Establishing Calibration Traceability for Quantitative Assays

Edutrak 3305

AACC Annual Meeting
Orlando, FL
30 July 2002
10:30am – 12:00noon
2:45 pm – 5:00 pm
Establishing Calibration Traceability

Sponsored by the AACC Industry Division
Establishing Calibration Traceability

Royden N. Rand, PhD
Past President, AACC
Past Chairholder, NRSCL
1925 - 2002
Establishing Calibration Traceability

Special thanks to:
- Abbott Diagnostics – CD-ROM
- AdvaMed – Handouts
- AACC Industry Division – Web site
Calibration Traceability: Edutrak Faculty

Morning session

- Donald M. Powers, PhD (Moderator)
  - Introduction to Traceability
- Neil Greenberg, PhD, DABCC
  - Calibrator Value Assignment
- Daniel W. Tholen, MS
  - Calculation of Uncertainty
Calibration Traceability: Edutrak Faculty

Afternoon session

Jean-Claude Forest, MD, PhD, FRCPC
  • Reference Materials/Measurement Procedures

Francesco Dati, PhD
  • Reference Measurement Laboratories

David R. Bullock, PhD
  • EQAS Role in Monitoring Calibration Traceability

William F. Koch, PhD
  • Future Directions
Establishing Calibration Traceability

Introduction to Traceability
Donald M. Powers, PhD

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10:30am – 11:00am
Introduction to Traceability

- Regulatory Requirements
- Metrological Concepts
- Expectations for Manufacturers
- Medical Implications
- Language of Metrology
Calibration Traceability

Why does the EU require traceability?

“It is essential that results reported to physicians and patients are adequately accurate (true and precise) to allow correct medical interpretation and comparability over time and space.”

ISO 17511
"The traceability of values assigned to calibrators and control materials must be assured through available reference measurement procedures and/or available reference materials of a higher order."

_Official Journal of European Communities (1998)_)
Calibration Traceability

Do US regulations require calibration traceability?

*Probably yes*
Calibration Traceability

Do US regulations require calibration traceability?

21 CFR 820.30 (design controls)

Accuracy is a design requirement for quantitative IVD assays, and the way to control accuracy over time is through traceability to higher order standards
Calibration Traceability

Do US regulations require calibration traceability?

21 CFR 820.70(a) (process controls)

*Metrological traceability is an essential control for a value assignment process*
Do US regulations require calibration traceability?

21 CFR 820.72 (b)(1) (inspection, measuring and test equipment)

“Calibration standards used for inspection, measuring and test equipment shall be traceable to national or international standards”

Analytical systems used to assign calibrator values fall in this category.
Calibration Traceability

Do US regulations require calibration traceability?

21 CFR 870.75 (process validation)

Test methods cannot be validated for the intended use of assigning accurate calibrator values if traceability to higher order reference materials/methods is not established and maintained.
Calibration Traceability

Do US regulations require calibration traceability?

FDA has cited IVD manufacturers for lack of calibration traceability.
Calibration Traceability

FDA Inspectional Observation*

“… procedures allow customer calibrators for several assays to be manufactured by matching ‘secondary’ reference material that is not directly tested against the original primary standard used to determine label claim accuracy.”

* IVD Manufacturer FDA-483 (2002)
Calibration Traceability

FDA Inspectional Observation*

“The firm does not control how many steps the ‘secondary’ reference material used in manufacture is from the primary standard and data has not been collected to assess the effect this practice has on the device’s ability to meet labeled accuracy claims.”

* IVD Manufacturer FDA-483 (2002)
Quality System Regulation

Traceability Requirements

- **21 CFR 820.30**, *Design controls* require a basis for calibration if accuracy is a user requirement.
- **21 CFR 820.70**, *Production and process controls* requires compliance with specified standards.
- **21 CFR 820.72** requires calibration standards . . . traceable to national or international standards.
- **21 CFR 820.75** requires validation of methods used for value assignment for accuracy [trueness] and precision.
Metrological Traceability

What is “metrological traceability”?
Metrological Traceability

Definition

Property of the result of a measurement or the value of a standard whereby it can be related to stated references, usually national or international standards, through an unbroken chain of comparisons all having stated uncertainties.

