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Centre for Metrological Traceability in Laboratory Medicine (CIRME)

Director: Prof. Mauro Panteghini

site: http://users.unimi.it/cirme

EQALM

EQALM symposium 2017

October 19, Dublin, Ireland

**Adam Uldall Lecture**

# The role of EQA in the verification of in vitro medical diagnostics

**Mauro Panteghini**

**University of Milan Medical School**

**Research Centre for Metrological Traceability in Laboratory Medicine (CIRME)**

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## Steps of the process and different responsibilities in implementing traceability of patient results and defining their uncertainty

| | |
|---|---|
| Profession (e.g., JCTLM, IFCC, EFLM): | Define analytical objectives: reference measurement systems (traceability chain) and associated clinically acceptable uncertainty (fit for purpose) |
| ↓ | |
| Diagnostic manufacturers: | Implement suitable measuring systems (platform, reagents, calibrators, controls) fulfilling the above established goals |
| ↓ | |
| End users (clinical laboratories): | Survey assay and laboratory performance through IQC and EQA redesigned to meet metrological criteria |

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Adapted from Panteghini M, Clin Chem Lab Med 2010;48:7

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## Adam Uldall Lecture

| Name of awarded | Year | Lecture |
|---|---|---|
| Jean-Claude Libeer | 2009 | External Quality Control in medical laboratories: differences with other PT testing programs |
| Gunnar Nordin | 2010 | The Role of EQA in the Establishment of Analytical Quality Specifications |
| André Deom | 2011 | EQA in developing countries |
| Carmen Ricos | 2012 | Databases on Biological Variation. Establishment & uses |
| Linda Thienpont | 2013 | The role of EQA providers in the harmonization process: a plea for using native sera in external quality assurance |
| Dietmar Stöckl | | Newer trends in EQAS – continuous peer-group monitoring of laboratory data |
| David G Bullock | 2014 | Post Market Surveillance of Manufacturers Assays and the Effects of the Revised IVDD |
| Sverre Sandberg | 2015 | Performance criteria of point-of-care testing in modern medicine |
| Per Hyltoft Petersen | 2016 | The evolution of EQA through 50 years – a historical review |

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EQA in Europe

www.eqalm.org

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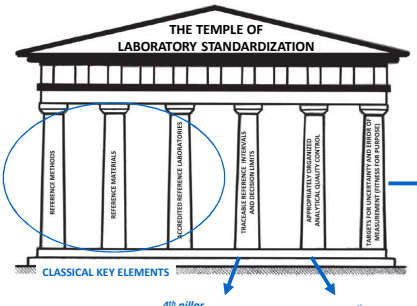


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Bruga F & Panteghini M, Clin Chim Acta 2014;432:55

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**Laboratory users (i.e., doctors and patients) expect lab results to be equivalent and interpreted in a reliable and consistent manner**

**STANDARDIZATION**
to achieve metrological traceability of patient results to higher-order references

***Unbroken traceability chain***
*Definition of higher order references to implement the appropriate trueness transfer process to commercial calibrators and patient results*

***Measurement uncertainty budget***
*Definition of allowable limits for clinical application of the measurements*

***Post-market surveillance***
*Survey the suitability of IVD assays for clinical use and of laboratory performance in using them*

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- **Definition and approval of reference measurement systems, possibly in their entirety;**
- **Implementation by IVD industry of traceability to such reference systems in a scientifically sound and transparent way;**
- **Definition by the profession of the clinically acceptable measurement uncertainty for each of the analytes used in the clinical field;**
- **Adoption by EQA providers of commutable materials and use of an evaluation approach exclusively based on trueness;**
- **Monitoring of the analytical performance of individual laboratories by the participation in EQA that meet metrological criteria and application of clinically acceptable limits;**
- **Abandonment by users (and consequently by industry) of nonspecific methods and/or of assays with demonstrated insufficient quality.**

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## Expected consequences

1. Experts defines reference measurement systems
2. Industry implements traceability to them
3. Users (and industry) abandon non-specific methods
4. EQAs provide commutable materials and trueness-based grading
5. Professionals establish clinically allowable errors
6. Individual laboratories monitor their performance by participating to EQA and applying allowable limits

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Adapted from Infusino I, Schumann G, Ceriotti F, Panteghini M. CCLM 2010;48:301

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## Fulfillment of the Requirements of the EU IVD Directive by Manufacturers

EU 98/79/EC-IVD Directive

- Preparation of the necessary technical documentation
- All data that characterize the product
- Testing protocols
- Labels and instruction for use
- Assigned values and metrological traceability
  - Traceability chain and calibration hierarchy
  - Transfer protocols
  - Commutability testing
  - Determination of uncertainty (fit for purpose)
- Stability testing

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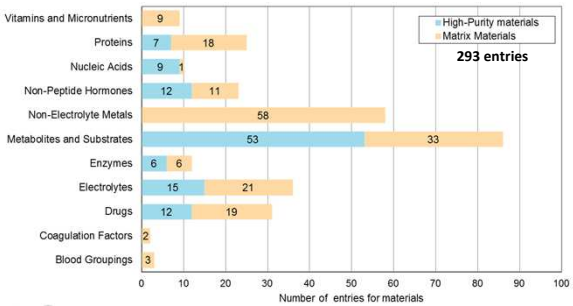
## JCTLM Database content

JCTLM Accurate results for patient care

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## Role of IVD manufacturers

**IVD manufacturers should define a calibration hierarchy to assign traceable values to their system calibrators and to fulfil during this process uncertainty limits, which represent a proportion of the uncertainty budget allowed for clinical laboratory results.**

