Standardization and Harmonization in Laboratory Medicine

Howard Morris
howard.morris@unisa.edu.au
President IFCC
Professor of Laboratory Medicine, University of South Australia, Clinical Scientist, Chemical Pathology, SA Pathology
Adelaide, Australia 5000
Acknowledgements:

• IFCC Scientific Division Executive Committee
• Dr Greg Miller, Virginia Commonwealth University Richmond, Virginia, USA
• Australasian Association of Clinical Biochemists Harmonization Working Group
Overview:

• The lack of comparability of patient results is a major issue for laboratory medicine
• Standardization and harmonization - what are the differences?
• Why do we need commutability?
• What are the international efforts being undertaken to improve harmonization?
Why do we need comparable results?

• Clinical practice guidelines are established to provide optimal clinical treatment

• They often include the use of laboratory test results to guide clinical practice – even when the different clinical assays provide different patient results
Examples of variation of immunoassays currently used for clinical decision limits included in clinical guidelines

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Reference Standard</th>
<th>Level</th>
<th>CV%</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Troponin I (ng/L)</td>
<td>SRM</td>
<td>51.4</td>
<td>34.3</td>
<td>23 – 90</td>
</tr>
<tr>
<td>HbA1c (mmol/mol)</td>
<td>RMP</td>
<td>49.9</td>
<td>3.6</td>
<td>40 – 55</td>
</tr>
<tr>
<td>GH (µg/L)</td>
<td>IS</td>
<td>0.58</td>
<td>12.0</td>
<td>0.24-0.9</td>
</tr>
<tr>
<td>PTH (pmol/L)</td>
<td>IS</td>
<td>10.8</td>
<td>21</td>
<td>6.6-11.9</td>
</tr>
<tr>
<td>hCG (U/L)</td>
<td>IS</td>
<td>5.1</td>
<td>14.9</td>
<td>2.0-9.0</td>
</tr>
<tr>
<td>CA125 (kU/L)</td>
<td>-</td>
<td>71</td>
<td>12.7</td>
<td>52-103</td>
</tr>
</tbody>
</table>

Adapted from Sturgeon CM, Clinica Chimica Acta 2014; 432: 122-126.
Why do we need comparable results?

- Clinical practice guidelines are established to provide optimal clinical treatment.
- They often include the use of laboratory test results to guide clinical practice.
- If different assays provide different results for the same patient sample clinical practice guidelines become less useful; at best the patient will not receive the optimal treatment, at worst the patient may receive incorrect treatment.
Terminology:

- **Standardization**: Results are uniform among routine clinical measurement procedures. Assay traceability is established to a recognised standard reference material defined by International System of Units (SI) providing uniform results independent of assay technique.

- **Harmonization**: Results are uniform among routine clinical measurement procedures. No reference measurement procedure or standard reference material exists and uniformity of results are likely to be dependent on analytical techniques.
<table>
<thead>
<tr>
<th>Category</th>
<th>Reference measurement procedure</th>
<th>Primary (pure substance) reference material</th>
<th>Secondary (value assigned) reference material</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Yes</td>
<td>Yes</td>
<td>Possible</td>
<td>Electrolytes, glucose, cortisol</td>
</tr>
<tr>
<td>2</td>
<td>Yes</td>
<td>No</td>
<td>Possible</td>
<td>Enzymes</td>
</tr>
<tr>
<td>3</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Hemostatic factors</td>
</tr>
<tr>
<td>4</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Proteins, tumor markers, HIV</td>
</tr>
<tr>
<td>5</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Proteins, EBV, VZV</td>
</tr>
</tbody>
</table>
## Traceability categories from ISO 17511

<table>
<thead>
<tr>
<th>Category</th>
<th>Reference measurement procedure</th>
<th>Primary (pure substance) reference material</th>
<th>Secondary (value assigned) reference material</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Yes</td>
<td>Yes</td>
<td>Possible</td>
<td>Electrolytes, glucose, cortisol</td>
</tr>
<tr>
<td>2</td>
<td>Yes</td>
<td>No</td>
<td>Possible</td>
<td>Enzymes</td>
</tr>
<tr>
<td>3</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Hemostatic factors</td>
</tr>
<tr>
<td>4</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Proteins, tumor markers HIV</td>
</tr>
<tr>
<td>5</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Proteins, EBV, VZV</td>
</tr>
<tr>
<td>Category</td>
<td>Reference measurement procedure</td>
<td>Primary (pure substance) reference material</td>
<td>Secondary (value assigned) reference material</td>
<td>Examples</td>
</tr>
<tr>
<td>----------</td>
<td>---------------------------------</td>
<td>---------------------------------------------</td>
<td>----------------------------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>1</td>
<td>Yes</td>
<td>Yes</td>
<td>Possible</td>
<td>Electrolytes, glucose, cortisol</td>
</tr>
<tr>
<td>2</td>
<td>Yes</td>
<td>No</td>
<td>Possible</td>
<td>Enzymes</td>
</tr>
<tr>
<td>3</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Hemostatic factors</td>
</tr>
<tr>
<td>4</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Proteins, tumor markers, HIV</td>
</tr>
<tr>
<td>5</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Proteins, EBV, VZV</td>
</tr>
</tbody>
</table>
Traceability based on ISO 17511
An ideal reference system

