Traceability in Laboratory Medicine: What Every Laboratory Specialist Should Know

Gary L. Myers, PhD; Chair, JCTLM
Robert Wielgosz, PhD; Director Chemistry, BIPM

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Outline

➢ Why we need comparable results

➢ How to achieve comparable results traceable to a reference system

➢ Global challenges to traceability

➢ Traceability resources
Primary reasons for testing

• To identify individuals at increased risk of disease and/or monitor disease management

• To develop epidemiologic data from which to establish public health strategies for disease management on a population level
Good laboratory medicine requires:

- Total error of a measurement result is small enough to reflect a patient’s true biological condition

- Test results are traceable (equivalent) and independent of:
  - where and when a test was performed
  - the measurement procedure used
In the context of laboratory medicine, “traceability” really means Metrological Traceability.
What is Metrological Traceability?

• Definition from the International vocabulary of metrology (VIM)

Metrological traceability – is the property of a measurement result whereby the result can be related to a reference through a documented unbroken chain of calibrations, each contributing to the measurement uncertainty.

Referred to as the Metrological Traceability Chain
Traceability of Laboratory Results

The concept of traceability is based on principles described in ISO Standard 17511.

In vitro diagnostic medical devices - Measurement of quantities in biological samples - **Metrological traceability of values assigned to calibrators and control materials**
Traceability to Système International

<table>
<thead>
<tr>
<th>MATERIAL</th>
<th>CALIBRATION VALUE ASSIGNMENT</th>
<th>PROCEDURE</th>
<th>IMPLEMENTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>a) definition of SI unit by CGPM</td>
<td>b) primary reference measurement procedure</td>
<td>BIPM, NMI, ARML</td>
</tr>
<tr>
<td>c) primary calibrator</td>
<td>d) secondary reference measurement procedure</td>
<td></td>
<td>BIPM, NMI</td>
</tr>
<tr>
<td>e) secondary calibrator$^b$</td>
<td>f) manufacturer's selected measurement procedure</td>
<td></td>
<td>NMI, ARML</td>
</tr>
<tr>
<td>g) manufacturer's working calibrator$^b$</td>
<td>h) manufacturer's standing measurement procedure</td>
<td></td>
<td>NMI, ARML, ML</td>
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<tr>
<td>i) manufacturer's product calibrator$^b$</td>
<td>j) end-user's routine measurement procedure</td>
<td></td>
<td>ML, ML, ML</td>
</tr>
</tbody>
</table>

routine sample

RESULT

ISO 17511 – Figure 2
Three Separate Measurement Components that Require Traceability

• Research Laboratories that support investigational studies

• Manufacturers that develop and provide routine clinical assays

• Clinical laboratories that provide test results for assessing risk and monitoring therapy
When and Why Is Traceability Most Important?

- To insure the reliability and comparability of research findings across studies
- When patients are seen in a variety of health care settings, each using different clinical labs
- When patient’s test results are being compared to clinical guidelines from the medical literature and/or large national or international research studies (e.g., estimated GFR for CKD, HbA1c for diabetes, cholesterol for CVD, etc.).
Test results that are not traceable (equivalent) are considered non-harmonized.
Why does it matter?

Non-harmonized laboratory testing

Why does it matter for patients?
- Creates difficulty in comparing results from different providers
- Makes it confusing to investigate the medical implications of test results
- May result in incorrect treatment
- May lead to unnecessary retesting and possible unnecessary visits to healthcare provider
Why does it matter for the Healthcare System?

- Problems for the portable medical record
- Outcomes-based reimbursement - If we can’t compare lab values, how can we tell who is doing a good job with their patients?
- Makes it more difficult to assess health trends
- Complicates longitudinal testing
- Inhibits the development of accurate national/international guidelines for treating patients
Challenges for achieving traceability

- Different methods
- No "gold standard" assay
- Different manufacturers
- Variability in what is being measured
- Materials are not commutable
- Material unlike patient sample
- No reference materials

Lack of traceability
Tools Needed for Traceability

- Reference measurement procedure(s)
  - Gold Standard
- Reference materials (commutable)
- Reference MP laboratories
JCTLM Formation

The JCTLM was formed in 2002 bringing together the sciences of metrology, laboratory medicine and laboratory quality management to promote global traceability.

