Roadmap for Harmonization of Clinical Laboratory Test Results

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Outline

- Why harmonized results are needed
- How to achieve results traceable to a reference system
- Barriers to achieving harmonized results
- AACC’s global harmonization initiative
Good laboratory medicine requires:

- Total error of measurement small enough that a result reflects a patient’s biological condition

- Comparable results independent of
  - where and when a test was performed
  - the measurement procedure used
Why do we need comparable results

If different measurements give different results for the same patient sample:

- Clinical practice guidelines become less useful
- Patients may receive incorrect treatment
- Laboratory results in EHRs are less useful
How to achieve comparable results

- Calibration of all procedures is traceable to a common reference system
- All measurement procedures measure the same quantity
- Surveillance (PT or EQA) to monitor and maintain consistent performance
Traceability of Laboratory Results

Standardization and harmonization are based on traceability principles described in ISO Standard 17511. Differences between standardization and harmonization

- **Standardization**: all measurement procedures get the same result for a sample and the result is traceable to SI with a reference measurement procedure

- **Harmonization**: all measurement procedures get the same result for a sample when there is no reference measurement procedure
## 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>
</tbody>
</table>

**Harmonization**
Traceability (based on ISO 17511)

A reference system

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 with NIST mass standards)

Secondary Reference Measurement Procedure
(IDMS)
Traceability (based on ISO 17511)

Primary Reference Material (pure substance)

Secondary Reference Material (matrix)

Mfr Working Calibrator

Mfr Product Calibrator

Patient sample result

SI unit

Reference Procedure (e.g. IDMS)

Mfr Selected Procedure

Mfr Standing Procedure

Routine Procedure

Patient sample results are equivalent to the reference procedure results.
Traceability (based on ISO 17511)

Primary Reference Material (pure substance)

Panel of patient samples

Mfr Working Calibrator

Mfr Product Calibrator

Patient sample result

SI unit Reference Procedure (e.g. IDMS)

Mfr Selected Procedure

Mfr Standing Procedure

Routine Procedure

(calibrator)

Panel of patient samples are equivalent to the reference procedure results
Traceability requires commutable calibration materials

Commutable means that values measured for a calibration material and for native clinical samples have the same relationship between two, or more, measurement procedures for the same measurand.
Commmutable: same relationship for clinical samples and reference materials
Non-commutable: different relationship for clinical samples and reference materials
Use of a non-commutable material for calibration traceability will cause:

- Incorrect value assignment for a routine (field) measurement procedure calibrator
- Incorrect results for patient samples

Traceability to a Reference Material

Reference Material must be commutable with patient samples for all measurement procedures with which it will be used.

Secondary Reference Material

Procedure 1
Procedure 2
Procedure 3
Procedure n

Patient Samples

Results 1
Results 2
Results 1-n the same
Results n
EQA/PT materials are usually not commutable with patient samples

- Magnitude of a matrix-related bias is unknown
  - Observed bias = calibration bias + matrix-related bias
- Cannot compare a lab’s result to:
  - Another method’s mean value
  - An all methods’ mean value
  - A reference method assigned value
- Cannot compare mean values between different methods
Some EQA/PT programs use commutable samples

- Samples are typically prepared from freshly collected and minimally processed human samples.
- May be limited to one or a small number of analytes due to availability of samples with appropriate concentrations.
- Can compare results across assay systems.
- Can evaluate success of harmonization and standardization.
Practical Considerations
Traceability (an application)

Primary Ref Material (pure substance)

SI unit

Reference Procedure (e.g. IDMS)

Panel of patient samples

Results equivalent to those from the Reference Procedure

Routine Procedure

Mfr Product Calibrator

Value is assigned to produce traceable results for patient samples
Traceability (an application)

Primary Ref Material (pure substance) → SI unit

Reference Procedure (e.g. IDMS) → Results equivalent to those from the Reference Procedure

Panel of patient samples → Routine Procedure

Mfr Product Calibrator

May be non-commutable, but has a procedure-specific factor to correct non-commutability bias
A manufacturer's product calibrator is intended for use with a specific measurement procedure.