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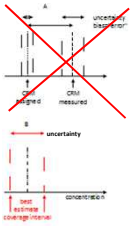
[Braga F & Panteghini M, Clin Chim Acta 2014;432:55]

## Role of IVD manufacturers




1) Elimination of measurement bias

2) Estimation of measurement uncertainty @ the calibrator level

*[Adapted from Kallner A, Scand J Clin & Lab Invest 2010; 70(Suppl 242): 34]*

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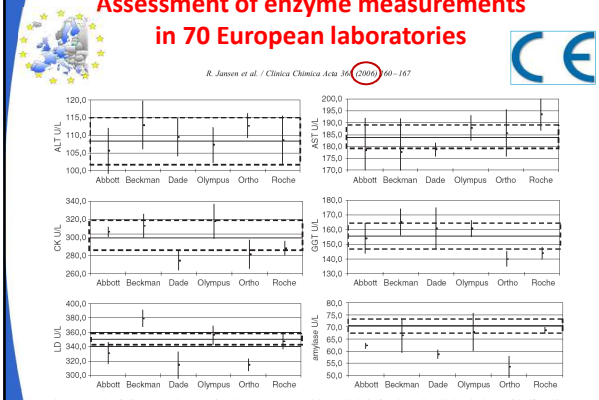
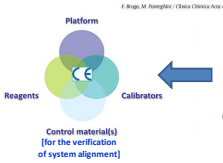
**Clinical laboratories need to rely on the manufacturers who must ensure traceability of their analytical systems to the highest available level**

## Assessment of enzyme measurements in 70 European laboratories




## Paradigm shift in the thinking




- **If the manufacturer has to assume total responsibility for supplying products of acceptable quality in terms of traceability and uncertainty of the system ("CE marked"), it is no longer possible to consider separately the components of each analytical system (i.e., platform, reagents, calibrators and control materials), which in terms of performance can only be guaranteed and certified by the manufacturer as a whole.**
- **Any change introduced by users or third parties (e.g., the use of reagents, calibrators or control materials from other suppliers) may significantly alter the quality of the analytical system performance, removing any responsibility from the manufacturer and depriving the system (and, consequently, the produced results) of the certification originally provided through CE marking.**

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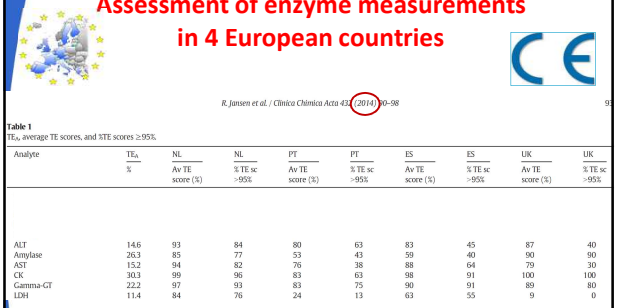
## Assessment of enzyme measurements in 4 European countries

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CK is nicely standardized and a substantial improvement in analytical performance of marketed GGT assays was demonstrated. Conversely, aminotransferases, LDH and AMY still showed major disagreement suggesting the need for improvement in implementing traceability to higher order references.

## Limitations of CE mark

[stating compliance with legislation, mainly by means of European standards]

- Does ***not*** mean that manufacturer has transferred trueness successfully
- Does ***not*** mean that uncertainty of calibrator meets clinical needs


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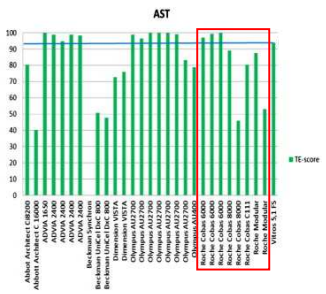


**TE scores per analytical platform: TE scores vary considerably within users of instruments from the same manufacturer!!**

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Rob Jansen et al. Clinica Chimica Acta, Volume 432, 2014, 90–98

## Analytical systems measuring serum ALT marketed by four IVD companies

| Company | Platform | Principle of method | Calibrator | Declared uncertainty | Higher-order reference employed |
|---|---|---|---|---|---|
| Abbott | Architect | with P-5-P | Calibration factor | NA | IFCC Reference Method |
| | | without P-5-P | Calibration factor | NA | NADH molar extinction factor |
| Beckman | AU | with P-5-P | System calibrator | 6% | IFCC Reference Method |
| | | without P-5-P | System calibrator | NA | Beckman Coulter Master Calibrator |
| | Synchron | with P-5-P | Enzyme Validator Level 1 | 14.48% | IFCC Reference Method |
| | | | Enzyme Validator Level 2 | 7.53% | IFCC Reference Method |
| Roche | Cobas c | with P-5-P | C.f.a.s. | 0.66% | IFCC Reference Method |
| | | without P-5-P | C.f.a.s. | 0.66% | IFCC Reference Method modified |
| | Integra | with P-5-P | C.f.a.s | 1.50% | IFCC Reference Method |
| | | without P-5-P | C.f.a.s | 1.50% | IFCC Reference Method modified |
| | Modular | with P-5-P | C.f.a.s | 1.09% | IFCC Reference Method |
| | | without P-5-P | C.f.a.s | 1.09% | IFCC Reference Method modified |
| | | without P-5-P HiCo | C.f.a.s | 1.09% | IFCC Reference Method modified |
| Siemens | Dimension Vista | with P-5-P | Enzyme II Calibrator Level 2 | 5.21% | IFCC Reference Method |
| | | | Enzyme II Calibrator Level 3 | 5.24% | IFCC Reference Method |
| | Advia | with P-5-P | Chemistry calibrator control 1 | 2.71% | IFCC Reference Method |
| | | | Chemistry calibrator control 2 | 2.40% | IFCC Reference Method |
| | | without P-5-P | Chemistry calibrator control 1 | 2.50% | IFCC Reference Method |
| | | | Chemistry calibrator control 2 | 1.30% | IFCC Reference Method |