VIM 1993
Metrological Traceability

Concept

- Each calibrator value or test result must come from a calibrated test method.
- Each calibrator must have a value assigned by a calibrated test method.
Calibration Traceability

International Standards
- Calibrator and control materials
  - ISO 17511
- Enzyme assays
  - ISO 18153
Calibration Traceability

International Standards *

- Calibrator and control materials
  - ISO 17511
- Enzyme assays
  - ISO 18153

* May be obtained from NCCLS, ANSI and other national standards organizations.
Metrology: Learn the language!

- Traceability
- Accuracy
- Trueness
- Uncertainty
Accuracy, Trueness and Uncertainty

- Method is True
- High Uncertainty
- Results are not Accurate

- Method is True
- Low Uncertainty
- Results are Accurate
Traceability Chain

RM → SI Unit → MP → Result

- RM
- 1º Calibrator
- 2º Calibrator
- Working Calibrator
- Product Calibrator
- Routine Sample

SI Unit:
- 1º Reference MP
- 2º Reference MP
- Selected MP
- Standing MP
- Routine MP

RESP.: NMI, Mfgr, Lab
Analyte Classification

Type A
- Well defined compounds
- Approx. 25-30 analytes (e.g., glucose, electrolytes, urea, cholesterol, steroid hormones)
- Results are not method dependent
- Concentrations expressed in SI units
- Full traceability chains
Analyte Classification

Type B

- Not well defined (e.g., heterogeneous)
- 400 - 600 analytes (e.g., tumor markers, viral antigens, enzymes, glycoproteins, coagulation factors)
- Arbitrary or conventional units (e.g., WHO International Units)
- Full traceability chains not practical
Traceability is not . . .

- Accuracy
- Equivalence to a reference standard
- A property of a method
- Only demonstrated once
Traceability is . . .

- A tool to ensure accurate results
- A process that relates measurement values to a reference standard
- A property of the test result
- Maintained over time through monitoring and bias correction
Traceability requires . . .

Higher order Reference System
Reference System

- Definition of the measurand
- Reference Measurement Procedure
  \textit{(ISO 15193)}
- Reference Material
  \textit{(ISO 15194)}
- Reference Measurement Laboratory
  \textit{(ISO 15195)}
Traceability requires . . .

- Higher order Reference System
- Validated measurement procedures
- Qualified reference materials
Metrology: Learn the language!

- Traceability
- Accuracy
  - Trueness
  - Uncertainty
  - Measurand
  - Commutability
Commutability

Definition

“closeness of agreement between the mathematical relationship of the measurement results obtained by two measurement procedures for a stated quantity in a given material, and the mathematical relationship obtained for the quantity in human samples”
Commutability

Concept

- A patient sample and a calibrator each contains 100.0 mmol/L of sodium
Commutability

Concept

- A patient sample and a calibrator each contains 100.0 mmol/L of sodium

- Measure each sample using
  - Reference Measurement Procedure
  - Routine Measurement Procedure
## Commutable

<table>
<thead>
<tr>
<th>Procedure Material</th>
<th>Reference</th>
<th>Routine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Calibrator</strong></td>
<td>100.3</td>
<td>99.7</td>
</tr>
<tr>
<td><strong>Patient Sample</strong></td>
<td>99.8</td>
<td>100.1</td>
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*Results in mmol/L*
## Not Commutable

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*Results in mmol/L*
Traceability requires . . .

- Higher order Reference System
- Validated measurement procedures
- Qualified reference materials
- Suitable reference laboratory
- Unbroken chain of comparisons
- Complete documentation
Traceability?

Complete documentation!
Traceability requires . . .

