Getting the Right Answer
The Importance of Traceability

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Acknowledgements
Contents

• History and philosophy
• Interpreting laboratory results
• Performing measurements
• The science and practice of Metrology
• Improving metrological traceability today
• (creatinine as an example)
Combination of five volume measures.

2 he = 1 ho, 10 ho = 1 sheng, 10 sheng = 1 tou, 10 tou = 1 hu.

Inscription of 249 characters explains the origins, individual parts, and dimensions of the individual parts.
Chia Measure: China 45 BC – AD 23

Multiple copies made - Sent around the country
Standardised measurement and trade
Authenticity “certified” by inscription

→ same result in different times and places
Measurements

• Every civilisation and every craft has its tools for spreading measurement standards
• Traceability is the modern version
• Let’s apply this to Laboratory Medicine ....
Terminology

- **Measurement** Traceability
- Trueness
- Bias
- “Getting the right answer”
• **Our goal:** To improve patient health

• **Our tools:** Laboratory tests

• **Our mechanism:** Support medical decisions
Numerical laboratory results

Example:

Mr Bill Bloggs (DoB 1 Jul 1950)
Sample Collected: 21 Aug 2012, 10:00 am

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine:</td>
<td>125</td>
<td>umol/L</td>
</tr>
</tbody>
</table>

How is this number interpreted?
Interpreting laboratory results

All results are interpreted by comparison.

Comparison may be with:

• A clinical decision point

• A population reference interval

• A previous result from the patient

5-Aug  1-Aug
Creatinine:  110  125  umol/L

Professor Per-Hyltoft Petersen, Sydney 2005
For valid comparisons ...

• **Results** must be **unbiased** relative to the results used to create the **comparator**

• **Clinical Decision Point**
  – Method used to perform the study

• **Population reference interval**
  – Method used for the reference interval study

• **Previous result on the patient**
  – Method used for the previous result
Are Unbiased Results Important?
Bias: Adverse clinical effects

Biased results ➔
(results not comparable with the comparator):
• Wrong diagnosis
• Wrong management
• Incorrect monitoring

➔ patient harm
Bia: Applying Evidence

Comparison may be with:

• A clinical decision point
• Derived from the medical literature

• Comparable results required for evidence-based medicine
Bias: Financial issues?

• Unnecessary testing costs due to analytical factors (patient recalls, follow-up, treatment):
  • Germany 1.5 Billion US$ per year
    – German Health Report 1998
  • USA 7.5 Billion US$ per year
    – Willie May, Chief Analytical Chemistry NIST

→ Wasteful

Bias: E-Health

• Combining results in an Electronic Medical Record
• Valid only if results comparable
• The public expects this!

→ IT Ready
Without comparable results..

Laboratory Medicine is:

Not safe

Not evidence-based

Wasteful

Not IT Ready
Laboratory Measurements
Laboratory Measurements

• All numerical laboratory measurements are made by comparison

• Analyte concentration in the sample is compared with concentration in the assay calibrators.

• Done using a standard curve

• Value assignment of calibrators establishes assay trueness (bias)
Calibrator value “sets” assay trueness / bias

How is the value of the calibrator set?
**Materials**

- manufacturer's product calibrator
- routine sample

**Methods**

- end-user's routine measurement
- RESULT
Materials

- manufacturer's working calib.
- manufacturer's product calibrator
- routine sample

Methods

- manufacturer's standing measurement
- end-user's routine measurement

RESULT
Materials

Methods

- Primary calibrator
- Manufacturer's working
- Manufacturer's product calibrator
- Routine sample
- Secondary reference measurement
- Manufacturer's standing measurement
- End-user's routine measurement
- RESULT
Calibration Hierarchy
or
Traceability chain
Materials

- primary calibrator
- manufacturer's working
- manufacturer's product calibrator
- routine sample

Methods

- definition of (SI) unit
- primary reference measurement
- secondary reference measurement
- manufacturer's standing measurement
- end-user's routine measurement