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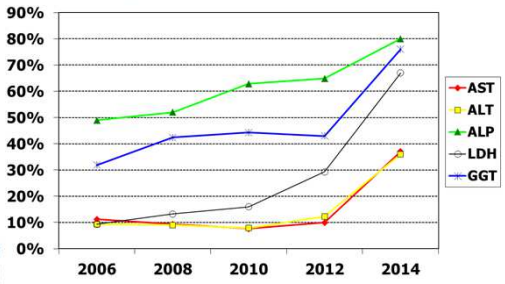
## Percentage of Italian laboratories declaring to use methods for measuring enzyme employing the IFCC analytical principles

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Clinical Chemistry 63:7
1196-1198 (2017)

Opinion

## American Liver Guidelines and Cutoffs for "Normal" ALT: A Potential for Overdiagnosis

Mauro Panteghini,[1*] Khosrow Adeli,[2] Ferruccio Ceriotti,[3] Sverre Sandberg,[4] and Andrea Rita Horvath[5]

Despite the availability of a reference measurement system (RMS) for standardizing ALT results in clinical samples, the current evidence is, however, that ALT is still measured by methods that give quite differing values *(3)*. Assay performance also varies considerably within users of instruments from the same manufacturer *(4)*. This is mainly due to the use on the same platforms of various reagents with different analytical selectivity for ALT.

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## But, those who said to report enzyme results traceable to the IFCC RMPs, did they accurately recover the targets set by the reference laboratory?

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## Expected consequences

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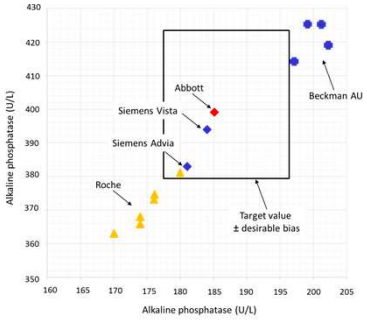
DE GRUYTER Clin Chem Lab Med 2017; 55(3): e47–e50

Letter to the Editor

Federica Braga*, Erika Frusciante, Ilenia Infusino, Elena Aloisio, Elena Guerra, Ferruccio Ceriotti and Mauro Panteghini

## Evaluation of the trueness of serum alkaline phosphatase measurement in a group of Italian laboratories

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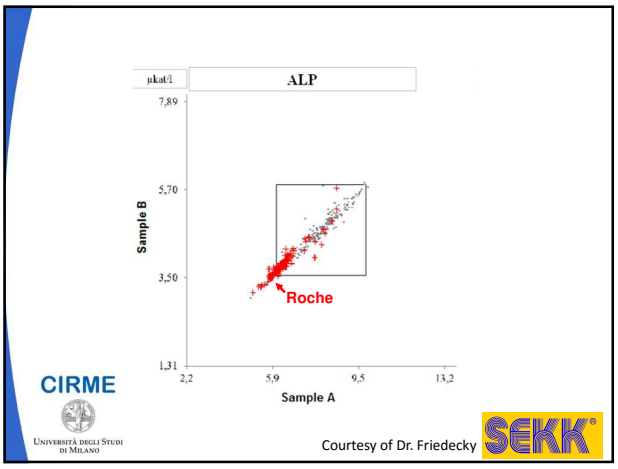
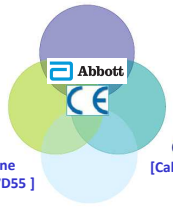



## Case study #1: Alkaline Phosphatase @

**Platform** [Architect c16000]




**Reagents**
[Architect Alkaline Phosphatase cod. 7D55 ]

**Calibrators**
[Calibration factor]

**Control material(s)**
[Technopath Multichem-S plus]
[for the verification of system alignment]

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## Analytical systems measuring serum ALP marketed by four IVD companies

| Ditta | Piattaforma analitica | Principio del metodo | Calibratore | Incertezza tipo dichiarata[a] | Riferimento di ordine superiore utilizzato |
|---|---|---|---|---|---|
| Abbott | Architect | p-NPP | Fattore di calibrazione | ND | Procedura di riferimento IFCC (2011) |
| | | p-NPP | Fattore di calibrazione | ND | Coefficiente di estinzione molare |
| Beckman | AU | IFCC (1983) | System calibrator | 6,00% | Calibratore Master Beckman Coulter |
| | | DEA | System calibrator | ND | Calibratore Master Beckman Coulter |
| | Synchron | AMP | Enzyme Validator Level 1 | 6,22% | Procedura di riferimento IFCC (2011) |
| | | | Enzyme Validator Level 2 | 1,86% | Procedura di riferimento IFCC (2011) |
| | | AMP | Enzyme Validator Level 1 | 3,64% | Metodo standard DGKC |
| | | | Enzyme Validator Level 2 | 1,27% | Metodo standard DGKC |
| Roche | Cobas c | IFCC gen.2 | C.f.a.s. | 0,59% | Procedura di riferimento IFCC (1983) |
| | Integra | IFCC gen.2 | C.f.a.s. | 1,22% | Procedura di riferimento IFCC (1983) |
| | Modular | IFCC liquido | C.f.a.s. | 1,65% | Procedura di riferimento IFCC (1983) |
| Siemens | Dimension Vista | AMP | ALPI calibrator | 4,51%[b] | Procedura di riferimento IFCC (2011) |
| | Advia | AMP | Chemistry calibrator control 1 | 3,70%[c] | Procedura di riferimento IFCC (2011) |
| | | | Chemistry calibrator control 2 | 1,00%[c] | Procedura di riferimento IFCC (2011) |
| | | DEA | Chemistry calibrator control 1 | 1,40%[c] | Coefficiente di estinzione molare |
| | | | Chemistry calibrator control 2 | 1,30%[c] | Coefficiente di estinzione molare |

