Metrological aspects and External Quality Assurance Programs

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Interlaboratory comparison

- Proficiency testing (PT)
- External quality control (EQC)
- External quality assessment (EQA)
- External quality assurance programs (EQAP)
EQA: where it started

Am J Clin Pathol 17: 853-861, 1947
Objectives of EQAP

- Laboratory performance evaluation for regulatory purpose (PT)
- Laboratory performance evaluation (EQA schemes)
- Method performance evaluation (EQAS/EQAP)
- Vigilance role (EQAP)
- Training & help, (EQAP)
- Continuing education (EQAP)
We focus today on:

- Promotion of interchangeability of laboratory results
- Follow-up of standardisation
- Improving laboratory service
Interchangeability of laboratory results

Why?

Patient comfort

Efficiency

Cost effectiveness
Harmonisation
TRACEABILITY

“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: 6.10, 1993
European parliament and council directive on in vitro diagnostic medical devices: 98/79/EC

Annex 1: Essential requirements

I. GENERAL REQUIREMENTS

3. ......

“The traceability of values assigned to calibrators and/or control materials must be assured through available reference measurement and/or available reference materials of higher order”
Advantages of traceability

- Transferability of results between laboratories based on true values
- Possibility to use common reference intervals
EQAS ORGANISATION

- choice of samples
- sample preparation
- validation
- storage

EQAS PARTICIPANT

error handling, remarks, corrective actions

mailing

samples

survey preparation

report

statistical evaluation

data registration

analysis

data reporting

mailing

PLAN

DO

ADJUST

CHECK

influence on samples
We focus today on:

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Prerequisites

- Appropriate samples
  - Genuine material
  - Assured sample integrity
- Appropriate scheme design
- Target values with stated measurement uncertainty
Appropriate sample material

- Fresh serum
- Frozen single donation serum
- Frozen human pool serum

- More attention to sample integrity
Sample integrity during transport conditions
Bias of cholesterol methods against the RMV in lyophilised control samples
Bias of cholesterol methods against the RMV in frozen patient samples
Method performance evaluation

**CREATININE (µmol/l)**

- **Method 2: Jaffé methods**
  - $N = 206$  
  - $M = 172.0$  
  - $SD = 35$  
  - $CV(%) = 20.4$

- **Method 7: Enzymatic method**
  - $N = 7$  
  - $M = 54.9$  
  - $SD = 51.7$  
  - $CV(%) = 94$

- **Method 9: Reflectance photometry**
  - $N = 54$  
  - $M = 62.0$  
  - $SD = 0.83$  
  - $CV(%) = 1.3$

*best method?*
Reproducibility of PSA testkits (results of BEQAS 1995)
PSA (F/T ratio)

- Patient samples:
  - Normal: 20%
  - Benign prostate hypertrophy: < 20%
- EQA control samples (spiked with semen fluid): 50 - 95%
Example of scheme design for bias

- Multiple determinations
- Homogeneous groups
  - Recommended calibrator
  - Protocol according to the recommendations of the manufacturer

Reference measurement values

DRAFT INTERNATIONAL STANDARD ISO/DIS 15195
ISO/TC 212
Secretariat: ANSI
Voting begins on 2000-08-17
Voting terminates on 2000-01-17

INTERNATIONAL ORGANIZATION FOR STANDARDIZATION

Clinical laboratory medicine — Requirements for reference measurement laboratories

EUROPEAN STANDARD
EN ISO/IEC 17025

NORME EUROPÉENNE
EUROPÄISCHE NORM

May 2000

General requirements for the competence of testing and calibration laboratories (ISO/IEC 17025:1999)

Richtlinien der Bundesärztekammer zur Qualitätssicherung quantitativer laboratoriums-medizinischer Untersuchungen
24 August 2001
Follow-up of standardisation efforts

- **International**
  - Specific proteins (calibration according to CRM 470)
  - HbA1c
  - NCCLS guidelines microbiology

- **National**
  - Common normal control plasma
  - Measurement uncertainty
How to promote the use of CRM 470 for calibration?

- From survey 1996: letter to participants announcing that only acceptable results will be possible if specific proteins are calibrated against CRM 470.
- Advice to calibrate against CRM 470 even if the manufacturer still continue to give also the old calibration values
- Advice to change reference intervals
Commutability of Serum Protein Values: Persisting Bias among Manufacturers Using Values Assigned from the Certified Reference Material 470 (CRM 470) in the United States

Thomas B. Ledue¹ and A. Myron Johnson²
¹Foundation for Blood Research, Scarborough, ME, USA
²University of North Carolina School of Medicine, Chapel Hill, NC, USA

Several quality control schemes in Europe have already shown a significant improvement in among-laboratory variance (7–9). In addition, two publications

Effect of Certified Reference Material 470 (CRM 470) on National Quality Assurance Programs for Serum Proteins in Europe