RESULT

uncertainty
Alternative traceability chain for some in-house assays
The top of the traceability chain

• All assays are “anchored” in one of the following
  – A Material
  – A Method (e.g., Enzymes)
Reference Materials

- **Certified Reference Materials**
  - Produced by National Measurement Institutes
  - Highly purified
  - Purity verified (and certified)
  - Very accurately weighed (and certified)
  - Reconstituted very accurately

- May also be "**Matrix matched**" eg urine, serum
  - Values assigned by comparison with pure materials
# CERTIFICATE OF ANALYSIS

**ERM®- DA252a**

**Frozen Human Serum**

<table>
<thead>
<tr>
<th>Constituent</th>
<th>Certified value (^1) (mg/kg)</th>
<th>Uncertainty (^2) (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine</td>
<td>3.1</td>
<td>0.5</td>
</tr>
</tbody>
</table>

1) The certified value is traceable to the standards and analytical procedures used at LGC.

2) The quoted uncertainty is the half-width of the expanded uncertainty calculated using a coverage factor, \(k\), of 2.6, which gives a level of confidence of approximately 95 %.

This certificate is valid for 3 months from the date of shipment provided the sample is stored under the recommended conditions.

The minimum amount of sample to be used is 0.4 g.

**NOTE**

European Reference Material ERM®-DA252a was produced and certified under the responsibility of LGC according to the principles laid down in the Technical Guidelines of the European Reference Materials® cooperation agreement between BAM-LGC-IRMM. Information on these guidelines is available on the Internet (http://www.erm-crm.org).

Accepted as an ERM®, Teddington, September 2006
Certificate revised July 2008

Signed: ____________________________

Dr Derek Craston, UK Government Chemist
LGC Limited
Other Reference materials

• **International conventional calibrator**
  – Eg WHO standards

• **Other suppliers**
  – Eg US Pharmacopoeia, commercial suppliers

• **Manufacturer’s In-house materials**
Reference Methods

• For some analytes the a method **defines** the true result

• Examples: IFCC methods for AST, ALT, ALP

• Assays NOT calibrated with pure material

• For most analytes reference methods are **calibrated** by a material

• Examples: Isotope Dilution Mass Spectrometry
Who decides?

The top of the chain is vital to accuracy.
What Reference Material or Method is the top of the Traceability Chain?
Joint Committee on Traceability in Laboratory Medicine

• JCTLM - Joining of:
  – Metrology Community (BIPM)
  – Laboratory Medicine Community (IFCC)
  – Accreditation Community (ILAC)

• Different languages, different journals, different traditions, different history

• Aim to bring rigour and processes of metrology to laboratory medicine
Metrology - BIPM

Bureau International de Poids et Mesures
(International Bureau of Weights and Measures)

(Pont de Sevres, Paris)
The **Metre Convention (1875)**

- Treaty to oversee the keeping of metric standards (SI – Systeme Internationale).
- 56 signatory countries in 2012
- “..to promote world wide uniformity in units of measurement..”

- Chinese Taipei is an associate member of the General Committee of Weights and Measures
Metrology in practice

- **International network of Laboratories**
  - National Measurement Institutes

- **International Treaties**
  - Recognition of measurements

- **Metrology Research**
  - All aspects
VIM – International Vocabulary of Metrology

- Measurand
- Measurement Uncertainty
- Traceability
Guide to the Uncertainty of Measurement
<table>
<thead>
<tr>
<th>Base quantity</th>
<th>SI base unit</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Name</strong></td>
<td><strong>Name</strong></td>
</tr>
<tr>
<td>length</td>
<td>metre</td>
</tr>
<tr>
<td>mass</td>
<td>kilogram</td>
</tr>
<tr>
<td>time, duration</td>
<td>second</td>
</tr>
<tr>
<td>electric current</td>
<td>ampere</td>
</tr>
<tr>
<td>thermodynamic temperat</td>
<td>kelvin</td>
</tr>
<tr>
<td>amount of substance</td>
<td>mole</td>
</tr>
<tr>
<td>luminous intensity</td>
<td>candela</td>
</tr>
<tr>
<td></td>
<td>Symbol</td>
</tr>
<tr>
<td></td>
<td>m</td>
</tr>
<tr>
<td></td>
<td>kg</td>
</tr>
<tr>
<td></td>
<td>s</td>
</tr>
<tr>
<td></td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>K</td>
</tr>
<tr>
<td></td>
<td>mol</td>
</tr>
<tr>
<td></td>
<td>cd</td>
</tr>
</tbody>
</table>
The kilogram