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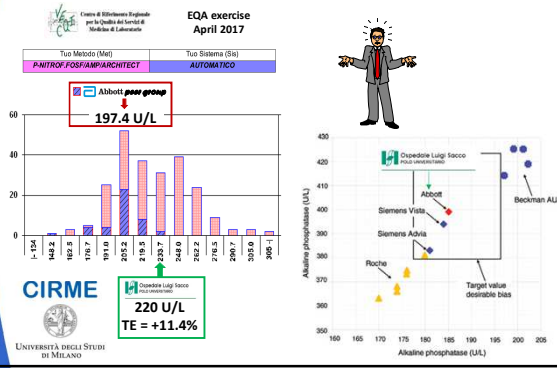
Braga F et al. Biochim Clin, Volume 41, 2017, 64–71

## Case study #1: Alkaline Phosphatase @

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## What is a "peer group"?

- ✓Same model instrument/reagents/calibrator from one manufacturer?
- ✓Same instrument family from one manufacturer?
- ✓Instruments from different manufacturers that use the same reagent and calibrator?
- ✓Methods with the same measurement principle with different reagents and calibrators?

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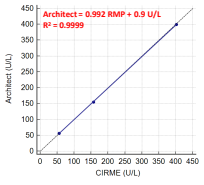
## Case study #1: Alkaline Phosphatase @

**Trueness verification of ALP measurement**

Methods: ALP target values were assigned to 3 fresh serum pools by the IFCC RP. The pools were then assayed in triplicate using the Abbott ALP assay (cod. 7D55) carried out on Architect




**Architect ALP combined measurement uncertainty ($u_c$)**

**based on:**

- **uncertainty of values assigned by RMP ($u_{rel}$) = 1.25%**
- **bias ($u_{bias}$) = 0.4%**
- **imprecision ($u_{imp}$) = 1.5% (average CV Jan-Aug 2017)**

**$u_c$ = 2.0%**


Table 2: Allowable maximum uncertainty for enzyme measurements performed by clinical laboratories.

| Enzyme | Quality level | | |
|---|---|---|---|
| | Minimum | Desirable | Optimum |
| AST | ±9.3% | ±6.2% | ±3.1% |
| ALT | ±14.6% | ±9.7% | ±4.9% |
| γGT | ±5.6% | ±3.7% | ±1.9% |
| LDH | ±6.5% | ±4.3% | ±2.2% |
| CK | ±17.1% | ±11.4% | ±5.7% |
| ALP | ±4.5% | ±3.0% | ±1.5% |
| AMY | ±6.6% | ±4.4% | ±2.2% |

Infusino I et al. Clin Chem Lab Med 2017;55:334

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## Case study #1: Alkaline Phosphatase @

Background: Starting from 2015, Abbott correctly validates the traceability of its enzyme calibrator factors (CF) for the Architect system by comparison to results from IFCC reference procedure (RP). For ALP, they provide this experimental CF (eCF, 2290) to users as an optional alternative to the theoretical CF (tCF, 2150) derived from the p-nitrophenol molar extinction.

PI30JAN2015

| Procedure | Theoretical Calibration Factor (recommended) | IFCC Standardized Calibration Factor (optional) |
|---|---|---|
| Alkaline Phosphatase | 2150 | 2290 |

Based on molar extinction coefficient of p-nitrophenol

EU 98/79/EC-IVD Directive

....the metrological traceability of values assigned to calibrators shall be assured through suitable reference measurement procedures... *where available*....

Metrological Traceability of ARCHITECT Amylase and Alkaline Phosphatase Assays to IFCC Reference Methods

D. Armbruster[1], D. Yahalom[1], L. Lennartz[1], M. Orth[2] *[1]Abbott Laboratories, Lake Villa, IL, [2]Abbott Laboratories, Dallas, TX, [3]Abbott Laboratories, Wiesbaden, Germany, [4]Institute von Paul Ehrlich, Institute for Laboratory Medicine, Stuttgart, Germany*

*CLINICAL CHEMISTRY*, Vol. 61, No. 10, Supplement, 2015

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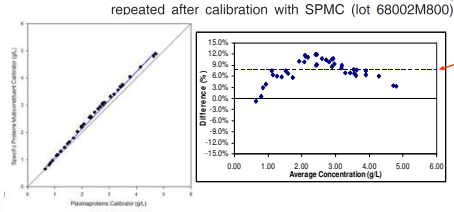
## Case study #2: Transferrin @

Given the availability of two options warranting the CE mark provided by Abbott to calibrate the Architect Transferrin method

a correlation study (CLSI-EP 09A3) was performed to investigate the effect of different manufacturer's calibrators on the same measuring system

Methods: 40 leftover fresh-frozen serum samples were assayed in duplicate using Abbott TF immunoturbidimetric assay (cod. 1E04) on Architect c16000, calibrated with PC. The measurements were then immediately repeated after calibration with SPMC (lot 68002M800).




In average, results were 7.6% biased

Transferrin Bias

2.0% minimum
1.3% desirable
0.7% optimum

Centro di Riferimento Regionale per la Qualità dei Servizi di Medicina di Laboratorio

Azienda Ospedaliero Universitaria Careggi

In collaboration with the EQA provider, a survey was issued to assess among participating laboratories using the Architect system which calibration factor was used.