A. Myron Johnson¹ and John T. Whicher²
¹ Departments of Pediatrics and Obstetrics-Gynecology, University of North Carolina, Chapel Hill, NC, USA
² Rush House, Leeds, UK
Standardization of HbA1c

- Step 1: DCCT harmonisation
- Step 2: IFCC: metrological traceability
### HbA1c: Menarini 8140

<table>
<thead>
<tr>
<th>selections for report</th>
<th>statistical results</th>
</tr>
</thead>
<tbody>
<tr>
<td>sample no.</td>
<td>group</td>
</tr>
<tr>
<td></td>
<td>instrument(s)</td>
</tr>
<tr>
<td>EURO113</td>
<td>IFCC 4.3</td>
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<tr>
<td>deadline</td>
<td>4.3</td>
</tr>
<tr>
<td>unit</td>
<td>DCCT 6.1</td>
</tr>
<tr>
<td>group</td>
<td>6.1</td>
</tr>
<tr>
<td>all labs (gray bars)</td>
<td>your value -</td>
</tr>
<tr>
<td>instrument(s)</td>
<td>mean 6.2</td>
</tr>
<tr>
<td>Menarini 8140 (red bars)</td>
<td>n 348 6.3</td>
</tr>
<tr>
<td></td>
<td>77</td>
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</tbody>
</table>
# HbA1c: Tinaquant

<table>
<thead>
<tr>
<th>sample no.</th>
<th>EURO109</th>
<th>group</th>
<th>instrument(s)</th>
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<tbody>
<tr>
<td>deadline</td>
<td>7-2-2002</td>
<td>IFCC</td>
<td>7.4</td>
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<tr>
<td>unit</td>
<td>%</td>
<td>DCCT</td>
<td>9.0</td>
</tr>
<tr>
<td>group</td>
<td>all labs (gray bars)</td>
<td>your value</td>
<td>-</td>
</tr>
<tr>
<td>instrument(s)</td>
<td>Tina Quant (Hitachi) (red bars)</td>
<td>mean</td>
<td>9.0</td>
</tr>
<tr>
<td>n</td>
<td>359</td>
<td></td>
<td>37</td>
</tr>
</tbody>
</table>
Promotion of standards

Proportion of Labs (%) performing QC on purchased media
Evaluation of measurement uncertainty in clinical chemistry
Applications to determinations of total concentration of calcium and glucose in human serum
**Case 3. Uncertainty budget for $c_{\text{Gluc}}$ with pre-analytical, analytical and patient-related contributions.**

<table>
<thead>
<tr>
<th>Quantity</th>
<th>Value</th>
<th>Standard Uncertainty</th>
<th>Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>$c_0$</td>
<td>0.0 mmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$A_s$</td>
<td>0.152000 AU</td>
<td>760·10^{-6} AU</td>
<td>0.5 %</td>
</tr>
<tr>
<td>$A_0$</td>
<td>-1.150·10^{-3} AU</td>
<td>127·10^{-6} AU</td>
<td>0.0 %</td>
</tr>
<tr>
<td>$A_{\text{cal}}$</td>
<td>0.265650 AU</td>
<td>889·10^{-6} AU</td>
<td>0.2 %</td>
</tr>
<tr>
<td>$c_{\text{cal}}$</td>
<td>10.5000 mmol/L</td>
<td>0.0500 mmol/L</td>
<td>0.5 %</td>
</tr>
<tr>
<td>$k_{\text{intra}}$</td>
<td>1.0000</td>
<td>0.0650</td>
<td>86.4 %</td>
</tr>
<tr>
<td>$k_{\text{drift}}$</td>
<td>1.00000</td>
<td>5.77·10^{-3}</td>
<td>0.7 %</td>
</tr>
<tr>
<td>$k_{\text{prec}}$</td>
<td>0.0 mmol/L</td>
<td>0.144 mmol/L</td>
<td>11.7 %</td>
</tr>
<tr>
<td>$c_{\text{gluc}}$</td>
<td>6.027 mmol/L</td>
<td>0.421 mmol/L</td>
<td></td>
</tr>
</tbody>
</table>
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Smear from male urethra
Gram: neutrophils and *H. influenzae*
Culture: *H. influenzae*

<table>
<thead>
<tr>
<th>Challenge Results</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>No <em>N. gonorrhoeae</em></td>
<td>55%</td>
</tr>
<tr>
<td>No <em>N. gonorrhoeae; H. influenzae</em></td>
<td>28%</td>
</tr>
<tr>
<td><em>H. influenzae</em></td>
<td>15%</td>
</tr>
<tr>
<td>Other</td>
<td>2%</td>
</tr>
</tbody>
</table>
From analytical result to useful information

The uncertainty in the result is the sum of a bias with respect to the reference method plus a 95% confidence interval of 2 coefficients of variation and additional smaller components due to calibration error and ....
Congratulations ma’am, according to your HCG concentration, you are a little pregnant.