CRMs) and the content of their supporting documentation for them to be considered of higher metrological order according to ISO 17511. It is applicable to CRMs classifiable as primary and secondary measurement standards and international conventional calibrators…..

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Normative referenced documents

ISO 15194: 2002

EN 375: 1992 In vitro diagnostic systems – Requirements for labelling of in vitro diagnostic reagents for professions use

ISO 31: 1992, Quantities and units

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Normative referenced documents

ISO 15194:2009

ISO 17511:2003, Metrological Traceability of values assigned to calibrators and control materials

ISO 18153:2003, Metrological Traceability of values for catalytic concentration of enzymes assigned to calibrators and control materials

ISO Guide 31, Reference materials – Contents of certificates and labels

ISO Guide 34:2000, General requirements for the competence of reference material producers

ISO Guide 35:2006, Reference Materials – General and statistical principles for certification

Guide to the expression of uncertainty in measurement (GUM)

International Vocabulary of Metrology (VIM)

ISO 5725-2:1994, Accuracy (trueness and precision) of measurement methods and results

ISO 31 (all parts), Quantities and units

ISO 15194 Revision

ISO 15194: 2002

Contents

4. Classification and naming of reference materials
5. Description of a reference material
6. Label
7. Certificate
8. Package insert

Annex A (informative) Materials with properties other than quantities

ISO 15194:2009

Contents

4. Systematic format of properties in the supporting documentation of a CRM
5. Properties, production and characterization of a CRM
6. Content of supporting documentation

Annex A (informative) CRMs with nominal properties or ordinal quantities

CIRME CELEBRATING 10 Years

Normative Referenced Documents

4. Systematic format of properties in the supporting documentation of a CRM

ISO 31

5. Properties, production and characterization of a CRM

ISO Guide 34

ISO Guide 35

ISO 17511

ISO 18153

GUM

6. Content of supporting documentation

6.2 Label

6.3 Certificate

6.4 Certification Report

ISO Guide 31

ISO 15194:2009

Stages of ISO Standards: ISO 15193:2009

- Stage 1: Proposal stage
- Stage 2: Preparatory stage
- Stage 3: Committee stage
- Stage 4: Enquiry stage
- Stage 5: Approval stage
- Stage 6: Publication stage

ISO 15193:2009

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ISO 15193 Revision

ISO 15193: 2002

In vitro diagnostic medical devices – Measurement of quantities in samples of biological origin – Presentation of reference measurement procedures

ISO 15193:2009

In vitro diagnostic medical devices – Measurement of quantities in samples of biological origin – Requirements for content and presentation of reference measurement procedures

CIRME CELEBRATING 10 Years

Modified Scope

ISO 15193:2009 (Scope)

This International Standard specifies requirements for the content of a reference measurement procedure for in vitro diagnostic medical devices and medical laboratories

Full descriptions of measurement methods are usually published in the scientific literature, in which methods are described in sufficient detail that they can b used as the basis of a documented measurement procedure.

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ISO 15193:2009 and ISO 15194:2009
Harmonized standards

Commission communication in the framework of the implementation of the Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices

(Text with EEA relevance)

(Publication of titles and references of harmonised standards under the directive)

(2010/C 183/04)

ESO (1)	Reference and title of the harmonised standard (and reference document)	First publication OJ	Reference of superseded standard	Date of cessation of presumption of conformity of superseded standard Note 1
CEN	EN ISO 15193:2009 In vitro diagnostic medical devices - Measurement of quantities in samples of biological origin - Requirements for content and presentation of reference measurement procedures (ISO 15193:2009)	This is the first publication		
CEN	EN ISO 15194:2009 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 15194:2009)	This is the first publication		

CIRMI
CELEL Years

Standards under Revision

ISO 15195: 2003

Laboratory Medicine – Requirements for Reference Measurement Laboratories

ISO/CD 15195 Draft Document:

Laboratory medicine – requirements for the competence of calibration laboratories using reference measurement procedures

CIRME CELEBRATING 10 Years

Standards under Revision

ISO /CD 15195 Draft Document:

Laboratory medicine – requirements for the competence of calibration laboratories using reference measurement procedures

2 Normative references

The following referenced documents are indispensable for the application of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO/IEC 17025: 2005, General requirements for the competence of testing and calibration laboratories

……..