**Among 39 interviewed laboratories:**
- 87% used theoretical CF [2150]
- 13% used experimental CF [2290]

The 'peer-group' consensus value used in the EQA was therefore expected to be strongly influenced by the type of calibration adopted by the majority of laboratories, i.e. the 'theoretical' CF.

We assume that this significantly lowers the EQA median value used as reference for evaluating the performance of individual participating laboratories and may explain our [apparent] positive total error.

We expect that Abbott does indicate only one CF, i.e. that obtained by correlation results using clinical samples with RMP-assigned values.

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**DIFFERENT CALIBRATOR OPTIONS MAY STRONGLY INFLUENCE THE TRUENESS OF SERUM TRANSFERRIN MEASURED BY ABBOTT ARCHITECT SYSTEMS**

E. Aloisio[1,2,3], S. Pasqualetti[1,2], A. Carnevale[1], A. Dolci[1], M. Panteghini[1,2,3]

[1]*Clinical Pathology Unit, 'Luigi Sacco' University Hospital, Milan*
[2]*Research Centre for Metrological Traceability in Laboratory Medicine (CIRME), University of Milan*

Conclusions: Despite both calibrators used in this study are CE marked for the same measuring system and are declared traceable to the same reference material, a clinically significant bias was observed between TF results obtained with the two options. Problems in PC value-assignment protocols can be hypothesized.

biochimica clinica, 2017, vol. 41 SS2 S73

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## Case study #2: Transferrin @

**Platform** [Architect c16000]

**Reagents** [Architect Transferrin cod. 1E04]

**Calibrators**

**Control material(s)** [Technopath Multichem-S plus] [for the verification of system alignment]

**OPTION #1**
Plasmaproteins Cal (PC) cod. 11200D manufactured by Sentinel for Abbott

| | | | | | |
|---|---|---|---|---|---|
| Transferrin | ERMDA-470 | Immunoturbidimetric | 726 | mg/dL | 30.25 |
| | | | 7.26 | g/L | 0.303 |

$u_c$ = 1.7% → $u_c$ = 2.1%

**OPTION #2**
Specific Proteins Multiconstituent Calibrator (SPMC) cod. 1E78 Abbott

$u_c$ = 0.92% $u_c$ = 1.7%

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## Therefore, we must improve

- **Post-market surveillance of IVD medical devices**


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## The role of the laboratory profession (including EQA): "check"

1. Availability and quality of information about IVD metrological traceability and uncertainty

2. Surveillance of IVD system traceability

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Braga F & Panteghini M, Clin Chim Acta 2014;432:55

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Steps of the process and different responsibilities in implementing traceability of patient results and defining their uncertainty

Profession (e.g., JCTLM, IFCC, EFLM): Define analytical objectives: reference measurement systems (traceability chain) and associated clinically acceptable uncertainty (fit for purpose)

Diagnostic manufacturers: Implement suitable measuring systems (platform, reagents, calibrators, controls) fulfilling the above established goals

Post-marketing surveillance of IVD metrological traceability

End users (clinical laboratories): Survey assay and laboratory performance through IQC and EQA redesigned to meet metrological criteria

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Adapted from Panteghini M, Clin Chem Lab Med 2010;48:7

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**Houston** we have a problem.

**Currently, the full information about calibration is usually not available**

**Manufacturers only provide the name of higher order reference material or procedure to which the assay calibration is traceable, without any description of implementation steps and their corresponding uncertainty.**

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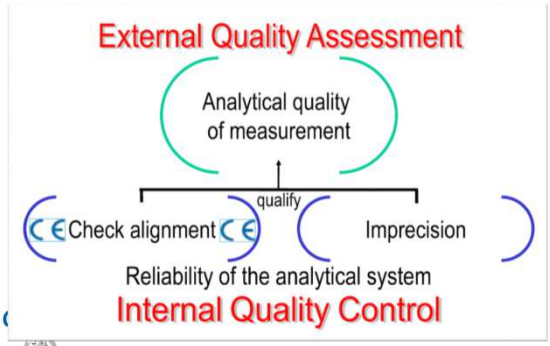
## Analytical Quality Control in the Traceability Era

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Panteghini M, Clin Chem Lab Med 2010;48:7
Braga F & Panteghini M, Clin Chim Acta 2014;432:55

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DE GRUYTER Clin Chem Lab Med 2015; 53(6): 905–912

Opinion Paper

Federica Braga*, Ilenia Infusino and Mauro Panteghini

**Table 2:** The information that in vitro diagnostics manufacturers should provide to laboratory users about the implementation of metrological traceability of their commercial systems. Adapted from [7].

a) An indication of higher order references (materials and/or procedures) used to assign traceable values to calibrators;
b) Which internal calibration hierarchy has been applied by the manufacturer, and
c) A detailed description of each step;
d) The (expanded) combined uncertainty value of commercial calibrators, and
e) Which, if any, acceptable limits for uncertainty of calibrators were applied in the validation of the analytical system.

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## The role of the laboratory profession: "check"

### Daily surveillance of IVD system traceability

1. Verification of the consistency of declared performance during routine operations performed in accordance with the manufacturer's instructions

2. Participation to appropriately structured EQA schemes ("meeting metrological criteria")

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[Braga F & Panteghini M, Clin Chim Acta 2014;432:55]

## Expected consequences

1. Experts defines reference measurement systems
2. Industry implements traceability to them
3. Users (and industry) abandon non-specific methods
4. EQAs provide commutable materials and trueness-based grading
5. Professionals establish clinically allowable errors
6. Individual laboratories monitor their performance by participating to EQA and applying allowable limits

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## Quality of EQA target – Concepts

- Analytically *valid* reference measurement procedure (ISO 15193)
- *Competent* reference laboratory (ISO 17025/ISO 15195 accreditation)

➔Joint Committee for Traceability in Laboratory Medicine listed

JCTLM Accurate results for patient care

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## Quality of EQA target – Concepts

True value assignment to EQA materials allows objective evaluation of the performance of laboratory measurements through an trueness-based (instead of inferior consensus-based) grading of the competency of participating clinical laboratories.

