The International Consortium for Harmonization of Clinical Laboratory Results

★ An AACC initiative ★

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What is the problem

- Many laboratory measurement procedures give different results for the same specimen.
Why does it matter

- Patients may get the wrong treatment
  - Many clinical decisions are informed by laboratory results
  - Many clinical guidelines use a fixed laboratory test value for treatment decisions
Current parathyroid hormone immunoassays do not adequately meet the needs of patients with chronic kidney disease.


Treatment variation caused by comparing highest and lowest PTH concentrations in 18 patients.
Why else does it matter

- Clinical studies may use a central lab with a single method
  - Guidelines from the study cannot be implemented until all other methods are harmonized to the central lab

- Clinical studies may use different methods
  - Data cannot be aggregated to develop guidelines until the results are harmonized
What is harmonization

- Equivalent results among different measurement procedures for the same laboratory test
  - Nomenclature
  - Patient preparation
  - Specimen collection and handling
  - **Result value** (Today’s topic)
  - Reporting units
  - Interpretive information
Terminology

- **Harmonization**: achieving equivalent results among different measurement procedures
  - Frequently implies there is no reference measurement procedure

- **Standardization**: achieving equivalent results by having calibration traceable to SI using a reference measurement procedure
How to achieve equivalent results

- Calibration of all measurement procedures is traceable to a common reference system
- All measurement procedures measure the same quantity
Calibration traceability does not ensure accuracy for an individual patient sample

- Measurement procedure may not be specific for the measurand
  - Interfering substances may influence the result

- Measurand may not be well defined
  - Molecular form(s) of clinical interest may not be understood
Measurands for which no reference procedures exist nor are likely to be developed

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

(calibrator)

Mfr Selected Procedure

Mfr Standing Procedure

Routine Procedure

Patient sample result

Patient sample results are traceable to a reference material.
Approaches to value assignment

- Arbitrary units, e.g. U/L

- A nominal concentration based on a pure substance (e.g. purified or recombinant protein)
  - may not be the same as the clinical measurand
  - may contain reactive impurities or aggregated forms

- By a designated comparison procedure, or mean of a group of procedures
Consensus values are adequate

- The actual quantity value (e.g. concentration) may not be known

- Harmonization can be achieved

- Clinical guidelines can be implemented
Value assignment must be sustainable

- Replacement batches must be consistent
  - Quantity values
  - Other reactive characteristics
    - Measurand molecular form
    - Commutability
What happens when there is both:

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

- A harmonization process is needed
- The process needs to be fit-for-purpose

Mfr Working Calibrator
Mfr Product Calibrator

Mfr Standing Procedure
Routine Procedure

Patient sample result

Patient sample results are not traceable to any international reference
Where is the low hanging fruit?

Reference methods are the most robust.

Reference materials seem more challenging!
Where is the low hanging fruit?

How will we harmonize without reference materials?

Reference methods are relatively challenging!

Reference methods are the most robust.
Opinion:

Accuracy in clinical chemistry – who will kiss Sleeping Beauty awake?


“have the courage to agree on pragmatic solutions”
Prince Harmonization finds the Sleeping Beauty
Roadmap for Harmonization of Clinical Laboratory Measurement Procedures

W. Greg Miller,1* Gary L. Myers,2 Mary Lou Gantzer,3 Stephen E. Kahn,4 E. Ralf Schönbrunner,5
Linda M. Thienpont,6 David M. Bunk,7 Robert H. Christenson,8 John H. Eckfeldt,9 Stanley F. Lo,10
C. Micha Nübling,11 and Catharine M. Sturgeon12

- International Forum organized by AACC in October, 2010
- 90 participants from 12 countries
- Representing 62 organizations & manufacturers
Challenges for harmonization

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

- Inadequate understanding of the measurand – the quantity intended to be measured.

