Why was the ICHCL created

What does the ICHCLR do
What is harmonization

Equivalent results among different measurement procedures for the same laboratory test

Standardization:

equivalent results are achieved by metrological traceability to a fit-for-purpose higher order reference system
Equivalent

- Equivalent does not mean identical
- Equivalent means within a total allowable error consistent with an acceptable risk of harm from decisions based on a lab test result

The problem we need to fix!

Treatment variation caused by comparing highest and lowest PTH concentrations in 18 patients.

How did this happen?

1. Non-commutable reference materials

2. Methods do not measure the same quantity

IFCC is addressing this problem

For results to be harmonized / standardized:

- All IVD medical devices must have metrological traceability to the same higher order reference system
  - must be fit-for-purpose

- All IVD medical devices must measure the same measurand
  - must have adequate selectivity for the measurand

Source of lab testing errors

46-68%  7-13%  20-45%
Pre-analytical  Analytical  Post-analytical
Ordering  Collection  Transportation  Reporting  Received by MD  Interpretation

Does not include contribution from medical errors caused by non-harmonized results


What is metrological traceability?

A
An unbroken chain of calibrations from a clinical sample result to a higher order reference system.

B
A process that specifies the source of calibration for an IVD medical device.
Metrological traceability: an unbroken chain of calibrations from a clinical sample result to a higher order reference system component (ISO 17511)

Commutability is?

A property of results from measurement procedures.

A property of a reference material for use with measurement procedures.
**Commutable**

RM and CS results have the same relationship between measurement procedures.

**Non-Commutable**

RM and CS results have a different relationship between measurement procedures.
Non-Commutable Calibrator

causes CS results to be different

---

SI unit

Certified reference material (pure substance)

Primary CRM in solution

Certified reference material (matrix-based and commutable with clinical samples)

Manufacturer’s working calibrator (master lot)

End-user calibrator

Clinical sample result

Reference measurement procedures to characterize CRM (e.g. mass balance)

Reference measurement procedure (e.g. gravimetry)

Reference measurement procedure (e.g. IDMS)

Manufacturer’s selected measurement procedure

Manufacturer’s standing measurement procedure

End-user IVD medical device

Commutability is critical
A non-commutable calibrator breaks the traceability chain

SI unit

Certified reference material (matrix-based and commutable with clinical samples)

Manufacturer’s working calibrator (master lot)

End-user calibrator

Clinical sample result

Reference measurement procedures to characterize CRM (e.g. mass balance)

Manufacturer’s selected measurement procedure

Manufacturer’s standing measurement procedure

End-user IVD medical device

Commutability is critical

Even though manufacturers show traceability, the process fails to provide equivalent results for patient samples among different measurement procedures

SI unit

Certified reference material (matrix-based and commutable with clinical samples)

Manufacturer’s working calibrator (master lot)

End-user calibrator

Clinical sample result

Reference measurement procedures to characterize CRM (e.g. mass balance)

Manufacturer’s selected measurement procedure

Manufacturer’s standing measurement procedure

End-user IVD medical device

Commutability is critical
Commutability is important for:

Matrix-based CRMs used as calibrators
EQA materials used to assess harmonization

IFCC Working Group on Commutability

Recommendations for assessing commutability:

Part 1: general experimental design; *Clin Chem* 2018;64:447-54

Part 2: using the difference in bias between a reference material and clinical samples; *Clin Chem* 2018;64:455-64

Part 3: using the calibration effectiveness of a reference material; *Clin Chem* 2018;64:465-74
Approximately 100 measurands have reference system components

* Not all matrix-based CRM’s listed have been validated for commutability *

JCTLM now requires commutability assessment for matrix-based CRMs

WHO International Standards and Reference Preparations have historically not been validated for commutability and many are not commutable

WHO Consultation on Commutability of WHO Biological Reference Preparations for In Vitro Detection of Infectious Markers.
WHO Headquarters, Geneva, 18-19 April, 2013

http://www.who.int/bloodproducts/norms/BS_2230_Addendum1_Commutability.pdf
Higher order references do not exist or are not fit-for-purpose for a large number of measurands

SI unit
Certified reference material (pure substance)
Primary CRM in solution
Certified reference material (matrix-based and commutable with clinical samples)
Manufacturer's working calibrator (master lot)
End-user calibrator
Clinical sample result

Assign value
Calibrate

Reference measurement procedures to characterize CRM (e.g. mass balance)
Reference measurement procedure (e.g. gravimetry)
Reference measurement procedure (e.g. IDMS)
Manufacturer's selected measurement procedure
Manufacturer's standing measurement procedure
End-user IVD medical device

What happens when metrological traceability ends at the IVD manufacturer’s master lot of working calibrator?

