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 et Mesures
International Coordination:
- Infrastructure for committees
- Technical coordination

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

104th meeting of the CIPM (March 2015)
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.
The Role of Metrology in National Quality Infrastructure

ISO Guide 62, 65, etc

Accreditation

e.g. IAF ILAC
PAC APLAC

ISO 17025

ISO, CODEX
ACCSQ

Comparison measurement

Proficiency tests

Metrology
- Calibration laboratories
- Metrology in chemistry
- Verification system

National standards
International standards

Certificates

Product certification

Table: www.bipm.org

Source: PTB
BIPM/CCQM Workshops with Stakeholder Communities

UNITED NATIONS INTERNATIONAL ORGANIZATION FOR FOOD AND AGRICULTURE 2005

FORENSICS 2010

FOOD ANALYSIS 2005

MICROBIOLOGY 2011

ANTI-DOPING ANALYSIS 2016

WORLD ANTI-DOPING AGENCY

AIR QUALITY 2007, 2010

WMO

GREENHOUSE GASES 2015

IAEA

PHARMA 2008

USP

EDQM

European Directorate for the Quality of Medicines & HealthCare

www.bipm.org
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)
JCTLM Database: Laboratory medicine and in vitro diagnostics

JCTLM-DB
- Search Form
- General information
- List of reference materials no longer listed
- Leaflet
- Contact us

Highlights
- Extension of the JCTLM-DB
- Publication of new data

JCTLM
- General information

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

You are here: JCTLM-DB

JCTLM database: Laboratory medicine and in vitro diagnostics

Type an analyte name in part or full, e.g. cholesterol

Refine search by analyte category
- All

Refine search by matrix category
- All

Please select your requirement:
- Higher-order reference materials
- Reference measurement methods/procedures
- Reference measurement services

Reset ▼ Search ►
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

www.bipm.org
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)

<table>
<thead>
<tr>
<th>Matrix or material</th>
<th>Analyte or component</th>
<th>Dissemination range of measurement capability</th>
<th>Range of certified values in reference materials</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mass fraction in mg/kg</td>
<td>Relative expanded uncertainty in %</td>
</tr>
<tr>
<td>serum</td>
<td>creatinine</td>
<td>3 to 50</td>
<td>0.3 to 0.5</td>
</tr>
</tbody>
</table>

Mechanism(s) for measurement service delivery: Calibration and ERM-DA250 to DA253

Expanded uncertainty for certified values estimated with \( k = \sim 2 \) (level of confidence 95%)

Uncertainty convention 1.

Approved on 06 December 2011

Internal NMI service identifier: LGC/Org-019

**CMC – ‘Capability’**

**List of higher-order reference materials**

**Available CRMs**

**creatinine in human serum**

**LGC Limited (LGC), United Kingdom**

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Email : uksales@lgcstandards.com
Web : http://www.lgc.co.uk

<table>
<thead>
<tr>
<th>Name of the reference material</th>
<th>ERM-DA252a</th>
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</thead>
<tbody>
<tr>
<td>Quantity</td>
<td>Mass concentration</td>
</tr>
<tr>
<td>Analyte certified/assigned value</td>
<td>3.1 mg/kg</td>
</tr>
<tr>
<td>Expanded uncertainty (level of confidence 95 %)</td>
<td>0.2 mg/kg</td>
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<tr>
<td>Other relevant publication(s)</td>
<td>Stokes P and O Connor G, Journal of Chromatography B, 2003.1,125-136</td>
</tr>
<tr>
<td>Traceability</td>
<td>SI</td>
</tr>
<tr>
<td>CRM listing</td>
<td>List I</td>
</tr>
</tbody>
</table>

This (Certified) Reference Material has been reviewed for compliance with ISO 15194:2003 but not been reviewed against ISO 15194:2009
BIPM/CCQM Small Organic Calibrator Comparison Program

Higher profile for Metrology and Traceability in Organic Analysis

Universal Calibrators for qNMR

Increase in availability of pure material CRMs for IVDs

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

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

2012
2015

Number of CRMs
68
93

NMIs with CRMs
7
7

FUNDED
Enabling the adoption of SI traceable reference measurements systems

Higher profile for Metrology and SI Traceability for Diagnostics and Therapeutics

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

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

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)
Council Directives related to medical devices

• 90/385/EEC of 20 June 1990 relating to active implantable medical 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 blood or human plasma as amended by 2001/104/EC

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
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 vitro diagnostic medical devices - Measurement of quantities in biological samples - Metrological traceability of 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 Metrological traceability of values for catalytic concentration of enzymes assigned to calibrators and control materials

Revised version to be incorporated into revised ISO 17511

ISO 15195:2003 Reference Measurement Laboratories

Revised version at CD in ISO TC 212
Evolving calibration hierarchies for C-peptide

WHO
International Conventional System

Implementing a Reference Measurement System for C-peptide: Successes and Lessons Learned
Randie R. Little1, Robert I. Wielgosz2, Ralf Josephs2, Tomoya Kinumi3, Akiko Takatsu3, Hongmei Li4, Chris Burns5

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

www.bipm.org
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
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
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.

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.....
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
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
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

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

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

- 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
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
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 be used as the basis of a documented measurement procedure.
Harmonized standards


(Text with EEA relevance)

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

(2010/C 183/04)

<table>
<thead>
<tr>
<th>ESO (1)</th>
<th>Reference and title of the harmonised standard (and reference document)</th>
<th>First publication OJ</th>
<th>Reference of superseded standard</th>
<th>Date of cessation of presumption of conformity of superseded standard Note 1</th>
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<tbody>
<tr>
<td>CEN</td>
<td>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)</td>
<td>This is the first publication</td>
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<tr>
<td>CEN</td>
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<td>This is the first publication</td>
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</tbody>
</table>
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
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
## 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)

<table>
<thead>
<tr>
<th>Clause, subclause of ISO/IEC 17025:2005</th>
<th>Supplementary clause, subclause of this International Standard</th>
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<tr>
<td>4.3</td>
<td>-</td>
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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
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
<table>
<thead>
<tr>
<th>ISO 17025: 2005 (Structure)</th>
<th>CD1 ISO 17025 (Structure)</th>
</tr>
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<tbody>
<tr>
<td>1. Scope</td>
<td>1. Scope</td>
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<tr>
<td>2. Normative References</td>
<td>2. Normative References</td>
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<tr>
<td>3. Terms and Definitions</td>
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<tr>
<td>5. Technical Requirements</td>
<td>5. Structural Requirements</td>
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<tr>
<td>Annex B (Guidelines for establishing applications for specific fields)</td>
<td>7. Process requirements</td>
</tr>
<tr>
<td></td>
<td>8. Management requirements</td>
</tr>
<tr>
<td></td>
<td>Annex A (Metrological Traceability)</td>
</tr>
<tr>
<td></td>
<td>Annex B (Management System)</td>
</tr>
</tbody>
</table>
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.....
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