It cannot be used with a different manufacturer's measurement procedure.
Measurands for which reference procedures exist or can be developed
What happens when there is no reference measurement procedure
Traceability (based on ISO 17511)

- Value assignment
- Commutability

Secondary Reference Material (matrix)

- Mfr Working Calibrator
- Mfr Product Calibrator

Mfr Selected Procedure
Mfr Standing Procedure
Routine Procedure

Patient sample results are traceable to a reference material
Examples: traceable to a reference material
(no reference measurement procedure)

- Human chorionic gonadotropin
- Prostate-specific antigen
- Thyroid stimulating hormone
- Human immunodeficiency virus
Value assignment when there is no reference measurement procedure

⇒ Arbitrary, e.g. U/L, or nominal concentration without a "true" value

⇒ Traceable to a pure substance (e.g. recombinant protein) – may not be the same as the clinical measurand

⇒ By a designated comparison procedure

⇒ Called an International Conventional Calibrator (or International Conventional Reference Material)
Traceable to an international conventional reference material

- The true value is not known
- Since the goal of harmonization is comparable results irrespective of the measurement procedure used,
- Clinical guidelines can still be implemented
Many secondary reference materials are not commutable with native clinical samples for routine clinical laboratory procedures.
The Problem

Many secondary reference materials are not commutable with native clinical samples for routine clinical laboratory procedures

- Historically, commutability of reference materials was not validated for use with routine clinical laboratory measurement procedures
Many secondary reference materials are not commutable with native clinical samples for routine clinical laboratory procedures.

- A manufacturer’s standing procedure is frequently the same as the clinical laboratory procedure but calibrated with a "master lot of calibrator" that may be traceable to a non-commutable reference material.
Many secondary reference materials are not commutable with native clinical samples for routine clinical laboratory procedures.

- A manufacturer's standing procedure is frequently the same as the clinical laboratory procedure but may be calibrated with a "master lot of calibrator" that is traceable to a non-commutable reference material.

The Problem

Breaks the traceability chain

<table>
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<th>Secondary Reference Material (matrix)</th>
<th>Mfr Selected Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mfr Working Calibrator</td>
<td>Mfr Standing Procedure</td>
</tr>
<tr>
<td>Mfr Product Calibrator</td>
<td>Routine Procedure</td>
</tr>
<tr>
<td>Patient result</td>
<td>calibrator</td>
</tr>
</tbody>
</table>

- The diagram illustrates the chain of events from secondary reference material to patient result, with the red circle indicating the break in traceability.

- The problem is that the traceability chain is broken at the manufacturer's selected procedure, making the calibration less reliable.

- The diagram highlights the need for a more direct and traceable calibration process to ensure accurate results.
The Problem

Many secondary reference materials are not commutable with native clinical samples for routine clinical laboratory procedures

- Even though manufacturers show traceability, the process fails to provide equivalent results for patient samples when different measurement procedures are used
TSH methods
All traceable to IS 94/674 (WHO)

Mean ± 95% CI for 40 patient samples

Calibration traceability does not ensure accuracy for an individual patient sample

- Measurement procedure may not be specific for the measurand
- Measurand may not be well defined
  - Molecular form(s) of clinical interest
- Interfering substances present in a patient’s sample may influence the result
Other examples:

- **Follicle stimulating hormone** (Clin Chim Acta 1998;273:103-17)
- **C-peptide** (Clin Chem 2008;54:1023-6)
- **Human chorionic gonadotropin** (Clin Chem 2009;55:1484-91)
- **Cytomegalovirus** (Clin Chem 2009;55:1701-10)
- **Troponin I** (Pathology 2010;42:402-8)
Must change practice to require commutability validation for reference materials intended for use with:

- Manufacturer’s standing procedures
- Routine clinical laboratory procedures

New biomarkers

Sustainable calibration traceability needs to be part of the development process:

- Definition of the measurand
- Requirements for measurement specificity
- Reference measurement procedure
- Commutable reference materials
What happens when there is both:

- no reference measurement procedure
- no reference material
Traceability (based on ISO 17511)

- There is no common calibrator
- Method specific reference intervals or decision values are used

Mfr Working Calibrator

Mfr Product Calibrator

Mfr Standing Procedure

Routine Procedure

Patient sample result
Examples: traceable to a manufacturer’s working calibrator

(no reference material nor reference measurement procedure)

- B-type natriuretic peptide
- CA-125
- Epstein-Barr virus
- Varicella zoster virus
ISO 17511 category 5 needs practical procedures to achieve harmonization

Possibilities for consideration:

- traceable to an all methods mean (outliers removed) of a panel of patient samples
- traceable to a designated measurement procedure (arbitrary, but which has good correlation with clinical outcome)
Progress has been made!