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## JCTLM Database Status – June 2015
## Reference measurement services

JCTLM Accurate results for patient care

- 130 reference measurement services listed
- 12 Reference Laboratories accredited for compliance with ISO 15195/ISO 17025 and 2 NMIs

| Analyte Categories | Number of Services listed | Number of Analytes | Analytes | Number of Reference Laboratories | Country |
|---|---|---|---|---|---|
| Drugs | 3 | 3 | digitoxin, digoxin, theophylline | 2 | Germany |
| Electrolytes | 15 | 6 | Li, K, Na, Cl, Mg, Ca | 4 | Germany, United Kingdom |
| Enzymes | 45 | 7 | ALP, ALT, AST, CK, GGT, alpha-amylase, LDH | 7 | Germany, Italy, Spain, United Kingdom, China |
| Metabolites and Substrates | 38 | 9 | creatinine, glucose, cholesterol (total), glycerides (total), urea, uric acid, bilirubin, HDL-Cholesterol, LDL-Cholesterol | 10 | Belgium, France, Germany, Italy, Japan, United Kingdom, China |
| Non-peptide Hormones | 21 | 10 | 17 beta-estradiol, 17-hydroxyprogesterone, aldosterone, cortisol, estriol (non conjugated), progesterone, testosterone, free thyroxine, total thyroxine (TT4), total triiodothyronine (TT3) | 4 | Belgium, Germany, United Kingdom |
| Proteins | 6 | 2 | HbA1c, total protein | 6 | France, Germany, Italy, Japan, China |
| Vitamins | 2 | 2 | Hydroxyvitamins D2 & D3 | 1 | Belgium |
| Total | 130 | 39 | | | |

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## Quality of EQA target – Concepts

- To ensure reliability in the estimate of end user uncertainty alone, the uncertainty of the values assigned by the reference laboratory to EQA materials should be maintained at a minimum.
- To achieve this, Stöckl & Reinauer [Scan J Clin Lab Invest 1993;53(suppl 212):16] have proposed that the uncertainty of the target should be <0.2 times the EQA maximal tolerated limit.

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JCTLM database : Laboratory medicine and *in vitro* diagnostics

JCTLM

### List of reference measurement services

This file was created on 04 November 2010 from the JCTLM-DB website (http://www.bipm.org/jctlm/)
Your search criteria: Reference measurement services; Analyte: ALT; Analyte category: Enzymes; Matrix category: Blood serum

**CIRME, Italy**

**Phone :** +39 02 3904 2806
**Fax :** +39 02 5031 9835
**Contact person :** Prof. Mauro Panteghini
**Email :** mauro.panteghini@unimi.it

| | |
|---|---|
| Analyte | alanine aminotransferase (ALT) |
| Material or matrix | blood serum, blood plasma |
| Applicable material or matrix | human serum or plasma (heparin), lyophilized, fresh, or frozen |
| Quantity | Catalytic activity concentration |
| Service measurement range | 0.063 µkat/l to 4.17 µkat/l<br>The conversion factor for enzyme catalytic activity concentrations: 1 U/L = 0.01667 µkat/L |
| Expanded uncertainty (level of confidence 95%) | (not available) to 2.3%<br>The uncertainty of the lower limit of the measurement range is not available as this enzyme value is clinically unrelevant |
| Interlaboratory comparison results | RELA - IFCC External Quality assessment scheme for Reference Laboratories in Laboratory Medicine at http://www.dgkl-rfb.de:81/index.shtml<br>Siekmann et al., *Clin. Chem. Lab. Med.*, 2002, **40**, 739-745 |
| Measurement principle | Kinetic spectrophotometry |
| JCTLM reference measurement method/procedure | IFCC reference measurement procedure (37 °C) for ALT |

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## Trueness verification in EQA: time to care about the quality of the samples!

LM Thienpont et al, Scand J Clin Lab Invest 2003;63:195

Linda Thienpont @ CIRME 2015

**Autem censeo Carthaginem delendam esse**

[However, I think that Carthage should be destroyed]

Cato Censorius 234 - 149 BC

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- EQA samples are frequently not validated to be commutable
- Commutability is assumed based on how the samples were prepared
  - May be reasonable for single donation
  - Potential limitation for spiked pools or supplemented


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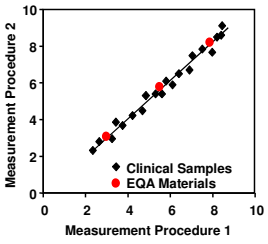
## Commutable




EQA and patient results have the same relationship between measurement procedures

EQA results reflect perfomance for patient results

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**Table 3.** Evaluation capabilities of PT/EQA related to scheme design.