A Clinical sample results can be different from different IVD medical devices.

B Test results interpreted using decision values in guidelines can cause different medical actions for the same condition.
Still traceable; however different working calibrators cause different results from different end-user IVD medical devices

Key challenge #1: non-commutable matrix-based CRMs are used

*** such a reference system is not fit-for-purpose ***

Key challenge #2: there is no reference system for a large number of measurands
Why was the ICHCL created

What does the ICHCLR do

How do we address the situation when there is no suitable CRM or RMP?

A. Modify the clinical decision values for use with different IVD medical devices.

B. Apply a harmonization protocol to make the results equivalent from different IVD medical devices.
Harmonization

One of the most important challenges in laboratory medicine

- International Forum organized by AACC in October, 2010
- Agreement that metrological traceability to higher order CRM and RMP is preferred when possible
- Endorsed a harmonization approach when no CRM or RMP
The Roadmap

Develop an infrastructure to coordinate harmonization activities world wide:

1. Prioritize measurands by medical importance

2. Coordinate the work of different organizations

3. Promote processes for harmonization of results
ICHCLR Timeline

2010 – AACC Conference recommends formation to address unmet needs; AACC supports an Organizing Committee

2011 – Roadmap recommendations in *Clinical Chemistry*

2013 – ICHCLR begins operation; AACC is Secretariat

2013 – [www.harmonization.net](http://www.harmonization.net) is launched

2013 – ICHCLR/AACC/AdvaMedDx conference on regulatory issues; 2014 follow up meeting

2013 – NWIP to ISO TC-212 for a harmonization protocol

2017 – Insoft hosts [www.harmonization.net](http://www.harmonization.net)

2018 – IFCC becomes Secretariat for ICHCLR
### 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>Resources</th>
<th>Organization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkaline Phosphatase (ALP)</td>
<td>Serum</td>
<td>Medium</td>
<td>Incomplete</td>
<td>JCTLM</td>
<td>IFCC</td>
</tr>
<tr>
<td>Alanine Aminotransferase (ALT)</td>
<td>Serum</td>
<td>Medium</td>
<td>Incomplete</td>
<td>JCTLM</td>
<td>IFCC</td>
</tr>
<tr>
<td>Albumin</td>
<td>Urine</td>
<td></td>
<td>Active</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>Serum</td>
<td>Medium</td>
<td>Needed</td>
<td>JCTLM</td>
<td></td>
</tr>
<tr>
<td>Alpha Fetoprotein</td>
<td>Serum</td>
<td></td>
<td>Adequate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amylase</td>
<td>Serum</td>
<td></td>
<td>Active</td>
<td>JCTLM</td>
<td>IFCC</td>
</tr>
<tr>
<td>Anti-DNA antibody (qualitative)</td>
<td>Serum</td>
<td>Low</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-DNA antibody (quantitative)</td>
<td>Serum</td>
<td>Medium</td>
<td>Needed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-Hepatitis C Virus antibody (Anti-HCV Ab)</td>
<td>Serum</td>
<td></td>
<td>Adequate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antinuclear antibody (ANA)</td>
<td>fixed cells or serum</td>
<td></td>
<td>Active</td>
<td></td>
<td>International Workshops and Consensus Conferences</td>
</tr>
<tr>
<td>Antistreptolysin O</td>
<td>Serum</td>
<td>Low</td>
<td>Needed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspartate Aminotransferase (AST)</td>
<td>Serum</td>
<td>Medium</td>
<td>Incomplete</td>
<td>JCTLM</td>
<td>IFCC</td>
</tr>
<tr>
<td>B-type Natriuretic Peptide (BNP)</td>
<td>Serum</td>
<td>High</td>
<td>Needed</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### B-type Natriuretic Peptide (BNP)

B-Type natriuretic peptide (BNP) is a marker of cardiac function and is used for diagnosis, risk stratification and follow-up of patients with chronic or acute heart failure. Laboratory assessments have determined that the agreement among results for different measurement procedures is not suitable to support uniform clinical decision values for interpretation of results (i.e., both a candidate reference material (a) and a candidate reference measurement procedure (i) have been recently reported).