- Inadequate analytical specificity for the measurand.
Challenges for 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
Challenges for harmonization

- Despite many organizations in many countries working to improve harmonization:
  - The work is not coordinated to prevent
    - Duplication of effort
    - Different approaches by different groups
  - People do not know what others are doing
Challenges for harmonization

- Regulatory requirements
  - Changing calibration requires regulatory approval
  - Does the clinical benefit justify the cost to meet regulatory requirements?
  - Can regulatory guidance be modified to lower the cost?
The Roadmap

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

1. Prioritization of measurands
2. Coordination of work by different organizations
3. Developing technical processes to achieve harmonization
4. Surveillance of success of harmonization
Focus technical work on measurands for which no reference measurement procedure exists

- Measurands in this category have been technically challenging
- There have been few effective procedures implemented for harmonization of these measurands
Cooperation

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

- Steering Committee
- 3 Task Forces
  1. Administrative operations
  2. Checklists for submission and evaluation of measurands; now used for web site
  3. Tool box of approaches to harmonization; now available on web site
AN INFRASTRUCTURE FOR HARMONIZATION

International Consortium for Harmonization of Clinical Laboratory Results

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

Review and Recommend

Secretariat/Host - AACC
Strategic Partners Group

Key stakeholders:

Clinical practice groups
Metrology Institutes

Laboratory practice groups
Standards organizations

IVD manufacturers
Regulatory organizations

Public health organizations
PT/EQA organizations
Strategic Partners Group

Members of the Strategic Partners Group have the opportunity to support the program by submitting measurands in need of harmonization and to nominate experts for consideration to serve on the Harmonization Oversight Group. Members will receive project plans and milestone updates from Harmonization Implementation Groups for review and comment. Stakeholders who are committed to harmonization of clinical laboratory results (e.g. clinical laboratory and medical organizations, IVD manufacturers, metrology institutes, standard-setting organizations, public health organizations, regulatory agencies and individuals) may become members of the Strategic Partners Group. The annual membership fee for a Strategic Partners Group member is $500. Subscription to the Strategic Partners Group during 2013 will carry a Strategic Partner's membership status forward through December of 2014 to coincide with an annual membership period.

Click here for more information on the operation of the International Consortium for Harmonization of Clinical Laboratory Results.

Join the Strategic Partners Group
Measurands

This section provides information on the status of harmonization or standardization of measurands. Information on reference measurement procedures and reference materials under development is provided when such information is available as well as information on commutability of existing reference materials where information exists. Links to organizations actively addressing harmonization of particular measurands are provided for inquiry on additional information on those projects. For measurands not yet harmonized, information is provided on the priority and technical feasibility for harmonization determined by the Harmonization Oversight Group.

Submit a Measurand

Review my Submissions

Download the submission form data elements.
Harmonization Oversight Group

Greg Miller (chair), USA
Eun-Hee Lee, Korea
Stephen Master, USA
Joseph Passarelli, USA
William Rosner, USA

Sverre Sandberg, Norway
Thomas Scholl, USA
Linda Thienpont, Belgium
Ian Young, UK
Strategic Partners Group (Stakeholders):
- Clinical practice groups
- Laboratory practice groups
- IVD manufacturers
- Public health organizations
- Metrology Institutes
- Standards organizations
- Regulatory organizations
- PT/EQA organizations

Coordination / Cooperation
- If work is underway, refer to that group
- If RMP is possible, refer to another group
- If interest by another group, coordinate

Harmonization Oversight Group

Evaluate measurand proposals
When no RMP
- Solicit champion and funding
  - Clinically affected entity
  - Economically affected entity

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

Communication
Special Working Group
- Review priority and technical feasibility
- Recommendation to Harmonization Oversight Group
Toolbox of technical procedures for harmonization

International Consortium for Harmonization of Clinical Laboratory Results

Toolbox of technical procedures to be considered when developing a process to achieve 
harmonization for a measurand
Toolbox

- Integrated Harmonization Protocol
- Step-up Design for Harmonization
Integrated Protocol

Assessment study using:

- Clinical samples
- Pooled clinical samples
- Admixed clinical samples for linearity
- Candidate reference materials
Integrated Protocol

Information regarding:

- Measurement procedures
  - Reproducibility
  - Linearity
  - Heterogeneity
  - Correlation
  - Calibration

- Candidate RMs
  - Commutability
  - Stability
  - Availability
  - Costs
Integrated Protocol

Enables decisions:

