Harmonization of Clinical Laboratory Results is Essential for Quality Patient Care

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What is the problem

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

- Patients get the wrong treatment
- Most clinical decisions are informed by laboratory results
- Many clinical guidelines use a fixed laboratory test value for treatment decisions
Diabetes and urine albumin

• Diabetics are tested annually to identify early kidney damage

• KDIGO (2012) and other guidelines recommend a decision value of 30 mg/g creatinine

• Results for urine albumin could differ as much as 78% in this concentration range
  - Based on assessment of 16 routine measurement procedures with 332 patient samples (manuscript submitted)
Parathyroid hormone in kidney disease

Biological activity resides in N-terminal 34 amino acids.

Intact and N-terminal PTH have a short half life in plasma. C-terminal PTH fragments have a long half life and create assay interference issues, especially in renal patients.

PTH is the key hormone in calcium homeostasis acting on bone, the kidney and the gut.

PTH is a key biomarker in renal osteodystrophy.

84 AA peptide MW = ~9500

PTH slides courtesy of Graham Beastall
Current parathyroid hormone immunoassays do not adequately meet the needs of patients with chronic kidney disease. 

How to achieve comparable results

- Calibration of all measurement procedures is traceable to a common reference system
- All measurement procedures measure the same quantity
Case study: cardiovascular disease

- Framingham: cholesterol predicts risk of CVD
- NCEP ATP-1: results do not agree
- WSJ - NCEP LWG
- CLIA ‘88
- EU IVD directive
- JCTLM
- ISO 17511
- Direct HDL & LDL limitations
  - IFCC – apo A and B, Lp(a);
  - also many other analytes

- 1960
- 1970
- 1980
- 1990
- 2000
- 2010

- NRSCL
- CDC LSP – TC then TG and HDLC
- Matrix reference materials
  - commutability issues
- Automated direct serum assays
- Standard methods for xxx
- CDC LRC
ISO 17511:2003

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

- CLSI: implementation guideline
  - X5R (2006) and C29 (in preparation)
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

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

Patient sample result
Traceability (based on ISO 17511)

- Primary Reference Material (pure substance)
- Reference Procedure (e.g. IDMS)
- SI unit
- Patient sample results are equivalent to the reference procedure results

Panel of patient samples
- Mfr Working Calibrator
- Mfr Product Calibrator
- (calibrator)
- Mfr Selected Procedure
- Mfr Standing Procedure
- Routine Procedure

Patient sample result
Measurands for which reference procedures exist or can be developed.
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)

Secondary Reference Material (matrix)

- Mfr Working Calibrator
- Mfr Product Calibrator
- (calibrator)

Mfr Selected Procedure
Mfr Standing Procedure
Routine Procedure

• Value assignment
• Commutability

Patient sample results are traceable to reference material

Patient sample result
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

- The actual concentration may not be known
- An arbitrary value can be assigned (e.g. U/L)
- Since the goal of harmonization is comparable results irrespective of the measurement procedure used,
- Clinical guidelines can still be implemented
Traceability to a Reference Material

Secondary Reference Material (calibrator)

Procedure 1

Procedure 2

Procedure 3

Procedure n

Must be commutable with patient samples for all measurement procedures with which it will be used

Patient Samples

Results 1

Results 2

Results 3

Results n
Commutable means that values measured for a calibration material and for representative clinical samples have the same relationship between measurement procedures for the same measurand.
Commutable: 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

Calibration with non-commutable materials

**Measurement Procedure 1**

**Measurement Procedure 2**

- Clinical Samples
- RM as Calibrator
The Problem

Many secondary reference materials are not commutable with native clinical samples for routine clinical laboratory procedures.
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- 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 may be calibrated with a “master lot of calibrator” that is 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.
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.
Thyroid Stimulating Hormone

From the Clinical Practice Guidelines for Hypothyroidism in Adults (American Association of Clinical Endocrinologists and American Thyroid Association):

- According to NHANES III, the upper normal of serum TSH levels is 4.5 mIU/L.
- According to NACB, the upper normal of serum TSH levels is 2.5 mIU/L.
Thyroid Stimulating Hormone

Neither study mentioned the measurement procedure used to make the measurements

- According to NHANES III, the upper normal of serum TSH levels is 4.5 mIU/L.
- According to NACB, the upper normal of serum TSH levels is 2.5 mIU/L.
TSH methods
All traceable to IS 94/674 (WHO)

Mean ±95% CI for 40 patient samples

Δ = 0.7

35%

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
Other examples:

- Follicle stimulating hormone (Clin Chim Acta 1998;273:103-17)
- C-peptide (Clin Chem 2008;54:1023-6)
- Cytomegalovirus (Clin Chem 2009;55:1701-10)
- Troponin I (Pathology 2010;42:402-8)
What do we do?
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
International Forum organized by AACC in October, 2010
90 participants from 12 countries
Representing 62 organizations & manufacturers
Barriers to 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.
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
Barriers to 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
Barriers to harmonization

- Regulatory requirements
  - Changing calibration requires regulatory approval
  - Is the clinical benefit worth the cost to meet regulatory requirements
The Roadmap

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

1. Prioritization of measurands
2. Gap analysis for what needs to be done
3. Technical processes to achieve harmonization
4. Surveillance of success of harmonization
Path Forward
2011-2012

➤ Steering Committee

➤ 3 Task Forces

1. Administrative operations
2. Checklists for submission and evaluation
3. Tool box of approaches to harmonization
AN INFRASTRUCTURE FOR HARMONIZATION

International Consortium for Harmonization of Clinical Laboratory Results

- Strategic Partners Group
- Council
- Harmonization Oversight Group
  - Harmonization Implementation Groups
  - Special Working Groups

Approval

Governance, Administration

Operations Management

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

Harmonization Oversight Group

Communication

Evaluate measurand proposals

Operation

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

When no RMP
- Solicit champion and funding
  - Clinically affected entity
  - Economically affected entity
www.harmonization.net

An information portal for global standardization / harmonization activities

- Communication with Strategic Partners Group
- On-line submission of measurands to be harmonized
- Information on harmonization status of measurands
- Information on global harmonization activities
- Useful technical information for harmonization
Questions / Comments