Harmonization: why you should care!

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Cooperation

Harmonization

Regulation
Deming’s Key Principles

- Cooperation improves quality, productivity, profit
- Understand and eliminate variation
- Use statistical process control, not inspection
- Value customer - supplier relationships
- Implement continuous quality improvement
Institute of Medicine

1999: *To Err Is Human: Building a Safer Health System*

- Mistakes happen
- Caused by lack of systematic work practices
- Teamwork, practice guidelines, checklists

*Cooperation*
Clinical practice guidelines

Based on cooperation
to eliminate variation
to achieve uniform quality
How has the lab been involved

1988


Did not know cholesterol was not standardized

CRMLN
Still ignoring laboratory medicine

Wide disparity in HbA1c results among labs
“They” did it again

2002

- Asked labs to report eGFR
- Creatinine was not standardized

Laboratory Working Group
Defect rate in laboratory medicine

20 defects per 1 M test results

- Defect creates a hazardous condition (risk)
- Harm only if the hazardous condition affects patient care
Lab tests are important

Patient Encounters Informed by Lab Tests

- Inpatient: 98%
- Emergency Department: 56%
- Outpatient Clinic: 29%

Source of lab testing errors

46-68% Pre-analytical
  Ordering
  Collection
  Transportation

7-13% Analytical

20-45% Post-analytical
  Reporting
  Received by MD
  Interpretation

3-12% of errors caused adverse events (4 reports)

Institute of Medicine

2015: *Improving Diagnosis in Health Care*

- Reinforced guidelines and cooperation
- The clinical laboratory is part of the team
Failed to mention that when applying guidelines, non-harmonized lab results can cause errors in diagnosis or in decisions for treatment / non-treatment
Human growth hormone
Tumor markers
Testosterone
Estradiol
Viral load
Troponin I
BNP
AST
LDH
Amylase
Lipase
Albumin
“We” need to engage “Them”

Lab specialists cannot wait to be asked to collaborate on guidelines

- Engage clinical colleagues
- Join rounds teams in hospitals
- Establish consultative lab orders
- Talk to patient advocate groups

Cooperation
Harmonization

One of the most important challenges in laboratory medicine
What is harmonization

Equivalent results, within clinically meaningful limits, among different measurement procedures for the same laboratory test.
Terminology

- **Harmonization**: achieving equivalent results among different measurement procedures
  - Implies there is no reference measurement procedure or certified reference material

- **Standardization**: achieving equivalent results by having calibration traceable to a higher order reference system
Cholesterol: first integrated program

1960
- Framingham study
- CDC LRC measurement procedures
- EQA program for LRC labs

1970
- Framingham: cholesterol predicts risk of CVD

1980
- CDC CRMLN & LSP
- Mutability issues recognized for routine laboratory methods
- NCEP & NCEP LWG: results do not agree

1990
- EU IVD directive
- ISO 17511
- JCTLM

2000

2017
- Manufacturers (patient samples)
- Laboratories (commutable EQA samples)
What’s the problem; we have infrastructure for harmonization

- 17511:2003, Calibration Traceability
- 15195:2003, Reference Measurement Laboratories

Database of reference materials, reference measurement procedures, and reference (calibration) laboratories that conform to the ISO standards
ISO built on a legacy of harmonization infrastructure


Standard Methods of Clinical Chemistry. AACC, seven volumes 1953-1972


A national understanding for the development of reference materials and methods for clinical chemistry. Conference sponsored by CDC, FDA, NBS/NIST, 1978

National Reference System for the Clinical Laboratory. NCCLS/CLSI, 1978
How to achieve equivalent results

1. Calibration of all measurement procedures is traceable to a common reference system
   ❖ ISO 17511:2003

2. All measurement procedures measure the same quantity (the same molecular form)
   ❖ Analytical selectivity for the measurand
Panel of Patient Samples

Primary Reference Material (pure substance)

Pure Substance Calibrator

Secondary Reference Material (matrix)

Manufacturer’s Product Calibrator

Patient’s Sample

Patient’s Result

ISO 17511

Procedures for identity and mass balance

Reference Measurement Procedure (e.g. Gravimetry)

Reference Measurement Procedure (e.g. IDMS)

Manufacturer’s Internal Procedures

Medical Laboratory Procedure

TRACIBILITY
How many tests are in ARUP’s directory?

