40 years EQA experience – on the road to harmonisation?

Prof. Dr. med. Michael Spannagl

Munich- Heart of?

40 years EQA experience – on the road to harmonisation?

09.10.2015 - Michael Spannagl, Bergen, Norway
„O’zapft is“ - Oktoberfest 2015

Key facts
- Date: September - October (15 days)
- Location: Munich - Theresenwiese
- 6.3 Mio. Visitors
- 7.4 Mio. Liter beer = 7.4 Mio. Maß sold...

Exactly 7.4 Mio Liter?

How to standardize the „Maß“?

1. Standardization of the “Maß” in the Kingdom of Bavaria
2. Standardization to the “German Liter”

"Coalition against fraudulent pouring [of beer]"

Is it really one liter?

1,069 Liter = 1,000 Liter

1811 1892 2015
Potency Labeling

How to declare F VIII content??

FVIII:c  ( RV Jan 03: Refacto 2000 E iv in sev. hemophilia)

Chromogenic substrate

clotting
ReFacto AF vs. Xyntha

### Worldwide
- CS Assay WHO 6. IS
  - ReFacto 1000 IU 83 μg

### Europe
- CS Assay WHO 7. IS
  - ReFacto AF 1000 IU 95 μg

### USA/Canada
- OS Assay WHO 7. IS
  - Xyntha 1000 IU 131 μg

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**Instand e.V.**

- 28 Employees in Düsseldorff
- 104 Experts
- 360 EQA-programs
- Participants in 93 countries

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INSTAND e.V. Society for Promoting Quality Assurance in medical Laboratories e.V.

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09.10.2015 - Michael Spannagl, Bergen, Norway
Society for Promoting Quality Assurance in medical Laboratories e.V.

INSTAND e.V.

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Number of participants from 1993-2015

INSTAND e.V. - EQAS worldwide

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Number of EQA-schemes

Number of shipped samples
RiliBÄK - Guidelines of the German Medical Association on Quality Assurance in Medical Laboratory Testing

Section A

Sections
B1 B2 B3 B4 B5

New Guideline for Quality Assurance of the German Medical Association (RiliBÄK)
-> mandatory for all medical laboratories in Germany

<table>
<thead>
<tr>
<th>Section</th>
<th>Description</th>
<th>Effective Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Section A</td>
<td>Fundamental requirements for quality assurance</td>
<td>Effective since 1 April 2008</td>
</tr>
<tr>
<td>Specific Section B 1</td>
<td>Quantitative analyses in laboratory medicine - internal QA - external QA</td>
<td>Effective since 1 April 2008</td>
</tr>
<tr>
<td>Specific Section B 2</td>
<td>Qualitative analyses in laboratory medicine - internal QA - external QA</td>
<td>Effective since 1 July 2011</td>
</tr>
<tr>
<td>Specific Section B 3</td>
<td>Direct detection and characterization of pathogens - internal QA - external QA</td>
<td>Effective: 1 June 2015</td>
</tr>
<tr>
<td>Specific Section B 4</td>
<td>Analyses of ejaculate - internal QA - external QA</td>
<td>Effective since 1 July 2011</td>
</tr>
<tr>
<td>Specific Section B 5</td>
<td>Molecular- and cytogenetic analyses - internal QA - external QA</td>
<td>Effective since 1 October 2011</td>
</tr>
</tbody>
</table>
### Guideline of the German Medical Association on Quality Assurance in Medical Laboratory Examinations (RiliBAEK)

(extract from annex B1)

