Traceability in laboratory medicine: A driver for accurate results for patient care

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For the Joint Committee for Traceability in Laboratory Medicine (JCTLM)

Presentation to ICSH General Assembly, Lucerne: 26 October 2016
Outline of talk

• Traceability in laboratory medicine and JCTLM
• Case study: HbA1c
"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
Why is traceability an essential requirement?

Non-traceable IVD measurement systems may lead to:
- Lack of product control
- Non comparable measurement results
- Incorrect patient diagnosis and treatment
- Uncertainty of compliance with the IVD Directive
What is traceability in laboratory medicine?

- Metrological traceability is the property of a measurement result, which can be related to a reference through a documented unbroken chain of calibrations, each contributing to the measurement uncertainty.
- Traceability requires both (certified) reference materials and the reference measurement procedures (methods) in which they are used.
- For structurally simple measurands (analytes) it is possible to get pure substance primary reference materials. For more complex measurands pure substance may not be available.
- Primary reference measurement procedures are often based on isotope dilution mass spectrometry.

Reference materials (calibrators)
- Primary reference material (pure substance)
- Primary calibrator (SI traceable)
- Secondary calibrator
- Product calibrator

Reference measurement procedures
- Primary reference measurement procedure
- Secondary reference measurement procedure
- Manufacturer selected procedure
- Routine laboratory procedure
The metrological traceability chain

- Primary reference material
- Primary calibrator
- Secondary calibrator
- Manufacturer master calibrator
- Product calibrator
- Patient result
- Primary reference measurement procedure
- Secondary reference measurement procedure
- Manufacturer selected measurement procedure
- Manufacturer standing measurement procedure
- Routine laboratory method
- Metrology institute / Reference lab
- IVD method manufacturer
- Routine lab

Definition of measurand: Concentration in SI units

Adapted from EN ISO 17511 2003
JCTLM: formed in 2002: sponsoring organisations

- Intergovernmental treaty organisation for measurement standards
- International NGO for professionals in laboratory medicine
- International NGO for accreditation bodies
JCTLM: what does it do?

1. Maintains the JCTLM IVD Reference Measurement Systems Database
2. Coordinates the nomination and review process for database entries
3. Contributes to ISO TC 212 WG2 on Reference Systems
   a) Currently revising two key standards ISO 17511 and ISO 15195
4. Holds a biennial scientific meeting
5. Provides educational materials to support an understanding of the importance of traceability in laboratory medicine
   a) A new website (www.jctlm.org) containing educational support materials and references will be launched in January 2017
JCTLM database: Laboratory medicine and *in vitro* diagnostics

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

**Analyte keyword search for reference materials, measurement methods/procedures and services**

- **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

**Buttons:**
- Reset
- Search
JCTLM database: requirements for nomination

- Annual call for nominations from JCTLM Secretariat
- Nominations should comply with:
  - ISO 15193:2009 reference measurement procedures
  - ISO 15194:2009 reference materials
  - ISO 15195:2003 reference measurement laboratories
What is a commutable reference material?

After Miller WG 2012
JCTLM database: current status

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

- Database contains (October 2016):
  - 298 Certified reference materials
  - 180 Reference methods
  - 146 Reference measurement services
<table>
<thead>
<tr>
<th>JCTLM Database Users</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>IVD Manufacturer</td>
<td>20%</td>
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<tr>
<td>Clinical Laboratory</td>
<td>33%</td>
</tr>
<tr>
<td>Reference Laboratory</td>
<td>20%</td>
</tr>
<tr>
<td>Reference Material Producer</td>
<td>5%</td>
</tr>
<tr>
<td>Accreditation Body</td>
<td>2%</td>
</tr>
<tr>
<td>NMI/DI</td>
<td>7%</td>
</tr>
<tr>
<td>Other Industrial Company</td>
<td>3%</td>
</tr>
<tr>
<td>Other</td>
<td>10%</td>
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</table>

JCTLM database survey – January 2015
What is the initial purpose of your visit to the website today?

- 46.7% for information on available certified reference materials
- 33.3% for information on published reference measurement methods
- 16.7% for information on providers of reference measurement services
- 3.3% Other (please specify)
Outline of talk

• Traceability in laboratory medicine and JCTLM
• Case study: HbA1c
Case study: haemoglobin A$_{1c}$ (HbA$_{1c}$)

Established from major clinical trials as key analyte for long-term monitoring of diabetes

Method improvement following IFCC standardiation [Ref 1]

IFCC reference laboratory network established [Ref 2]

Many laboratory and POCT methods available

2. IFCC network laboratories for HbA1c [www.ifcchba1c.net](http://www.ifcchba1c.net)
Why is HbA\textsubscript{1c} so important?

DCCT* showed that HbA\textsubscript{1c} is the best long-term marker of diabetes control.

Better control of HbA\textsubscript{1c} leads to better outcomes in people with diabetes.

- Deaths related to diabetes: 21%
- Microvascular complications: 37%
- Myocardial infarction: 14%

* DCCT = Diabetes Control and Complications Trial

International consensus statement 2010

1. HbA$_{1c}$ results standardised worldwide
   • Reference system and results reporting
2. IFCC reference system is the only valid anchor for standardisation
3. HbA$_{1c}$ reported in IFCC (mmol/mol) and derived NGSP (%) units
4. HbA$_{1c}$ conversion tables (IFCC-NGSP) easily accessible
5. Editors to recommend publication in both IFCC and NGSP units
6. Reportable term is HbA$_{1c}$
   • Other terms (e.g. A1C may be used in guidelines and educational material)

Ann Clin Biochem 2010; 47: 290-1

IFCC Task Force on Implementation of HbA1c Standardization
Chair: Prof Garry John (UK)
HbA1c: typical current EQA

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<th>SD</th>
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</table>

**Your result**: 52  
**Target value (ALTM)**: 48.1  
**Your specimen**: 
- %bias: +8.2  
- Transformed bias: +160  
- Accuracy Index: 160  
**2ndary IFCC value**: 47.8  
**DCCT comp. value**: 6.52  
**ALTM (for information only)**: 48.07

**Between-laboratory agreement by concentration for HbA1c (IFCC)**

**UK NEQAS**
HbA1c as a diagnostic test for diabetes

Many clinical practice guidelines exist that link monitoring of diabetic control to target HbA1c levels. Recent guidelines are for HbA1c in diagnosis

WHO Guideline 2011

“HbA1c can be used as a diagnostic test for diabetes providing that stringent quality assurance tests are in place and assays are standardised to criteria aligned to international values, and there are no conditions present which preclude its accurate measurement. An HbA1c of 48mmol/mol (6.5%) is recommended as the cut point for diagnosing diabetes. A value of <48mmol/mol does not exclude diabetes diagnosed using glucose tests.”
Investigation of 2 models to set and evaluate quality targets for HbA1c: biological variation and sigma-metrics

Cas Weykamp, Garry John, Philippe Gillery, Emma English, Linong Ji, Erna Lentes-Westra, Randie R. Little, Gojka Roglic, David B. Sacks, Izumi Takei,

On behalf of the IFCC Task Force on Implementation of HbA1c Standardisation

_Clin Chem_ 2015; _61_: 752-9