JCTLM lists CRM and RMP for 80 analytes
Infrastructure: what’s needed

Reference Measurement Laboratories

No JCTLM listed reference lab in US that IVD manufacturers can use to establish traceability

- Accredited by an ILAC approved organization
  - e.g. American Association for Laboratory Accreditation (www.A2LA.org)
- Participate in IFCC ring trials for reference labs
Infrastructure: what’s needed

Commutable Reference Materials
Commutable: same relationship for clinical samples and reference materials
Non-commutable: different relationship for clinical samples and reference materials
Calibration with non-commutable materials

Measurement Procedure 1 vs Measurement Procedure 2

- Clinical Samples
- RM as Calibrator

causes patient sample results to be different
**Materials**

- Primary Reference Material (pure substance)
- Pure Substance Calibrator
- Secondary Reference Material (matrix)
- Secondary Reference Material (matrix)
- Manufacturer’s Product Calibrator

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**Procedures**

- Reference Measurement Procedure (e.g. Gravimetry)
- Reference Measurement Procedure (e.g. IDMS)
- Manufacturer’s Internal Procedures
- Medical Laboratory Procedure

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**Traceability**

- Commutability is critical

**Assign value**

- Assign value
- Assign value
- Assign value
- Assign value
- Assign value

**Calibrate**

- Calibrate
- Calibrate
- Calibrate
- Calibrate
- Calibrate

**Patient’s Result**
A non-commutable calibrator breaks the traceability chain.
Even though manufacturers show traceability, the process fails to provide equivalent results for patient samples among different measurement procedures.
Traceability stops here when no primary reference material or reference measurement procedure.
- Must be commutable
- Hasn’t always happened
Commutability: now an expectation


Consultation on Commutability of World Health Organization Biological Reference Preparations for In Vitro Detection of Infectious Markers, 2013.

2014, JCTLM requires commutability data when indicated by the intended use of a reference material.
What happens when there is both:

- no reference measurement procedure
- no certified reference material
Traceability is established to a material selected by the producer of a measurement procedure. No coordination among producers (IVD or LDT).
Roadmap for Harmonization of Clinical Laboratory Measurement Procedures


✧ International Forum organized by AACC in October, 2010
✧ Representation from 62 organizations & manufacturers
✧ 90 participants from 12 countries
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 when there is no reference measurement procedure or certified 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
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>IFCC</td>
<td></td>
</tr>
<tr>
<td>Alanine Aminotransferase (ALT)</td>
<td>Serum</td>
<td>Medium</td>
<td>Incomplete</td>
<td>IFCC EU-JRC (IRMM)</td>
<td></td>
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<tr>
<td>Albumin</td>
<td>Urine</td>
<td></td>
<td>Active</td>
<td>NKDEP IFCC JSCC</td>
<td></td>
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<tr>
<td>Albumin</td>
<td>Serum</td>
<td>Medium</td>
<td>Needed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amylase</td>
<td>Serum</td>
<td>Medium</td>
<td>Active</td>
<td>IFCC</td>
<td></td>
</tr>
<tr>
<td>Aspartate Aminotransferase (AST)</td>
<td>Serum</td>
<td>Medium</td>
<td>Incomplete</td>
<td>IFCC</td>
<td></td>
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<tr>
<td>B-type Natriuretic Peptide (BNP)</td>
<td>Serum</td>
<td>High</td>
<td>Needed</td>
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<td></td>
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<tr>
<td>Bilirubin, conjugated</td>
<td>Serum</td>
<td>Medium</td>
<td>Needed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin, total</td>
<td>Serum</td>
<td></td>
<td>Adequate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood gasses (pH, pO2, pCO2, oximetry)</td>
<td>Blood</td>
<td></td>
<td>Adequate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-Reactive protein, high sensitivity</td>
<td>Serum</td>
<td></td>
<td>Adequate</td>
<td></td>
<td></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 (P$_5$P) is included in reagents from IVD manufacturers. P$_5$P 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 P$_5$P to reagents reduces the reagent stability. Consequently P$_5$P 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 P$_5$P because there may be reagent waste in lower testing volume situations. Some countries do not typically include P$_5$P 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 P$_5$P 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 P$_5$P inclusion and the need for P$_5$P may vary among different regions of the world.