This international prototype, made of platinum-iridium, is kept at the BIPM under conditions specified by the 1st CGPM in 1889.
Measurements in general

- Weighing a reagent
- Pipetting a volume
- Measuring absorbance
- Timing a reaction

- These are all possible because of metrology!
JCTLM Output

- Database of “higher Order ... ”
- Reference Materials
- Reference Methods
- Reference Laboratories

Meets traceability requirements of European Union
Based on ISO standards
**JCTLM database: Laboratory medicine and *in vitro* diagnostics**

**Analyte keyword search for reference materials, measurement methods/procedures and services**

*Type an analyte name* in part or full, e.g. cholesterol

- creatinine

**Refine search by analyte category**

- All

**Refine search by matrix category**

- All

**Please select your requirement:**

- Higher-order reference materials
- Reference measurement methods/procedures
- Reference measurement services

[Reset] [Search]
### Results of the search

**Your search criteria produced 7 summary results.**
Select one or several higher-order reference material summary descriptions amongst the following list and click on 'View' to access more information.

#### Select all items from the list

**Sort by:**
- Analyte
- Matrix/Material
- Organization

<table>
<thead>
<tr>
<th>Select</th>
<th>Analyte</th>
<th>Analyte category</th>
<th>Matrix/Material</th>
<th>Organization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>creatinine</td>
<td>metabolites and substrates</td>
<td>creatinine crystalline material</td>
<td>NIST</td>
</tr>
<tr>
<td></td>
<td>creatinine</td>
<td>metabolites and substrates</td>
<td>creatinine crystalline material</td>
<td>NMIJ</td>
</tr>
<tr>
<td></td>
<td>creatinine</td>
<td>metabolites and substrates</td>
<td>frozen human serum</td>
<td>CENAM</td>
</tr>
<tr>
<td></td>
<td>creatinine</td>
<td>metabolites and substrates</td>
<td>frozen human serum</td>
<td>NIST</td>
</tr>
<tr>
<td></td>
<td>creatinine</td>
<td>metabolites and substrates</td>
<td>human serum</td>
<td>IRMM</td>
</tr>
<tr>
<td></td>
<td>creatinine</td>
<td>metabolites and substrates</td>
<td>human serum</td>
<td>LGC</td>
</tr>
<tr>
<td></td>
<td>creatinine</td>
<td>metabolites and substrates</td>
<td>human serum</td>
<td>NIST</td>
</tr>
</tbody>
</table>
The JCTLM database currently lists:

- 298 RM for 175 measurands
- 180 RMP for 80 measurands
- 146 RMS for 39 measurands.
Further Information
(www.bipm.org/jctlm/)

- the intergovernmental organization through which Member States act together on matters related to measurement science and measurement standards.
3 Pillars of Laboratory Standardisation

1. Primary reference material
2. Primary reference method
3. Primary reference laboratory
4 Pillars of Laboratory Standardisation

1. Primary reference material
2. Primary reference method
3. Primary reference laboratory
4. **External Quality Assurance**
   
   Traceable, commutable
5 Pillars of Laboratory Standardisation

1. Primary reference material
2. Primary reference method
3. Primary reference laboratory
4. External Quality Assurance
5. Reference Intervals / Clinical Decision limits
Common Reference Intervals

• Australian Project
• 2013 – 2015
• 12 Common tests
• Sodium, Potassium, Calcium ...
What can we do?