A number of organizations are addressing standardization / harmonization around the world

⇒ IFCC has been a key leader in global standardization

⇒ IFCC Scientific Division Current Activities
  ◆ Enzymes (pancreatic lipase; RMa for LD, CK, ATL)
  ◆ Thyroid Function Tests (FT4, TSH)
  ◆ Hemoglobin A2
  ◆ Carbohydrate-Deficient Transferrin
  ◆ Urine Albumin
  ◆ Pregnancy-Associated Plasma Protein A
  ◆ Insulin
  ◆ Troponin I
  ◆ Autoantibody Tests
  ◆ Parathyroid Hormone
  ◆ CSF-Proteins
  ◆ Bone Marker Assays
Progress has been made!

A number of organizations are addressing standardization / harmonization around the world

- IFCC has been a key leader in standardization
- Many other national and international groups are also engaged

However,

- The approach has been ad-hoc based on individual interests
- There is no central organizing body to coordinate the work of different groups
What do we do?
Roadmap for Harmonization of Clinical Laboratory Measurement Procedures


Report from an AACC conference, October, 2010: Improving Clinical Laboratory Testing through Harmonization: An International Forum
Barriers to harmonization

- Materials are labeled 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.
Barriers to harmonization

- Lack of a systematic process to identify and prioritize measurands in need of harmonization

- Lack of systematic procedures to implement harmonization, in particular:
  - when there is no reference measurement procedure
  - when there is no reference material
The Roadmap

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
Cooperation

- With other organizations already working to improve standardization / harmonization
- Provide a communications portal and prioritization scheme among organizations to coordinate standardization / harmonization activities
- Maintain an open and transparent process
Path Forward
2011-2012

- Steering Committee
- 3 Task Forces
  1. Operations
  2. Checklists
  3. Tool box
Focus technical work on measurands for which no reference measurement procedure exists

Measurands in ISO 17511 categories 4 and 5 have been technically more difficult to address, thus there have been few effective procedures implemented for harmonization in these categories.
AN INFRASTRUCTURE FOR HARMONIZATION

International Consortium for Harmonization of Clinical Laboratory Results

- Approval
- Governance, Administration
- Operations Management
- Strategic Partners Group
- Council
- Harmonization Oversight Group
- Harmonization Implementation Groups
- Special Working Groups
- Work Groups

Secretariat/Host - AACC
Stakeholders (Strategic Partners Group):
- Clinical practice groups
- Laboratory practice groups
- IVD manufacturers
- Public health organizations
- Metrology Institutes
- Standards organizations
- Regulatory organizations
- PT/EQA organizations

Communication

Harmonization Oversight Group

Operation

Evaluate measurand proposals

When no RMP

Solicit champion and funding
- Clinically affected entity
- Economically affected entity

Special Working Group
- Review priority and technical feasibility
- Recommendation to Harmonization Oversight Group

Harmonization Implementation Group
- Technical plan
- Surveillance plan
- Implement the plans
- Achieve JCTLM listing

Coordination / Cooperation

- If work is underway, refer to that group
- If RMP is possible, refer to another group
International Consortium for Harmonization of Clinical Laboratory Results

Council Members

AACC

College of American Pathologists

The Korean Society for Laboratory Medicine

Chinese Association for Clinical Laboratory Management
International Consortium for Harmonization of Clinical Laboratory Results

Harmonization Oversight Group

Greg Miller – Chair (USA)
Eun-Hee Lee (Korea)
Stephen Master (USA)
Joe Passarelli (USA)
William Rosner (USA)
Sverre Sandberg (Norway)
Thomas Scholl (USA)
Linda Thienpont (Belgium)
Ian Young (UK)
A general information portal for global standardization/harmonization activities

- Communicate with stakeholders
- Status reports on measurands
- Useful technical information
- Information on global activities
- Links to other organizations
Thank You!!