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

**External link**
International Consortium for Harmonization of Clinical Laboratory Results – Current Status and Future Promise

Lecture presented at the IFCC 2014 WorldLab Conference

**Content**
Council/HOG Meeting Summaries

**Document**
Toolbox of technical procedures for developing a process to achieve harmonization for a measurand

**Content**
Strategic Partners Group Update Reports

Strategic Partners Group Update Reports

**Read more**

**Read more**

**Read more**

**Read more**
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*

Will enable JCTLM listing
Manufacturer’s Working Calibrator (master lot)

Manufacturer’s Product Calibrator

Patient’s Sample

Patient’s Result

Manufacturer’s Internal Procedures

Medical Laboratory Procedure

Calibrate

Assign value

TRACEABILITY
Example: harmonization protocol

Clinical samples as reference materials

Process for value assignment

End user product calibrator

Algorithm to assign the value of end-user product calibrator to recover the values for clinical sample RMs

Supported by producer (IVD or LDT) master lot(s) with appropriate target values and transfer procedures

Equivalent results for patients’ samples

Medical lab measurement procedure

EQA for surveillance

Reserve set of clinical samples for validation & sustainability
Perfect is the Enemy of Good

We need fit for purpose solutions
What is the ROI for harmonization

Cholesterol and lipids program

- CDC LSP-CRMLN cost $1.7M in 2007
- Reduction in deaths during 1980-2000 attributable to statin therapy saved $338M to $7.8B per year in USA

(Hoerger et al. A cost-benefit analysis of lipid standardization in the United States. Preventing Chronic Disease 2011;8:A136)
Harmonization is inadequately funded

We need to raise public awareness

Theranos attracted millions based only on marketing:

- Less blood volume
- Lower cost testing
Harmonization is inadequately funded

We need to raise public awareness

Harmonization can:

- Avoid medical errors in diagnosis and treatment
Other Harmonization Needs

- Nomenclature for test orders
- Reporting units
- Interpretive information – decision values and reference intervals
Focused attention on nomenclature and units

- RCPA – Australian Pathology Units and Terminology Standards
- UK Pathology Harmony
- USA – global; Unified Code for Units of Measure; part of Regenstrief Institute
- IFCC and IUPAC collaboration
What is the recommended lab test:

- Vitamin D
- Vitamin D2
- Vitamin D3
- 25 hydroxy Vitamin D
- 25-OH vitamin D
- 1,25 dihydroxy vitamin D
Which digoxin result is critical:

3 ng/mL
0.3 μg/dL
3.8 nmol/L
Interpretive Information

Decision values
Reference Intervals
Decision values

- Derived from clinical outcomes studies
- Or from clinical classification systems for diagnosis or therapy
- Preferred to reference intervals
- Key lab requirement is harmonization of results and units
Reference Intervals

- Central 95% of results from “reference individuals”
  - why not use the central 99%?
  - or the lower and upper confidence limits?
- How to qualify a “reference individual”
- Risk of adverse outcome may be different than the reference interval
Creatinine Example

✧ CKD has no symptoms until approaching kidney failure

✧ “Adult” RI is misleading:
  ▪ How many adult “reference individuals” have CKD
  ▪ What was the distribution of muscle mass
  ▪ What were the ages: GFR goes down with age

Upper limit of RI is consistent with loss of one-half of kidney function – NOT NORMAL
**AST**, RI = 10-40 U/L

- Does a value of 45 U/L mean liver disease or undetected hemolysis? What about 50 U/L?

