Objectives

- Understand and give examples of the problems which result from lack of comparability of patient results
- Understand the principles behind standardization and harmonization
- Understand the importance of commutability
- Awareness of international efforts to improve harmonization
PTH: Between Method Variability

Almond A, Ellis AR, Walker SW
Current parathyroid hormone immunoassays do not adequately meet the needs of patients with chronic kidney disease
Why do we need comparable results

- Clinical practice guidelines are established for interpretation of lab test results

- If different measurements give different results for the same patient sample:
  - The interpretive guidelines become less useful
  - Patients may receive incorrect treatment
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 traceable to a common reference system
- Performance is monitored and maintained by surveillance using PT, EQA or a certification program
Terminology

- **Standardization**: results are uniform among measurement procedures
  - traceability is established to SI using a reference measurement procedure

- **Harmonization**: results are uniform among measurement procedures
  - NO reference measurement procedure and no “pure substance” reference material exists
ISO 17511

In vitro diagnostic medical devices - Measurement of quantities in biological samples - **Metrological traceability of values assigned to calibrators and control materials**
### Traceability categories from ISO 17511

<table>
<thead>
<tr>
<th>Category</th>
<th>Reference measurement procedure</th>
<th>Primary (pure substance) reference material</th>
<th>Secondary (value assigned) reference material</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Yes</td>
<td>Yes</td>
<td>Possible</td>
<td>Electrolytes, glucose, cortisol</td>
</tr>
<tr>
<td>2</td>
<td>Yes</td>
<td>No</td>
<td>Possible</td>
<td>Enzymes</td>
</tr>
<tr>
<td>3</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Hemostatic factors</td>
</tr>
<tr>
<td>4</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Proteins, tumor markers, HIV</td>
</tr>
<tr>
<td>5</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Proteins, EBV, VZV</td>
</tr>
</tbody>
</table>

Traceability categories from ISO 17511

- **Standardization**
- **Harmonization**
Traceability (based on ISO 17511)

A reference system (ideal)

Primary Reference Material (pure substance)

Primary Calibrator

Secondary Reference Material (matrix)

SI unit

Primary Reference Measurement Procedure (e.g. gravimetry)

Secondary Reference Measurement Procedure (e.g. IDMS)
Traceability (based on ISO 17511)
A reference system for glucose

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

 TRACEABILITY

Patient sample results are equivalent to the reference procedure results

Patient sample result
Traceability (based on ISO 17511)

Primary Reference Material (pure substance)

Panel of patient samples

Mfr Working Calibrator

Mfr Product Calibrator

SI unit Reference Procedure (e.g. IDMS)

Mfr Selected Procedure (calibrator)

Mfr Standing Procedure

Routine Procedure

Patient sample results are equivalent to the reference procedure results
Picking the low-hanging fruit!

-omics  HCG  Troponin I
TSH  PSA
Epstein Barr virus

AST  urea  HbA1c  ALT
cholesterol  glucose  homocysteine
uric acid  creatinine
Harmonization

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

Patient sample result

Patient sample results are traceable to a reference material
Assign a value

Secondary Reference Material

(matrix)

Demonstrate commutability
Value assignment when there is no reference measurement procedure

International conventional calibrator (reference material)

⇒ Arbitrary e.g. U/L

⇒ Bioassay for hormone activity

⇒ An arbitrary designated comparison procedure
Traceable to an international conventional reference material

- The true value is not known
- Since the goal of harmonization is comparable results irrespective of the measurement procedure used,
- Clinical guidelines can still be implemented
Examples: traceable to a reference material
(no reference measurement procedure)

- Human chorionic gonadotropin
- Prostate-specific antigen
- Thyroid stimulating hormone
- Human immunodeficiency virus
Traceability requires commutable calibration materials

Commutable means that values measured for a calibration material and for native clinical samples have the same relationship between two, or more, 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

What happens when there is both:

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

- There is no coordination among manufacturers
- Method specific reference intervals or decision values are used

Mfr Working Calibrator
Mfr Product Calibrator
Mfr Standing Procedure
Routine Procedure

Patient sample result

Patient sample results are not traceable to any international reference
Examples: traceable to a manufacturer’s working calibrator

(no reference material nor reference measurement procedure)

- B-type natriuretic peptide
- CA-125
- Epstein-Barr virus
- Varicella zoster virus
ISO 17511 category 5 needs practical procedures to achieve harmonization

Possibilities for consideration:

- traceable to an all methods mean (outliers removed) of a panel of patient samples

- traceable to a designated measurement procedure (arbitrary, but which has good correlation with clinical outcome)
Barriers to harmonization

- Lack of a systematic process to identify and prioritize measurands
- Materials are labeled as “reference materials” that have not been validated to be commutable for the intended measurement procedures
- Inadequate definition of the measurand
- Inadequate analytical specificity for the measurand
- Lack of systematic procedures to implement harmonization, in particular:
  - when there is no reference measurement procedure
  - when there is no reference material
Challenged clinical laboratories to address the issues associated with harmonization

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


Report from an AACC conference, October, 2010: Improving Clinical Laboratory Testing through Harmonization: An International Forum
The Roadmap

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

1. Prioritization of analytes
2. Gap analysis for what needs to be done
3. 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 ISO 17511 categories 4 and 5 have been technically more difficult to address, thus there have been few effective procedures implemented for harmonization in these categories.
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

Work Groups
**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**

**Evaluation of measurand proposals**

**Operation**

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

**Special Working Group**
- Review priority and technical feasibility
- Recommendation to Harmonization Oversight Group

**Coordination / Cooperation**
- If work is underway, refer to that group
- If RMP is possible, refer to another group
- Solicit champion and funding
  - Clinically affected entity
  - Economically affected entity
www.harmonization.net

- A general information portal for global standardization / harmonization activities
  - Communication with stakeholders
  - Status reports on measurands
  - Useful technical information
  - Information on global activities
  - Links to other organizations
Coming soon: International Consortium for Harmonization of Clinical Laboratory Results

Harmonization.net