<table>
<thead>
<tr>
<th>No.</th>
<th>Analyte</th>
<th>Acceptable relative deviation of the single value or the relative root mean square</th>
<th>Range of validity of columns 3 to 5</th>
<th>Acceptable relative deviation in a round robin test</th>
<th>Type of target value in a round robin test</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>Haemoglobin A 1c (Hba1c)</td>
<td>9.0%</td>
<td>≤ 0.6</td>
<td>12.0%</td>
<td>SV</td>
</tr>
<tr>
<td>20</td>
<td>Erythrocytes</td>
<td>4.0%</td>
<td>≤ 1</td>
<td>8.0%</td>
<td>RMV</td>
</tr>
<tr>
<td>21</td>
<td>Estradiol 17 beta</td>
<td>22.0%</td>
<td>≤ 10000</td>
<td>38.0%</td>
<td>RMV</td>
</tr>
<tr>
<td>22</td>
<td>Ethanol (clinical toxicology)</td>
<td>9.0%</td>
<td>≤ 0.6</td>
<td>12.0%</td>
<td>SV</td>
</tr>
<tr>
<td>23</td>
<td>Ferritin</td>
<td>13.5%</td>
<td>≤ 0.6</td>
<td>21.0%</td>
<td>SV</td>
</tr>
<tr>
<td>24</td>
<td>FSH</td>
<td>14%</td>
<td>≤ 70</td>
<td>21.0%</td>
<td>SV</td>
</tr>
<tr>
<td>25</td>
<td>Gamma glutamyl transpeptidase (γ-GT) EC 2.3.2.2</td>
<td>11.5%</td>
<td>≤ 0.33</td>
<td>21.0%</td>
<td>RMV</td>
</tr>
<tr>
<td>26</td>
<td>Glucose</td>
<td>11.0%</td>
<td>≤ 0.33</td>
<td>15.0%</td>
<td>RMV</td>
</tr>
<tr>
<td>27</td>
<td>Haematocrit</td>
<td>5.0%</td>
<td>≤ 0.1</td>
<td>9.0%</td>
<td>SV</td>
</tr>
<tr>
<td>28</td>
<td>Haemoglobin</td>
<td>4.0%</td>
<td>≤ 0.1</td>
<td>6.0%</td>
<td>RMV</td>
</tr>
<tr>
<td>29</td>
<td>INSTAND e.V. Society for Promoting Quality Assurance in medical Laboratories e.V.</td>
<td>INSTAND Reference Laboratory</td>
<td>40 years EQA experience – on the road to harmonisation?</td>
<td>INSTAND e.V. Society for Promoting Quality Assurance in medical Laboratories e.V.</td>
<td></td>
</tr>
</tbody>
</table>

19.10.2015 - Michael Spannagl, Bergen, Norway
Reference laboratory

Accreditation according to ISO 17025 and ISO 15195

2006  Cholesterol
2009  Chloride, Potassium, Sodium, ALT, AST, GGT, CK, LDH
      Creatinine, Urea, Cortisol, Total Protein, HbA1c, Theophylline
2012  Calcium, Lithium, Magnesium, Uric Acid, Total Glycerides, Testosterone, Thyroxine
2015  Glucose, 17-β-Estradiol, Progesterone, Digoxin, Digitoxin

Reference measurement procedures established in the reference laboratory of INSTAND e.V.

Before 2002:  Cholesterol, Cortisol, Creatinine, 17β-Estradiol, Glucose, Progesterone, Testosterone, Thyroxine, Total Glycerides, Uric Acid
2002:  Theophylline
2003:  ALT, AST, CK, GGT, LDH, Calcium, Chloride, Potassium, Lithium, Magnesium, Sodium, Digoxin, Digitoxin
2004:  HbA1c, Total Haemoglobin, Total Protein
2006:  Urea
target values set by consensus value principle

manufacturer RO

40 years EQA experience – on the road to harmonisation?

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manufacturer BE
Glucose
EQAS results 2002 - 2015

time

0 1 2 3 4 5 6 7 8
coefficient of variation [%]

all manufacturers

target values set by reference measurement procedure

GGT
EQAS results 2003 - 2015

time

0 2 4 6 8 10 12
coefficient of variation [%]

all manufacturers

target values set by reference measurement procedure
HbA1c EQAS results
[mmol/mol]

<table>
<thead>
<tr>
<th>EQAS January 2009</th>
<th>EQAS May 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>acceptability range: ± 18 % from RMP value</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>INSTAND e.V. Society for Promoting Quality Assurance in medical Laboratories e.V.</th>
<th>40 years EQA experience – on the road to harmonisation?</th>
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<tbody>
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<td>23</td>
</tr>
</tbody>
</table>

EQAS for HbA1c with lyophilized and fresh whole blood samples

<table>
<thead>
<tr>
<th>Immunoassay</th>
</tr>
</thead>
<tbody>
<tr>
<td>deviation from target value [%]</td>
</tr>
<tr>
<td>lyophilized samples</td>
</tr>
<tr>
<td>fresh samples</td>
</tr>
</tbody>
</table>
RiliBÄK Specific Section B 3:
Direct Detection and Characterization of Pathogens
- Quantitative Detection of Nucleic Acid of HIV-1