| | | | | Evaluation capability | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Accuracy | | | | | | |
| | | | | Individual laboratory | | | | | Standardization or harmonization[b] | |
| | Sample characteristics | | | | Relative to participant results | | Reproducibility | | Measurement procedure calibration traceability | |
| Category | Commutable | Value assigned with RMP[a] or CRM | Replicate samples in survey | Absolute vs RMP or CRM | Overall | Peer group | Individual laboratory intralab CV | Measurement procedure interlab CV | Absolute vs RMP or CRM | Relative to participant results |
| 1 | Yes | Yes | Yes | X | X | X | X | X | X | X |
| 2 | Yes | Yes | No | X | X | X | | X | X | X |
| 3 | Yes | No | Yes | | | X | X | X | | X |
| 4 | | | No | | | X | | X | | X |
| 5 | | | Yes | | | X | X | X | | |
| 6 | | | No | | | X | | X | | |

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Miller WG et al. Clin Chem 2011;57:1670


## Working Group on Commutability upcoming recommendations for assessing commutability

| | |
|---|---|
| Manuscript Title: | IFCC working group recommendations for assessing commutability part 1: general experimental design |
| Manuscript No: | CLINCHEM/2017/277525 |
| Manuscript Type: | Special Report |
| Date Submitted by the Author: | 2 Jun 2017 |
| Complete List of Authors: | W Greg Miller, Heinz G Schimmel, Robert Rej, Neil Greenberg, Ferruccio Ceriotti, Chris John Burns, Jeffrey R Budd, Cas Weykamp, Vincent DELATOUR, Göran Nilsson, Finlay MacKenzie, Mauro Panteghini, Thomas Keller, Johanna Eltz Camara, Ingrid Zegers, and Hubert W Vesper |
| Keywords: | Commutability; Standardization; Traceability |

Part 1: General experimental design

| | |
|---|---|
| Manuscript Title: | IFCC working group recommendations for assessing commutability part 2: based on the difference in bias between a reference material and clinical samples |
| Manuscript No: | CLINCHEM/2017/277541 |
| Manuscript Type: | Special Report |
| Date Submitted by the Author: | 2 Jun 2017 |
| Complete List of Authors: | Göran Nilsson, Jeffrey R Budd, Neil Greenberg, Vincent DELATOUR, Robert Rej, Mauro Panteghini, Ferruccio Ceriotti, Heinz G Schimmel, Cas Weykamp, Thomas Keller, Johanna Eltz Camara, Chris John Burns, Finlay MacKenzie, and W Greg Miller |
| Keywords: | Commutability; Standardization; Traceability |

Part 2: Based on the difference in bias between a reference material and clinical samples

| | |
|---|---|
| Manuscript Title: | IFCC working group recommendations for assessing commutability part 3: based on the calibration effectiveness of a reference material |
| Manuscript No: | CLINCHEM/2017/277558 |
| Manuscript Type: | Special Report |
| Date Submitted by the Author: | 2 Jun 2017 |
| Complete List of Authors: | Jeffrey R Budd, Cas Weykamp, Göran Nilsson, Robert Rej, Finlay MacKenzie, Ferruccio Ceriotti, Neil Greenberg, Johanna Eltz Camara, Heinz G Schimmel, Thomas Keller, Vincent DELATOUR, Mauro Panteghini, Chris John Burns, and W Greg Miller |
| Keywords: | Commutability; Standardization; Traceability |

Part 3: Based on the calibration effectiveness of a reference material

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## Expected consequences

1. Experts defines reference measurement systems
2. Industry implements traceability to them
3. Users (and industry) abandon non-specific methods
4. EQAs provide commutable materials and trueness-based grading
5. Professionals establish clinically allowable errors
6. Individual laboratories monitor their performance by participating to EQA and applying allowable limits

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DE GRUYTER Clin Chem Lab Med 2015; aop

Sverre Sandberg*, Callum G. Fraser, Andrea Rita Horvath, Rob Jansen, Graham Jones, Wytze Oosterhuis, Per Hyltoft Petersen, Heinz Schimmel, Ken Sikaris and Mauro Panteghini

## Defining analytical performance specifications: Consensus Statement from the 1st Strategic Conference of the European Federation of Clinical Chemistry and Laboratory Medicine

*Model 1: Based on the effect of analytical performance on clinical outcomes*

a. Done by direct outcome studies – investigating the impact of analytical performance of the test on clinical outcomes;

b. Done by indirect outcome studies – investigating the impact of analytical performance of the test on clinical classifications or decisions and thereby on the probability of patient outcomes, e.g., by simulation or decision analysis.

*Model 2: Based on components of biological variation of the measurand.*

*Model 3: Based on state of the art of the measurement (i.e., the highest level of analytical performance technically achievable).*

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## *Grading different quality levels*

*The utility to elaborate specifications at different levels of quality to move, in case, from desirable to minimum quality goals and, in the meantime, ask IVD manufacturers to work for improving the quality of assay performance*

***IDEAL***

***OPTIMUM STANDARD (no need to improve)***

***DESIRABLE STANDARD (satisfactory)***

***MINIMUM STANDARD (just satisfactory)***

***UNACCEPTABLE***

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Panteghini et al.: Definition of performance specifications: 3 years from the Milan Conference Clin Chem Lab Med 2017

DE GRUYTER Clin Chem Lab Med 2017; 55(2): 189–194

**Opinion Paper**

Ferruccio Ceriotti*, Pilar Fernandez-Calle, George G. Klee, Gunnar Nordin, Sverre Sandberg, Thomas Streichert, Joan-Lluis Vives-Corrons and Mauro Panteghini, on behalf of the EFLM Task and Finish Group on Allocation of laboratory tests to different models for performance specifications (TFG-DM)