- Feasibility to achieve harmonization
- Approach to harmonization
- Commitment to proceed
Step Up Design

- No reference measurement procedure
- No reference material

- Developed by Linda Thienpont in the context of the IFCC Committee for Standardization of Thyroid Function Tests
Step Up Design

- Sequence of patient sample comparisons between clinical laboratory procedures
- Success at one phase allows to “step up” to the next phase
- After several qualification phases, a panel of patient sera is fit for purpose to harmonize a set of clinical lab measurement procedures
Step Up Design

- High-volume (~200 mL) single-donation normal samples (C37-A protocol)

- Single-donation samples (~20 mL) covering the most prevalent clinical conditions (typical laboratory blood collection tubes)
Step Up Design

- A statistically valid target as a surrogate “reference measurement procedure” applied to a panel of clinical samples that become a set of international conventional calibrators.

- Commutability is an inherent characteristic of these clinical samples by taking care in the origin of the clinical samples, and the way they are collected and handled.
Key attributes – step up

Measurement procedures:

- Meet performance requirements
- Correlate with each other
- Have acceptable sample specific influences
Key attributes – step up

- Value assignment by an all procedures trimmed mean

- Sustainability by a second panel to:
  - Harmonize new methods entering the market
  - Transfer values to a subsequent panel
Good enough

Time
ISO TC 212
Clinical laboratory testing and in-vitro diagnostic test systems

Approved a new Preliminary Work Item:

➢ Requirements for traceability of measured values when using harmonized measurement procedures not supported by SI-traceable references.
Preliminary Work Item

- Will provide objective performance criteria that a harmonization process needs to meet
- Will enable JCTLM to list a harmonization process
- Will enable IVD manufacturers to adopt a harmonization process
Joint Committee for Traceability in Laboratory Medicine (JCTLM)

- Reviews and lists reference system components based on conformance to ISO documents:
  - 15193 Reference measurement procedures
  - 15194 Reference materials
  - 15195 Reference measurement laboratories
  - PWI - Harmonized measurement procedures

http://www.bipm.org/jctlm/
Address metrological traceability of values assigned by clinical laboratory measurements for quantities in patient samples.

Include a category for measurands traceable to an international harmonization protocol when there are no reference materials nor reference measurement 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
This section provides information on the status of harmonization or standardization of measurands. Information on reference measurement procedures and reference materials under development is provided when such information is available as well as information on commutability of existing reference materials where information exists. Links to organizations actively addressing harmonization of particular measurands are provided for inquiry on additional information on those projects. For measurands not yet harmonized, information is provided on the priority and technical feasibility for harmonization determined by the Harmonization Oversight Group.

Below is a listing of analytes that are being addressed by the IFCC. This table will be updated in the coming weeks with additional information for analytes being addressed by other organizations and those still in review. Please check back often for the latest information.

### Summary of Measurands

<table>
<thead>
<tr>
<th>Measurand Name</th>
<th>Fluid</th>
<th>Priority</th>
<th>Technical Feasibility</th>
<th>Status</th>
<th>Reference Material Commutability</th>
<th>Reference Material Reference</th>
<th>JCTLM Listed</th>
<th>Organization</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG antibodies to myeloperoxidase</td>
<td>Serum</td>
<td></td>
<td></td>
<td>Harmonization Active</td>
<td></td>
<td></td>
<td></td>
<td>IFCC</td>
</tr>
<tr>
<td>Thyroid stimulating hormone (TSH)</td>
<td>Serum</td>
<td></td>
<td></td>
<td>Harmonization Active</td>
<td></td>
<td></td>
<td></td>
<td>IFCC</td>
</tr>
<tr>
<td>Thyroxine, free (FT4)</td>
<td>Serum</td>
<td></td>
<td></td>
<td>Harmonization Completed</td>
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<td>IFCC</td>
</tr>
<tr>
<td>Thyroxine (T4)</td>
<td>Serum</td>
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<td></td>
<td>Harmonization Completed</td>
<td></td>
<td></td>
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<td>IFCC</td>
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Thank you to many colleagues around the world who are contributing to improving harmonization of medical laboratory results.

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