**References**


---

<table>
<thead>
<tr>
<th>Measured</th>
<th>Matrix</th>
<th>Medical Impact of Harmonization</th>
<th>Harmonization Status</th>
<th>Resources</th>
<th>Organization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkaline Phosphatase (ALP)</td>
<td>Serum</td>
<td>Medium</td>
<td>Incomplete</td>
<td>JCTLM</td>
<td>IFCC</td>
</tr>
<tr>
<td>Alanine Aminotransferase (ALT)</td>
<td>Serum</td>
<td>Medium</td>
<td>Incomplete</td>
<td>JCTLM</td>
<td>IFCC</td>
</tr>
<tr>
<td>Albumin</td>
<td>Urine</td>
<td>Medium</td>
<td>Complete</td>
<td>JCTLM</td>
<td>IFCC</td>
</tr>
<tr>
<td>Albumin</td>
<td>Serum</td>
<td>Medium</td>
<td>Complete</td>
<td>IFCC</td>
<td>IFCC</td>
</tr>
<tr>
<td>Alpha Fetoprotein</td>
<td>Serum</td>
<td>High</td>
<td>Needed</td>
<td>IFCC</td>
<td>IFCC</td>
</tr>
<tr>
<td>Amylase</td>
<td>Serum</td>
<td>Low</td>
<td>Needed</td>
<td>IFCC</td>
<td>IFCC</td>
</tr>
<tr>
<td>Anti-DNA antibody (qualitative)</td>
<td>Serum</td>
<td>Medium</td>
<td>Incomplete</td>
<td>JCTLM</td>
<td>IFCC</td>
</tr>
<tr>
<td>Anti-DNA antibody (quantitative)</td>
<td>Serum</td>
<td>High</td>
<td>Needed</td>
<td>IFCC</td>
<td>IFCC</td>
</tr>
<tr>
<td>Anti-Hepatitis C Virus antibody (Anti-HCV Al)</td>
<td>Serum</td>
<td>Medium</td>
<td>Incomplete</td>
<td>JCTLM</td>
<td>IFCC</td>
</tr>
<tr>
<td>Antiinuclear antibody (ANA)</td>
<td>fixed cells or serum</td>
<td>Active</td>
<td></td>
<td>International Workshops and Consensus Conferences</td>
<td></td>
</tr>
<tr>
<td>Antistreptolysin O</td>
<td>Serum</td>
<td>Low</td>
<td>Needed</td>
<td>IFCC</td>
<td>IFCC</td>
</tr>
<tr>
<td>Aspartate Aminotransferase (AST)</td>
<td>Serum</td>
<td>Medium</td>
<td>Incomplete</td>
<td>JCTLM</td>
<td>IFCC</td>
</tr>
<tr>
<td>B-Type Natriuretic Peptide (BNP)</td>
<td>Serum</td>
<td>High</td>
<td>Needed</td>
<td>IFCC</td>
<td>IFCC</td>
</tr>
</tbody>
</table>

---

- JCTLM listing
- Links to commutable EQA programs
### Organizations with harmonization/standardization activities for the measurand

<table>
<thead>
<tr>
<th>Measurand</th>
<th>Matrix</th>
<th>Medical Impact of Harmonization</th>
<th>Harmonization Status</th>
<th>Resources</th>
<th>Organization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkaline Phosphatase (ALP)</td>
<td>Serum</td>
<td>Medium</td>
<td>Incomplete</td>
<td>JCTLM</td>
<td>IFCC</td>
</tr>
<tr>
<td>Alanine Aminotransferase (ALT)</td>
<td>Serum</td>
<td>Medium</td>
<td>Incomplete</td>
<td>IFCC, EU-JRC (HRMM)</td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>Urine</td>
<td></td>
<td>Active</td>
<td></td>
<td>NKDEP, IFCC, JSCC</td>
</tr>
<tr>
<td>Albumin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha Fetoprotein</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amylase</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-DNA antibody (qualitative)</td>
<td>Serum</td>
<td>Medium</td>
<td>Needed</td>
<td>IFCC</td>
<td></td>
</tr>
<tr>
<td>Anti-DNA antibody (quantitative)</td>
<td>Serum</td>
<td>Medium</td>
<td>Adequate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-Hepatitis C Virus antibody (Anti-HCV Ab)</td>
<td>Serum</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antinuclear antibody (ANA) fixed cells or serum</td>
<td></td>
<td>Active</td>
<td></td>
<td>International Workshops and Consensus Conferences</td>
<td></td>
</tr>
<tr>
<td>Antistreptolysin O</td>
<td>Serum</td>
<td>Low</td>
<td>Needed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspartate Aminotransferase (AST)</td>
<td>Serum</td>
<td>Medium</td>
<td>Incomplete</td>
<td>JCTLM</td>
<td>IFCC</td>
</tr>
<tr>
<td>B-Type Natriuretic Peptide (BNP)</td>
<td>Serum</td>
<td>High</td>
<td>Needed</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Resources**

Below are resources to aid global harmonization of clinical laboratory measurement procedures.