**Albumin**, RI = 3.5-5.0 g/dL

- Does a value of 32 g/L mean nutritional deficiency, sub-clinical inflammation, or posture (inpatients vs. outpatients)?
Reference Intervals

✦ Current practice is a mess

✦ Many IVD manufacturer RIs are from literature; may not even be for the same measurement procedure

✦ Labs are expected to establish or verify RIs but do not have resources
Common Reference Intervals

HERE I COME TO SAVE THE DAY!
Common Reference Intervals

Prerequisites:

- Harmonized results
- Similar population characteristics
Common Reference Intervals

- New Zealand: SIQAG, ARQAG, LNIQAG
- Australia: AACB Committee for Common Reference Intervals
- UK: Pathology Harmony
- Nordic Reference Interval Project 2000
- IFCC Committee on Reference Intervals and Decision Limits
## Common but not Universal

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Unit</th>
<th>AACB</th>
<th>Nordic</th>
<th>UK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>mmol/L</td>
<td>135-145</td>
<td>137-145</td>
<td>133-146</td>
</tr>
<tr>
<td>Potassium</td>
<td>mmol/L</td>
<td>3.5-5.2</td>
<td>3.6-4.6</td>
<td>3.5-5.3</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>mmol/L</td>
<td>22-32</td>
<td>22-32</td>
<td>22-29</td>
</tr>
<tr>
<td>Calcium</td>
<td>mg/dL</td>
<td>8.4-10.4</td>
<td>8.8-10.0</td>
<td>8.8-10.4</td>
</tr>
<tr>
<td>ALP</td>
<td>U/L</td>
<td>30-110</td>
<td>35-105</td>
<td>30-130</td>
</tr>
</tbody>
</table>

Adapted from an AACB Special Report (2014); www.aacb.asn.au/documents/.../3201
Harmonization

One of the most important challenges in laboratory medicine

Non-harmonized results contribute to medical errors
Regulation

A challenge to harmonization
Regulation

Medical laboratories are regulated to:

✧ Protect public safety

✧ Ensure appropriate health care is available
FDA

Premarket Notification (510K) and FDA clearance required to sell medical devices in USA

✧ Safe and effective
✧ Substantial equivalence to a predicate device
✧ Required for significantly changed or modified device to the extent that its safety or effectiveness could be affected
Recalibration to conform to a national or international harmonization recommendation has been interpreted to be a significant change.

Cost to resubmit is millions of dollars.

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FDA
Cooperation
AACC, FDA and AdvaMed sponsored a forum in 2013 to address recalibration issues (www.harmonization.net/Resources)

IFCC C-STFT has arranged coordination between FDA and IVD manufacturers
Below are resources to support global harmonization of clinical laboratory measurement procedures.

- External link: AACC Position Statement on Harmonization of Clinical Laboratory Test Results.
- Document: International Consortium for Harmonization of Clinical Laboratory Results: Operating Procedures.
What has changed by recalibration

- Numeric value
- Reference interval
- Measuring interval

Changes will be 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 laboratory results reduce medical errors

Patient safety is improved
FDA agrees with these concepts

FDA concerns are

- Coordination of implementation among measurement procedure producers
- Education of laboratories and clinical care providers to ensure a smooth transition to harmonized results
FDA is willing to develop guidance to simplify the process for clearance of recalibrated measurement procedures

FDA has suggested that manufacturers coordinate their submissions for recalibrated measurement procedures

FDA has requested to be kept informed and involved in harmonization activities
Remember

- Non-harmonized results cause medical errors
- Medical and economic impact is poorly studied
- “We” need to pay more attention to this defect

- Practitioners
- IVD Industry
- Public health organizations
- Metrology institutes
- Regulators
- Patient advocacy groups
The road ahead

- Be part of the health care team
- Cooperate with other stakeholders
- Engage in legislative and regulatory processes
- Engage with patient advocate groups
Cooperation

Harmonization

Regulation