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Standards under Revision

Annex A
(informative)
Relationship to ISO/IEC 17025:2005

Table A.1 — Clauses of ISO/IEC 17025:2005 which are supplemented by clauses within this International Standard (indicates the additional requirements in this standard and which clause in ISO/IEC 17025:2005 they relate to)

Clause, subclause of ISO/IEC 17025:2005	Supplementary clause, subclause of this International Standard
1	1
2	2
3	3
4	4
4.1	4.1, 4.1.1
4.2	4.2, 4.2.1, 4.2.2, 4.2.3, 4.2.4
4.3	-

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ISO/IEC 17025 and CASCO JWG 44

February 2015:	**1st WG meeting**
June 2015:	**2nd WG meeting WD1 developed**
August 2015:	**3rd meeting CD1 developed**
End August 2015:	**CD1 out for ballot: vote for approval but a substantial number of technical and editorial comments received**
January 2016:	**Drafting Group meeting**
February 2016	**4th meeting CD2 prepared**
July 2016	**Drafting Group meeting**
September 2016	**CD2 comments and prep for DIS**

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ISO/IEC 17025 and CASCO JWG 44

Nov/Dec 2016:	**Translation**
Jan-March 2017:	**DIS out for 3 month ballot**
May 2017:	**Drafting Group meeting**
June 2017:	**6th WG Meeting prepared FDIS**
Autumn 2017:	**Expectation is FDIS or publication**

CD1 ISO 17025 vs. ISO 17025: 2005 (and impact on ISO 15195)

ISO 17025: 2005 (Structure)

1.Scope
2.Normative References
3.Terms and Definitions
4.Management Requirements
5.Technical Requirements

Annex A (cross ref. to ISO 9001:2000)
Annex B (Guidelines for establishing applications for specific fields)

CD1 ISO 17025 (Structure)

1.Scope
2.Normative References
3.Terms and Definitions
4.General Requirements
5.Structural Requirements
6.Resource requirements
7.Process requirements
8.Management requirements

Annex A (Metrological Traceability)
Annex B (Management System)

CIRME CELEBRATING 10 Years

Metrological Traceability

ISO 17025: 2005

5.6 Measurement traceability

5.6.1 General

5.6.2 Specific Requirements

5.6.2.1 Calibration

5.6.2.1.1 For calibration laboratories…..

5.6.2.2.1 For testing laboratories……..

CD1 ISO 17025

6.6 Metrological Traceability

6.6.1.1 …metrological traceability to the SI…..

6.6.1.2…..traceability to (other) measurement standards…..

6.5.4 A calibration programme shall be established for measurement equipment unless….

Annex A……

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ISO 15195 revision: the way forward

CONSIDERATIONS:

i. ISO/IEC 17025 will go out for DIS vote and comments January 2017

ii. It is expected that comments will be received (major standard with considerable changes being seen for the first time outside the Drafting Committee)

iii. It is expected that an FDIS stage will be necessary

WAYFORWARD:

i. Start revision when FDIS document is available (Autumn 2017)

ii. ISO 15195 CD2 will be ready for 1st quarter 2018

iii. Starting ISO 15195 revision prior to this stage is likely to lead to double work for ISO 15195 drafting group

FOR DISCUSSION AT ISO TC 212 WG2 MEETING

WG2 Project Report – ISO 15195 Requirements for Reference Measurement Laboratories

- Robert Wielgosz, Project Lead
- Sept 2017 target date for DIS registration; CASCO developing next edition of normative reference, ISO/IEC 17025
- Proposed path forward:
  - Request timeline extension (9 months) from ISO CS - July 2017
  - Start ISO 15195 revision when FDIS 17025 document is available (Autumn 2017)
  - ISO 15195 CD2 will be ready for 1st quarter 2018
  - Move to DIS registration by May 2018

WG2 Project Report - ISO 17511 Traceability of Assigned Values - Calibrators, Controls, Patient Samples

- Dr N Greenberg (US) – Project Lead
- Working toward goal of DIS registration - Jan 2018
- Expecting new draft to be prepared by drafting team, to be made available for WG review/comment by end of March, 2017
- Anticipate moving to CD stage by August 2017. If tech comments received, may need to request project timeline extension to meet DIS registration target

WG2 Project Report – ISO NP 21151 Requirements for International Harmonization Protocols…metrological traceability

- Dr G Miller (US) – Project Lead
- Working toward goal of DIS registration - Jan 2018
- Expecting new draft NP21151 to be prepared and made available for WG comment by end of March, 2017
- Following comment period, additional comments will be addressed @ WG2 meeting to be held (May 2017)
- Anticipate moving to CD stage by August 2017. If tech comments received, may need to request project timeline extension to meet DIS registration target

WG2 Project Report – ISO TS 20914 Measurement Uncertainty (MU)

- Dr Graham White (AU) – Project Lead; In collaboration with WG1
- Supports MU requirements in ISO 15189:2012, clause 5.5.1.4
- Working toward goal of approved TS by Nov 2018 (no DIS stage required for TS)
- Expecting new draft to be prepared and made available for WG1 & 2 review/comment by end of March, 2017
- Anticipate moving to CD stage by August 2017

Thank you.

Dr R.I Wielgosz
BIPM

rwielgosz@bipm.org

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