Table B 3-2a
Evaluation thresholds for external quality assurance of nucleic acid detection of pathogens transmitted by blood/plasma/serum

<table>
<thead>
<tr>
<th>No.</th>
<th>Analyte</th>
<th>Acceptable deviation of log10 value of participant from log10 target value of EQA scheme</th>
<th>Range of validity in respect to column 3</th>
<th>Target value of EQA scheme</th>
<th>Frequency of EQA scheme</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CMV DNA</td>
<td>-0.8 to +0.8</td>
<td>5 000 to 5 000 000 IL/mL</td>
<td>Target value</td>
<td>2x/year</td>
</tr>
<tr>
<td>2</td>
<td>HBV DNA</td>
<td>-0.6 to +0.6</td>
<td>500 to 5 000 000 IL/mL</td>
<td>Target value</td>
<td>2x/year</td>
</tr>
<tr>
<td>3</td>
<td>HCV RNA</td>
<td>-0.6 to +0.6</td>
<td>500 to 5 000 000 IL/mL</td>
<td>Target value</td>
<td>2x/year</td>
</tr>
<tr>
<td>4</td>
<td>HIV-1 RNA</td>
<td>-0.6 to +0.6</td>
<td>500 to 5 000 000 copies/mL</td>
<td>Target value</td>
<td>2x/year</td>
</tr>
</tbody>
</table>
INSTAND-EQA schemes
for quantitative HIV-1 genome detection
for mimicking therapy monitoring

• quantitative genome determination
  - basis for therapy monitoring

• decrease of \( \geq \log_{10} \) copies/ml within 1 month
  - indicator for antiviral efficacy
  - if not: antiviral resistance?

• target
  - get viral load below level of detection

• example for EQA scheme
  dilution series of one and the same HIV stock:
  - \( 1 : 200 \times 10^7 \)
  - \( 1 : 50 \times 10^7 \)
  - \( 1 : 12.5 \times 10^7 \)
  - \( 1 : 3.125 \times 10^7 \)

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INSTAND e.V.

INSTAND-EQAS for HIV-1: Sample Dilution Series

EQAS Sep 2010, PCR/NAT HIV-1 (360)
sample 360008 (median 1,438 = 3.16 \( \log_{10} \) copies/ml)

Methods

<table>
<thead>
<tr>
<th>Methods</th>
<th>success rate within ( \frac{1}{10} ) ( \log_{10} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>all methods</td>
<td>+/- 1.0 ( \log_{10} ) = 100.0% (82/82)</td>
</tr>
<tr>
<td>+/- 0.5 ( \log_{10} ) = 96.3% (79/82)</td>
<td></td>
</tr>
<tr>
<td>+/- 0.25 ( \log_{10} ) = 72.0% (59/82)</td>
<td></td>
</tr>
</tbody>
</table>

40 years EQA experience – on the road to harmonisation?

09.10.2015 - Michael Spannagl, Bergen, Norway
INSTAND-EQAS for HIV-1: Test Performance

EQAS Nov 2008, HIV PCR/NAT (360)
sample 10114 (median 4,350 = 3.64 log₁₀ copies/ml)

Methods

all methods
11 PCR RO
11 PCR ZX
98 TM AB
13 TM RO
13 TM ZX
40 LC ZX
15 bDNA SI

EQAS Nov 2008, HIV PCR/NAT (360)
all methods

40 years EQA experience – on the road to harmonisation?
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INSTAND-EQAS for HIV-1: Sample Dilution Series

EQAS Nov 2008, HIV PCR/NAT (360)
all methods (3 samples: dilution factors: 10⁹, 10⁸, 10⁷; 1 sample: neg.)

median
neg. sample
median

2.68
3.64
4.58

2.68
cv
8.59%
cv
4.71%
cv
3.57%

N 90
N 90
N 90
N 90

Samples

40 years EQA experience – on the road to harmonisation?
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The last problems

- The survey manager and EvidenceBasedM..
- No punishment
- Communication with manufacturers
- Harmonization of acceptance criteria
TO...

Make RILIBAEK a success

Improve control material (like vs like, commutability...)

Skip artificial surveys (not to test the control mat...) Introduce new concepts (virtual..., educational...)

Miles vs. Kilometer

Will this ever be standardized?
Thank you for attention