Application & Applicability of Reference Method Values

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Reference Method Values (RMVs)

Where?

– Reference Materials (RMs)
  ➔ Certified RMs (CRMs)
  ➔ Standard RMs (SRMs)
  ➔ JCTLM
  ➔ In charge of individual client
  ➔ SI-traceable RMVs
Application of RMVs
In all situations where "trueness and nothing but trueness" is required

→ Limitations!
Certified Reference Materials

Types and characteristics

Primary CRMs

• Pure substances (usually)
• Target values: "Physicochemical" procedures

Secondary CRMs

• "Native"/"Reduced" or "processed" matrix
• Target values: Reference Measurement Procedures
Application of CRMs

ISO 15194 (4.2.1)

- **Calibration material** (calibrator)
  - to determine the calibration function

  or

- **Control material**
  - to assess the analytical trueness or uncertainty of measurement

A Reference Material shall perform only one of the functions at a time.
Reference Method Values – Applicability

Reference Method Values <> Reference Materials
- Must be viewed together!

< Right values on >
< Right materials in the >
< Right hands for >
< Right applications >

莫担忧！
Applicability of CRMs

Dependent on

Commutability

"Reduced matrix"
RM procedure

"Native"
Routine procedure

Reference laboratory

- Manufacturer
- EQA
- [Routine laboratory]
Application – Focus

Commutability

"Reduced matrix" RM procedure

"Native" CRM Routine procedure

> Quality of material
> Quality of target

• [Routine laboratory]

Reference laboratory
"Native" Reference Material

Production

• CLSI C37-A (1999)
  – Preparation and Validation of Commutable Frozen Human Serum Pools as Secondary Reference Materials for Cholesterol Measurement Procedures

• CLSI C53-P (started in 2005)
  – Validating and Implementing Commutable Reference Materials
Production – Some details

- Blood collection with plastic blood bag in ice water (to avoid contact with plastic, lipoprotein alteration)
- Centrifugation of cold blood bags (plasma with adequate platelets for clotting)
- Aseptic transfer of plasma into sterile glass bottles
- Clotting
- Aseptic separation of serum
- Filtration (measurement of critical analytes before and after)
- Aliquoting (in borosilicate glass vials with Teflon®-lined caps) and freezing at –70°C

All manipulations in one center within 48h
CRM target values

Quality of Reference Method Values

[Diagram showing targets with good and bad trueness and precision]
Reference Method Values

General requirements

• Adequate RM procedures
• Competent RM laboratories

→ JCTLM

• "Procedure Manual": ISO/EN 15193 & 15195
• Reference Measurement procedure

"... thoroughly investigated measurement procedure shown to yield values having an uncertainty of measurement commensurate with its intended use ..."
Reference Method Values

Proposed quality specifications


Reference Method Values

Proposed quality specifications

Models linked to the "intende use"

• Linked to EQA
• Linked to routine procedures
• State-of-the-art
Reference Method Values
Proposed quality specifications (Stöckl et al, 1996)

<table>
<thead>
<tr>
<th>Analyte</th>
<th>CV (%)</th>
<th>Bias (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloride</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Calcium</td>
<td>1.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.5</td>
<td>0.6</td>
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<tr>
<td>Thyroxine</td>
<td>2</td>
<td>0.9</td>
</tr>
<tr>
<td>Cortisol</td>
<td>2</td>
<td>1.4</td>
</tr>
</tbody>
</table>
Application

Commutability

"Reduced matrix"
RM procedure

"Native" CRM
Routine procedure

• Manufacturer
• EQA
• [Routine laboratory]

Reference laboratory

According to the rules as layed down in ISO 17511
Application


7 Validation of traceability
7 Validation of traceability

7.2 The commutability of the manufacturer's working calibrator(s) shall be assessed by the manufacturer applying both reference measurement procedure and the routine measurement procedure to the manufacturer's working calibrator and to a set of relevant human (routine) samples.