Primary Reference Material
Primary Calibrator
Secondary Reference Material

SI Unit
Primary Reference Measurement Procedure
Secondary Reference Measurement Procedure
Traceability based on ISO 17511
A reference system for glucose

Primary Reference Material (NIST SRM 917b) Crystalline glucose

Primary Calibrator (glucose in water, 1, 3, 6, 11 mmol/L)

Secondary Reference Material (NIST SRM 965b glucose in frozen human serum)

SI Unit (glucose, mmol/L)

Primary Reference Measurement Procedure (gravimetry, calibrated NIST mass standards)

Secondary Reference Measurement Procedure Isotope dilution-mass spectroscopy
Traceability based on ISO 17511

Primary Reference Material (pure substance)

Secondary Reference Material or Panel of patient samples

Mfr Working Calibrator

Mfr Product Calibrator

SI unit

Reference Procedure e.g. IDMS

Mfr Selected Procedure

Mfr Standing Procedure

Routine Procedure

Patient sample result
Traceability based on ISO 17511

A reference system for cortisol

Primary Reference Material (pure substance)

Panel of patient samples

Mfr Working Calibrator

Mfr Product Calibrator

Patient sample result

SI unit (nmol/L)

Reference Procedure e.g. IDMS

Mfr Selected Procedure

Mfr Standing Procedure

Routine Procedure

Traceability
www.jctlm.org

A general information portal for global standardization reference materials, reference measurement procedures and networks of accredited reference laboratories
Everything else we measure in the clinical laboratory

Measurands for which reference procedures exist or can be developed
What happens when there is no reference measurement procedure?
Traceable to an international conventional reference material (ISO1751 Category 4)

• The true value is unknown

• Since the goal of harmonization is comparable results irrespective of the measurement procedure used,

• Clinical guidelines can still be implemented
Examples of assays traceable to a reference material

Human chorionic gonadotropin

Prostate-specific antigen

Thyroid stimulating hormone

Human immunodeficiency virus

(no reference measurement procedure available)
Traceability can be established to a reference material such as a secondary reference material.
Traceability requires **commutable** calibration materials

**Commutable** means that values measured for a calibration material and for patient clinical samples have the same relationship between two, or more, measurement procedures for the same measurand.
Commutability:

A reference material is commutable if it demonstrates closeness of agreement

- for results obtained from two measurement procedures
- among results for clinical samples from the same two measurement procedures

(Rephrased from VIM 3: 2008)
Commutable: same relationship for clinical samples and reference materials
Non-commutable: different relationship for clinical samples and reference materials
Calibration with non-commutable materials

Patient results between the 2 measurement procedures are now different
IFCC Working Group on Commutability

Developing

• Operating procedures for the formal assessment of commutability

• Criteria for commutability taking into account the intended use of a reference material
What happens when there is:

- No reference measurement procedure
- No reference material

ISO 1751 Category 5

Harmonization strategies are implemented
Barriers to Harmonization

Lack of a systematic process to identify and prioritize measurands

Materials are labelled as “reference materials” that have not been validated to be commutable for the intended measurement procedures

Inadequate definition of the measurand

Inadequate analytical specificity for the measurand

Lack of systematic procedures to implement harmonization, in particular:
  - when there is no reference measurement procedure
  - when there is no reference material
International coordination of harmonization activities (International Collaboration for Harmonization of Clinical Laboratory Results)

Develop an infrastructure to coordinate harmonization activities world wide to include:

1. Prioritization of analytes
2. Gap analysis for what needs to be done
3. Technical processes to achieve harmonization
4. Surveillance of success of harmonization
www.harmonization.net

A general information portal for global standardization / harmonization activities

Currently 96 measurands are recorded with regard to medical impact and harmonization status.

This list is the subject of a major project by ICHCLR officers.
Thankyou