Accurate results for patient care
JCTLM Database


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

- **JCTLM** coordinates the nomination and review process for database entries
JCTLM Review for compliance with ISO standards

ISO 17511 In vitro diagnostic medical devices - Measurement of quantities in biological samples - Metrological traceability of values assigned to calibrators and control materials (under revision)

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 Metrological traceability of values for catalytic concentration of enzymes assigned to calibrators and control materials

ISO 15195: 2003 Reference Measurement Laboratories
Your search criteria: Higher-order reference materials; Analyte: cholesterol; Analyte category: метаболиты и производные; Matrix category: -

Results of the search

Your search criteria produced 9 summary results. Select one or several higher-order reference material summary descriptions amongst the following list and click on 'View' to access more information.

Select all items from the list

Sort by: Analyte, Matrix/Material, Organization

<table>
<thead>
<tr>
<th>Select</th>
<th>Analyte</th>
<th>Analyte category</th>
<th>Matrix/Material</th>
<th>Organization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>cholesterol</td>
<td>metabolites and substrates</td>
<td>cholesterol crystalline material</td>
<td>NIM</td>
</tr>
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<td>frozen human serum</td>
<td>LNE</td>
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<td>HSA</td>
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<td>total cholesterol</td>
<td>metabolites and substrates</td>
<td>frozen human serum</td>
<td>LNE</td>
</tr>
</tbody>
</table>

Deselect all items from the list

View
Result of the search: list of higher-order reference materials

Your search criteria: Higher-order reference materials; Analyte: cholesterol; Analyte category: -; Matrix category: -

Save as PDF  Modify your selection

Results of the search

total cholesterol in frozen human serum
Health Sciences Authority (HSA), Singapore
Phone: +65 6775 1605 ext 104
Fax: +65 6775 1398
Email: HSA_CML@hsa.gov.sg
Web: http://www.hsahsgov.sg

<table>
<thead>
<tr>
<th>Name of the reference material</th>
<th>HRM-3002A, Creatinine, Glucose, Total Cholesterol, Urea, and Uric Acid in Frozen Human Serum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantity</td>
<td>Amount-of-substance concentration</td>
</tr>
<tr>
<td>Analyte certified/assigned value</td>
<td>3.45 mmol/l to 5.92 mmol/l</td>
</tr>
<tr>
<td>Expanded uncertainty (level of confidence 95 %)</td>
<td>0.07 mmol/l to 0.11 mmol/l</td>
</tr>
<tr>
<td>Reference(s) on commutability</td>
<td>See Certificate of Analysis for HRM-3002A</td>
</tr>
<tr>
<td>Traceability</td>
<td>SI</td>
</tr>
<tr>
<td>CRM listing</td>
<td>List I</td>
</tr>
</tbody>
</table>
JCTLM Database: www.bipm.org/jctlm/

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

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

- Higher-order reference materials
- Reference measurement methods/procedures
- Reference measurement services

Select your requirement:

Search
JCTLM Database: Entries as of March 2017

- 293 Certified Reference Materials
- 184 RMPs that represent 80 different analytes in 9 categories
- 161 reference measurement services delivered by 17 reference labs
Challenges for traceability

Measurands for which reference procedures exist or can be developed
Picking the low-hanging fruit!