- Higher order Reference System
- Validated measurement procedures
- Qualified reference materials
- Suitable reference laboratory
- Unbroken chain of comparisons
- Complete documentation
- Hierarchical transfer of values
New Calibrator Lot

- RM
- MP
- Working Calibrator
- Standing MP
- Product Calibrator Lot #1
- Routine MP
- Product Calibrator Lot #2
- Routine Sample
- RESULT

Traceability
New Calibrator Lot

RM → MP → RESULT

Working Calibrator

Product Calibrator Lot #1

Routine Sample

RESULT

RM → MP → RESULT

Product Calibrator Lot #2

Routine Sample

RESULT
New Calibrator Lot

RM MP || RM MP

Working Calibrator

Standing MP

Product Calibrator Lot #1

Routine MP

Routine Sample

RESULT

Product Calibrator Lot #2

Routine MP

Routine Sample

RESULT

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Medical Traceability

Calibrators used to standardize routine methods must be traceable to the clinical studies from which medical decision criteria were derived.

EDMA Position Paper (2001)
Measurement Uncertainty

- A measurement result is only an estimate of the value of the measurand.
- Therefore – the result is only complete when accompanied by a quantitative statement of its uncertainty.
Measurement Uncertainty

Uncertainty plagues the nation

By Alan M. Webber

The biggest challenge facing business today isn’t the aftermath of Enron and Arthur Andersen, the accounting giant whose criminal case is now before a jury — although those scandals have cast a pall over big companies.

It isn’t New York Attorney General Eliot Spitzer’s current investigation of Wall Street — although its bad behavior, as highlighted recently by the $100-million fine imposed on Merrill Lynch, has caused investors to lose confidence.

And it isn’t even the prolonged hangover from the dot-com binge — although the bursting of the New Economy bubble has left investors in its wake.

On the issue of the next opportunities for technology, ways that technology will not only help improve productivity, speed business solutions and deliver profitability, but also fire up our imaginations. The truth is, we’re just starting to feel the real benefits of the Web. Business-to-business applications now are bringing significant opportunities. But given the dot-com bubble’s explosion, that simply won’t work as a compelling business story.

What we need to hear about, then, is a smart, concerted fashion, are the health-care, humanitarian and even national security promises of genomics, the branch of genetics that studies DNA. This revolution is just beginning, and instead of New York in the wake of Sept. 11 is that the first job of a leader in a time of great uncertainty is to be present, to be seen, to be heard, to be clear.

A first step: Very simply, it’s time for President Bush to convene a national business summit — one that addresses both homeland security and economic growth.

Policy uncertainty. This is the other side of political uncertainty, and today it permeates the Bush administration. Nowhere has this been clearer than on U.S. policy in the Middle East.

Want to end uncertainty and help the economic recovery gain steam? Put an end to policy schizophrenia and speak with one voice. That would make it a lot
Uncertainty
Traceability Chain

RM → SI Unit → 1º Calibrator → 1º Reference MP → 2º Reference MP → 2º Calibrator → Selected MP → Working Calibrator → Standing MP → Product Calibrator → Routine MP → Routine Sample → RESULT

Uncertainty:
- NMI
- NMI
- NMI
- Mfgr
- Mfgr
- Mfgr
- Lab
- Lab
- Lab

Resp.
Measurement Uncertainty

Definition

Parameter, associated with the result of a measurement, that characterizes the dispersion of the values that could reasonably be attributed to the measurand

VIM 1993
Measurement Uncertainty

- Uncertainty associated with each step is cumulative
- Uncertainty of the result is inherited from all transfer steps in the chain
- Therefore – include as few transfer steps as practical
Calculating Uncertainty

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<td>Laboratory</td>
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Control Materials

- Traceability requirement only applies to “accuracy controls”
- Target values should be assigned by a Reference Measurement Procedure if . . .
  - Routine method is traceable to the RMP
  - Control materials are commutable with patient samples
Measurement Traceability

Expectations

- Traceability must be supported by objective evidence
- Uncertainties mathematically quantified
- Monitored at appropriate intervals
- Systematic effects (bias) identified

NORAMET Z (1997)
Measurement Traceability

Expectations

- Bias will be removed (correction)
- If bias is not removed, explain reason and state magnitude
- Update uncertainties (both correction and uncorrected bias increases the uncertainty of results)
Metrology: Learn the language!

- Traceability
- Accuracy
  - Trueness
  - Uncertainty
  - Commutability
- Measurand
- VIM & GUM
Thank you!
Establishing Calibration Traceability for Quantitative Assays

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