>Method comparison >"Native" CRMs

Personal opinion about "Reference measurement procedure to working calibrator"

• Limited value: Reduced matrix
• Alternative: use "weighed-in" values
Case study – Testosterone

Value assignment to product calibrators

“Before”: calibrator values
= Added amount (weighing), or ID-GC/MS

Calibrators
\[ y = 1.0007x + 0.0003 \]

Sera
\[ y = 0.848x + 0.1925 \]
Case study – Testosterone

Value assignment to product calibrators

“After” = adjusted values by comparison, via the reverse regression line

\[
\text{Sera: } y = x - 3 \times 10^{-6}
\]

\[
\text{Assigned calibrators: } y = 1.18x - 0.2267
\]
ISO 17511

7 Validation of traceability

7.3 The commutability of the manufacturer's product calibrator, shall be demonstrated by comparing the results of measurements, made by both the reference procedure and the calibrated routine procedure on a set of actual samples of a type to which the routine measurement procedure is intended to be applied.

>Method comparison >"Native" CRMs (other set)
ISO 17511

Interpreting the method comparison

Traceability of **calibration** (7.4 Note)

A unit **slope** is expected but a deviation from unit slope within a stated interval of quantity values may be tolerable.

The observed value of the **intercept** should be stated. If a value significantly different from zero at a given probability is considered tolerable, the reasons for this shall be stated.
ISO 17511

Interpreting the method comparison

Traceability of the individual results (7.4)
Results by the routine procedure shall be related to those of the reference procedure, e.g., by linear regression.

• Compare the expected variability around the line to the observed one.

• A limit of maximum allowable relative variation between results by the reference and calibrated routine procedures may be specified by the manufacturer.
Case study – Testosterone

Variation around line: “17511 alternative”

⇒ Manufacturer limit

Analytical performance specifications from biological variation (www.westgard.com)

• CV = 4.7%
• Bias = 6.4%
• Total error = 14% (z = 1.65 for imprecision)

Select TE = 14%, but adapt in the following way

• 14% down to 5 nmol/l
• At 5 nmol/l constant absolute deviation:
  – 14% of 5 nmol/l = 0.7 nmol/l
Case study – Testosterone

TE = 14% (≥5 nmol/l) and 0.7 nmol/l (<5 nmol/l)
Case study – Testosterone

TE = 14% (≥5 nmol/l) and 0.7 nmol/l (<5 nmol/l)

→ Ask the manufacturer!!!
Application

Commutability

"Reduced matrix" RM procedure

"Native" CRM Routine procedure

- Manufacturer
- EQA
- [Routine laboratory]

Reference laboratory

According to the rules as laid down in EN 14136
Traceability of target values used in EQA – The “vigilance” function of EQA?

A challenge for the EQA Organizer
Application


4 Design requirements for EQAS

6 Assessment of analytical examination procedures
4 Design requirements for EQAS

4.1 The EQAS organization shall provide survey samples ... that ... simulate as closely as possible the relevant properties of the samples on which the diagnostic procedures are intended to be used. Note 3: EQAS organizations should not select survey materials which disadvantage an individual IVD MD.

4.3 In order to assess the performance of a particular IVD MD, the design of the EQAS shall enable a device-and procedure-specific specific evaluation of results.

4.4 Note 2 The EQA organization should have, if appropriate, access to laboratories ... which can assign reference measurement procedure values ...

>EQA >"Native" CRMs
EN 14136

6 Assessment of analytical examination procedures

6.1.5 The results obtained by EQAS shall be interpreted in comparison with criteria for acceptable performance, and in relation to the claims of the manufacturer for that IVD MD.

Note 1 Criteria for acceptable performance should reflect the medical use (e.g. based on biological variation or other means) and the "state-of-the-art" of the quality of the IVD MDs.

>EQA >IVD MD specific evaluation with respect for manufacturer's claims and reality
Trueness assessment in EQA

Ratification of EN 14136 in 2004
We were ahead of our time …


Trueness assessment in EQA

We continued to do it …


Trueness assessment in EQA

Trueness assessment in EQA

Trueness assessment in EQA

Trueness assessment in EQA

Biomedicum

PRACTICAL TOOLS IN QUALITY IMPROVEMENT

09:15 Benefits from EQA programme using authentic patient samples; Göran Lindstedt, Sweden
Thank you for your attention!

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