-omics  HCG  Troponin I  PTH  TSH  PSA  Epstein Barr Virus

AST  urea  HbA1c  ALT
cholesterol  glucose  homocysteine
uric acid  creatinine
Challenges for Traceability

- A national database in Finland suggests there are ~4000 clinically relevant analytes measured across the scope of laboratory medicine (P Laitinen, Finland)

- The Joint Committee for Traceability in Laboratory Medicine (JCTLM) database holds 293 certified reference materials; 184 reference measurement procedures covering 80 measurands
  
  [Link](http://www.bipm.org/jctlm/)

- The World Health Organisation (WHO) catalogue of blood products and related biological standards contains ~300 entries
  
  [Link](http://www.who.int/bloodproducts/catalogue/en/)
Challenges for Traceability

- Commutability is key to establishing traceability in laboratory medicine.

- Materials may be labeled as “reference materials”, but have not been validated to be commutable for the intended measurement procedures.
Commutable: same relationship for clinical samples and reference materials
Non-commutable: different relationship for clinical samples and reference materials
Metrological Traceability Chain

A non-commutable calibrator breaks the traceability chain

Key Step in Calibration

Pure Substance Reference Material

Secondary Reference Material (matrix)

Manufacturer's Product Calibrator

Patient's Sample

Reference Measurement Procedure

Manufacturer's Internal Procedure

Clinical Laboratory Method

Assign value

Calibrate
Why commutability matters

Even though manufacturers show traceability, if reference material is non-commutable the process will fail to provide equivalent results for patient samples among different measurement procedures.

Patients may receive incorrect treatment
IFCC Working Group on Commutability
(established March 2013)
Chair: Greg Miller, PhD, Virginia Commonwealth University

- Establish operating procedures for the formal assessment of commutability of a reference material

- Establish criteria for commutability taking into account the intended use of a reference material

- Propose standard terminology to describe commutability characteristics

- Provide guidance on specific information to be provided regarding commutability

- Develop educational materials on commutability for manufacturers, laboratories, and end users
Global challenges in implementing traceability in laboratory medicine

Lack of Global Coordination

➢ No definitive list of biomarkers used across laboratory medicine
➢ No systematic process to identify and prioritize measurands in need of harmonization
➢ Traceability activities among different organizations is not coordinated on a global level
International Consortium for the Harmonization of Clinical Laboratory Results

Primary Functions:

1. Prioritize measurands by medical importance

2. Maintain a website that will serve as a resource for information on traceability activities of different global organizations

3. Promote processes for harmonization when there is no reference measurement procedure or reference material
The International Consortium for Harmonization of Clinical Laboratory Results

OUR VISION

✓ Clinical laboratory test results will be equivalent independent of the clinical laboratory that produced the results

OUR MISSION

✓ To provide a centralized process to organize global efforts to achieve harmonization of clinical laboratory test results

Our specific objectives

✓ to improve the harmonization of results from clinical laboratory measurement procedures for measurands (analytes) that do not have reference measurement procedures

✓ to provide a resource center for information on global activities to harmonize and standardize clinical laboratory measurement procedures

Organization

Operating Procedures for the International Consortium for Harmonization of Clinical Laboratory Results describe the program. The governing body is a Council made up of organizations from around the world that contribute financially to support the administration of the program. A Harmonization Oversight Group (HOG) is responsible to manage the harmonization activities.

Interested stakeholders may become Organizational Members of the consortium or join the Strategic Partners Group to support and contribute to the harmonization activities.

The AACC is the secretariat for administration of the program.

Council Members

American Association for Clinical Chemistry

Japanese Committee for Clinical Laboratory Standards

Korean Society for Laboratory Medicine

Organizational Member

College of American Pathologists
This section provides information on the status of harmonization or standardization of measurands. Priorities based on medical impact are provided for measurands for which harmonization is needed or that have an incomplete or inactive implementation of a harmonization activity. Additional information regarding the harmonization status and medical impact is available by clicking on the measurand name. Information on reference materials, reference measurement procedures, and reference laboratory services is provided by the links in the JCTLM column. Links to organizations actively addressing harmonization of particular measurands are provided for additional information on those projects.

Comments on measurand status can be sent using the Contact Us tab. Download the form to submit a new measurand.