- Council HOG Meeting Summaries
- ICH-CLlr Activity Reports
- ICH-CLlr Activity Reports
- Document: International Consortium for Harmonization of Clinical Laboratory Results: Operating Procedures
- Document: Toolbox of technical procedures for developing a process to achieve harmonization for a measurand

[www.harmonization.net](http://www.harmonization.net)
An integrated protocol to assess potential effectiveness of candidate reference measurement procedures, reference materials and clinical sample panels for harmonizing results.

A harmonization protocol based on panels of clinical samples when there are no certified reference materials or reference measurement procedures.
IFCC Committee for Standardization of Thyroid Function Tests developed much of the science supporting a practical harmonization protocol.

Can the TSH approach be generalized?

A: Yes

B: No
17511 next revision: includes a harmonization protocol as one approach to achieve metrological traceability
NP 21151: *In vitro diagnostic medical devices - Measurement of quantities in samples of biological origin - Requirements for international harmonization protocols intended to establish metrological traceability of values assigned to product (end user) calibrators and human samples*

New project approved (2014)

Committee draft (2018)

Draft international standard (2019)

[Final draft international standard]

International standard
Metrological traceability: harmonization protocol

Replace these inadequate calibration hierarchies ...

Metrological traceability: harmonization protocol

... with metrological traceability to a harmonization protocol
Steps in the ISO NP 21151 Draft International Standard

Harmonization protocol:
qualify measurement procedures for inclusion

1. Measure the same quantity (molecular form)
   • Correlated measurement responses
   • Similar specimen specific influences = similar selectivity for the measurand

2. Adequate performance
   • Precision
   • Proportional response over concentration
Harmonization protocol: reference materials

1. Specification for the clinical samples

2. Process for value assignment of the clinical samples

Harmonization protocol: initial results

End user

Medical lab measurement procedures

Initial results for harmonization reference materials
Harmonization protocol: IVD-specific correction algorithm

Each IVD manufacturer develops a method-specific correction algorithm to achieve equivalent results for clinical samples.

- Can apply the correction to:
  1. Working (master) calibrator, or
  2. End-user calibrator, or
  3. Clinical sample result

Harmonization protocol: equivalent results

Each IVD manufacturer applies their method-specific correction algorithm.
Harmonization protocol: validation / sustainability

- **Clinical samples as harmonization reference materials**
- **Process for value assignment**
- **Reserve set of clinical samples for validation & sustainability**

Harmonization protocol: validate the protocol

- **Validate the protocol with a different set of clinical samples**
- **Reserve set of clinical samples for validation & sustainability**
- **End-user product calibrator**
- **Medical lab measurement procedures**
- **Equivalent results for clinical samples**
- **Each IVD manufacturer applies their method-specific correction algorithm**
Harmonization protocol: surveillance over time

1. Feedback to labs and IVD manufacturers
2. Repeat harmonization protocol if needed (reserve set)
3. Provision for harmonization of new or improved measurement procedures

Equivalent results

Surveillance of harmonized results
- EQA/PT (commutable samples)
- Other scheme; e.g. patient medians

STANDARDIZATION / HARMONIZATION
METROLOGICAL TRACEABILITY

ASSESSMENT
EQA
Harmonization needs EQA feedback to the IVD industry

We need a mechanism for EQA providers to cooperate to:

1. Cover measurands on an annual or biennial cycle
2. Prepare aggregated data summaries among schemes

An organizing role for ICHCLR, EQALM, IFCC, ???

Regulation

A challenge to harmonization
What has changed by recalibration to achieve equivalent results

- Numeric value

- Reference interval

- Measuring interval

Changes are proportional to the numeric value change

Nothing else is changed by recalibration

- Precision

- Selectivity

- Interfering substances

Should not require a full resubmission
The important change is that harmonized results reduce medical errors

Patient safety is improved

Agreed at a 2013 conference including ICHCLR, AACC, AdvaMedDx, IVD industry, FDA

www.harmonization.net/resources/

Summary

- Harmonization of results is important to reduce medical errors
- The ICHCLR:
  - prioritizes measurands in need of harmonization
  - provides an information portal for global harmonization activities
  - promotes collaborative activities to achieve harmonized results
- Global cooperation is needed to achieve harmonization
The path forward

- We now have more tools
- We need to work as a team
  - Laboratory practitioners
  - IVD industry
  - Regulatory bodies

The guiding principle

Perfect is the enemy of good