Professional Organisations
Manufacturers
Laboratories
Measurement Institutes
Regulators
Accreditation agencies
Researchers
Professional organisations: APFCB - 2016

**Symposium 2**
IFCC-SD
IFCC-SD Standardization Globally Activity
Ian Young (GB)
Kina Höglund (SE)
Graham Beastall (UK)

**Symposium 6**
JSCC
Standardization and Harmonization in Japan
Shigeru Ueda (JP)
Susumu Osawa (JP)
Naotaka Hamasaki (JP)

**Symposium 10**
KSCC
Standardization Effort in Korea
Junghan Song (KR)
Yeo-Min Yun (KR)
Gye-Cheol Kwon (KR)

**Symposium 14**
EFLM
EFLM Harmonization of Total Testing Process
Ferruccio Ceriotti (IT)
Ana-Maria Simundic (HR)
Mauro Panteghini (IT)
Éva Ajzner (HU)

All activities need international alignment
Welcome to the NGSP Web Site

The purpose of the NGSP is to standardize Hemoglobin A1c test results to those of the Diabetes Control and Complications Trial (DCCT) and United Kingdom Prospective Diabetes Study (UKPDS) which established the direct relationships between HbA1c levels and outcome risks in patients with diabetes.

Download Certification Packets

The Relationship Between HbA1c and Estimated Average Glucose (eAG)

More about the DCCT | More about the UKPDS

Convert between NGSP, IFCC and eAG

We have added a tool for converting between NGSP(%) , IFCC (mmol/mol) and eAG (mg/dL) units. Click here...
Key Resources

- HoSt Testosterone Certified Procedures [PDF - 297 KB] Updated September 2016
- VDSCP Vitamin D Certified Procedures [PDF - 312 KB] Updated September 2016
- HoSt Estradiol Certified Procedures [PDF - 292 KB] Updated September 2016
Laboratory Quality Assurance and Standardization Programs

Lipid Standardization Program

The Centers for Disease Control and Prevention (CDC) maintains a Lipid Standardization Program (LSP) that provides accuracy-based standards for measuring total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), apolipoprotein A-I (apo A-I), and apolipoprotein B (apo B) in U.S. and international laboratories.

The LSP is unique among external quality-control systems (EQAS) in that it provides a way to establish, assess, and improve the accuracy—or trueness—of analytical measurements over time. The LSP provides traceability to CDC’s reference measurement procedures (RMPs) for the measurement of TC, TG, and HDL-C. Traceability to designated comparison methods (DCMs) at Northwest Lipid Metabolism and Diabetes Research Laboratories (NWLMMDRL) for apolipoproteins is provided through the LSP. In this way, the LSP standardizes the resulting measured values of these lipids, lipoproteins, and apolipoproteins no matter what analytical system is used. Measurement standardization ensures the credibility of results and valid comparability among different...
Certification Programs

• NGSP – HbA1c
• CDC - Lipids
• CDC - Steroids

• All use/contribute to JCTLM listed materials / methods / services
• All collaborate with international partners
Commenced 1950’s
Related to Framingham Study
Remains vital today
Linked to JCTLM-listed methods
The role of Manufacturers

1. Actions
   - Traceable to best international references (JCTLM)
   - Good traceability practice (low uncertainty)
   - Confirmed low bias of final product

2. Words
   - Describe references used (JCTLM)
   - Describe uncertainty
   - Demonstrate quality of final product
   - Include in IFU / sales material
Routine Laboratories

• Choose methods which are:
  – Traceable to good references (JCTLM listed)
  – Have low uncertainties for calibrators
  – Minimise changes over time

• Select and promote unbiased comparators
  – Common decision points
  – Common reference intervals

• Confirm performance with traceable EQA
Conclusions

• Assay traceability is vital for lab medicine
  – Patient safety
  – Cost effectiveness
  – Evidence based medicine
  – IT-application
• Metrology already backs most of what we do
  – Weights, volumes, currents, lights
• Traceability is a global activity
• We all need to play our role in traceability
• Good results are our contribution to healthcare
Traceability – The Modern Tool