Summary of Measurand Harmonization Activities
<table>
<thead>
<tr>
<th>Measurand</th>
<th>Matrix</th>
<th>Medical Impact of Harmonization</th>
<th>Harmonization Status</th>
<th>JCTLM Listed</th>
<th>Organization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkaline Phosphatase (ALP)</td>
<td>Serum</td>
<td>Medium</td>
<td>Incomplete</td>
<td></td>
<td>IFCC</td>
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<tr>
<td>Alanine Aminotransferase (ALT)</td>
<td>Serum</td>
<td>Medium</td>
<td>Incomplete</td>
<td></td>
<td>IFCC</td>
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<tr>
<td>Albumin</td>
<td>Urine</td>
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<td>Active</td>
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<td>NKDEP IFCC JSCC</td>
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<td>Albumin</td>
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<tr>
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<td>Aspartate Aminotransferase (AST)</td>
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<td>Needed</td>
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<td>IFCC</td>
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<tr>
<td>Bilirubin, total</td>
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<td>Adequate</td>
<td></td>
<td>IFCC</td>
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<tr>
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<td></td>
<td>Adequate</td>
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<td>IFCC</td>
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<tr>
<td>C-Reactive protein, high sensitivity</td>
<td>Serum</td>
<td></td>
<td>Adequate</td>
<td></td>
<td>IFCC</td>
</tr>
</tbody>
</table>
Alanine Aminotransferase (ALT)

The IFCC has developed reference measurement procedures for AST and ALT enzymes. The IFCC reagent formulation is generally used by IVD manufacturers with some adaptation for the technology of a given instrument system. Standardization is thus easily achievable. The harmonization issue is whether or not pyridoxyl-5-phosphate (P₅P) is included in reagents from IVD manufacturers. P₅P is needed to fully activate the enzymes in situations when a patient has a deficiency in this vitamin as may occur in kidney failure and other conditions. A technical issue is that adding P₅P to reagents reduces the reagent stability. Consequently P₅P is supplied in a separate container to be mixed at the time a reagent is put into use. Furthermore, laboratories may prefer not to add P₅P because there may be reagent waste in lower testing volume situations. Some countries do not typically include P₅P and in other countries there is a mix of inclusion and exclusion in reagents. Differences in vitamin deficiency between countries may contribute to different practices. The ICHCLR recommends that manufacturers make available reagents that include P₅P so that laboratories can determine if their population would benefit from its use in the reagents. A medium priority was assigned because these two analytes are well standardized except for the P₅P inclusion and the need for P₅P may vary among different regions of the world.

Support actions for the routine lab to achieve traceability

- Define clinical decision values and analytical requirements
- Provide reference materials and higher-order reference methods
- Include traceability in training & in standards required for accreditation
- Lists available materials and methods. Promotes traceability
- Produce methods that are traceable to a reference system, when available
- Use commutable materials to monitor method performance

Adapted from White GH Ann Clin Biochem 2011; 48: 393-408
What can you do as a laboratory medicine specialist in your lab to assure method traceability?

1. Check the traceability status of the methods that you use. If uncertain check with your supplier.
2. Encourage key colleagues to learn more about traceability in laboratory medicine.
3. Check whether your EQA scheme provider is using commutable materials.
4. Analyse your EQA performance critically to assess the extent to which the lack of traceability may be negatively impacting laboratory results obtained.
Where can you find more information?

Websites
- JCTLM database of reference materials and measurement procedures [www.bipm.org/jctlm/](http://www.bipm.org/jctlm/)
- Joint Committee for Traceability in Laboratory Medicine (JCTLM): [www.jctlm.org](http://www.jctlm.org)
- International Consortium for Harmonization of Clinical Laboratory Results [www.harmonization.net](http://www.harmonization.net)
In Summary

How to reduce between method variability

➢ Calibration of all procedures is traceable to a common reference system (traceability chain)

➢ All measurement procedures measure the same quantity

➢ Surveillance (PT or EQA) is needed to monitor and maintain consistent performance

➢ Materials for calibration and surveillance purposes should be commutable
Thank You!!

Accurate results for patient care