## Criteria for assigning laboratory measurands to models for analytical performance specifications defined in the 1st EFLM Strategic Conference

| APS model 1: outcome-based | APS model 2: biological variation | APS model 3: state-of-the-art |
|---|---|---|
| P-Cholesterol+ester | P-Sodium ion | U-Sodium ion |
| P-Cholesterol+ester in LDL | P-Potassium ion | U-Potassium ion |
| P-Cholesterol+ester in HDL | P-Chloride | U-Chloride |
| P-Triglycerides | P-Bicarbonate | U-Calcium ion |
| P-Glucose | P-Calcium ion | U-Magnesium ion |
| B-Hemoglobin $A_{1c}$ | P-Magnesium ion | U-Phosphate (inorganic) |
| P-Albumin | P-Phosphate (inorganic) | U-Creatinine |
| P-Troponin T and P-troponin I | P-Creatinine | U-Urate |
| P-Thyrotropin | P-Cystatin C | |
| B-Hemoglobin | P-Urate | |
| B-Platelets | P-Proteins | |
| B-Neutrophil leukocytes | B-Erythrocytes | |
| | B-Erythrocyte volume fraction | |
| | B-Erythrocyte volume | |
| | P-Prothrombin time | |
| | P-activated partial thromboplastin time | |

**Table 1:** Examples of current variation in models used to assign analytical performance specifications (APS) to External Quality Assurance (EQA) schemes.

| EQA Program | Models |
|---|---|
| CSCQ Switzerland | Governmental regulations (combination of BV and state of the art) and Combination of limits given by scientific societies and Z-score |
| CTCB France | Z-score/state of the art/limits given by scientific societies or other/limits based on clinical impact |
| DEKS Denmark | Combination of BV, state of the art and expert opinion |
| NOKLUS Norway | Fixed percentage limits and based on a combination of BV, state of the art and expert opinion |
| RCPAQAP Australia | Combination of BV and state of the art |
| SEHH Spain | Statistical/state of the art/BV |
| SEQC Spain | Combination of BV and statistical results |
| SKML The Netherlands | Combination of BV and state of the art |
| WEQAS UK | Combination of BV and state of the art |
| CMCEQAS | Combination of state of the art and statistical considerations |

CSCQ, Suisse de Contrôle de Qualité; CTCB, Centre Toulousain pour le Contrôle de qualité en Biologie Clinique; DEKS, Danish Institute of External Quality Assurance for Laboratories in Health Care; NOKLUS, Norwegian Quality Improvement of laboratory examinations; RCPAQAP, Quality assurance Program of the Royal College of Pathologists of Australasia; SEHH, Spanish Society of haematology and haemotherapy; SEQC, Spanish Society of Clinical Biochemistry and Molecular Pathology; SKML, Dutch Foundation for Quality Assessment in Medical Laboratorie; WEQAS, Welsh EQA provider; CMCEQAS, Christian Medical College External Quality Assurance Scheme; BV, biological variation.

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Jones GRD et al., Clin Chem Lab Med 2017;55:949

## Analytical performance specification (APS) derivation should be added to the Miller's EQA categorization

| | | | | Evaluation capability | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | Accuracy | | | | |
| | | | | Individual laboratory | | | | |
| Sample characteristics | | | | Relative to participant results | | | Reproducibility | |
| Category | Commutable | Value assigned with RMP* or CRM | Replicate samples in survey | Absolute vs RMP or CRM | Overall | Peer group | Individual laboratory intralab CV | Measurement procedure interlab CV |
| 1 | Yes | Yes | Yes | X | X | X | X | X |
| 2 | Yes | Yes | No | X | X | X | | X |

**Category 1/2A → Milan model 1 or 2 as basis for APS**

**Category 1/2B → Other models**

Infusino I et al. Clin Chem Lab Med 2017;55:334

9th CIRME International Scientific Meeting
STRUCTURING EQAS FOR MEETING METROLOGICAL CRITERIA: READY FOR PRIME TIME
Milano – 27 November 2015

Accred Qual Assur (2008) 13:145–148
DOI 10.1007/s00769-008-0364-z

Marjan Van Blerk et al.

GENERAL PAPER

**There are as many limits as there are EQA providers**

## Comparison of evaluation procedures used by European external quality assessment scheme organizers for haemoglobin concentration and leukocyte concentration

**Table 1** Criteria used for acceptable performance for haemoglobin concentration in blood and leukocyte concentration (deviation from the target value)

| Scheme | Haemoglobin concentration | Leukocyte concentration |
|---|---|---|
| Belgium | ±2s | ±2s |
| France | ±2s | ±2s |
| Spain (two organizers) | ±2s | ±2s |
| Croatia | ±1s | ±1s |
| Germany | ±6% | ±18% |
| Finland | ±5% | ±10% |
| Hungary: consensus mean | ±3% | ±6% |
| Hungary: target value set by reference labs or manufacturers | ±5% | ±15% |
| Russia | ±1.64s | ±1.64s |
| Slovenia | ±4% | ±10% |
| Switzerland: QUALAB (official for licensing) | ±9% | ±25% |
| Switzerland: CSCQ (scientific approach) | ±3% | ±8% |
| New York State, USA | ±7% | ±15% |

**Table 2** Percentages of unsatisfactory results reported by the participating EQAS organizers for a fixed set of 262 results of haemoglobin concentration in blood and leukocyte concentration

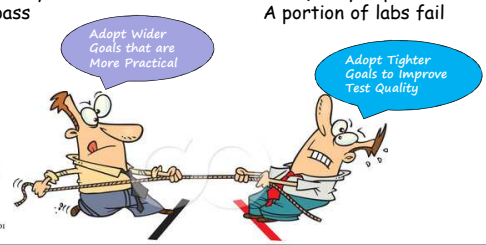
| Scheme | Haemoglobin concentration | Leukocyte concentration |
|---|---|---|
| Belgium | 6.9 | 7.3 |
| Croatia | 14.9 | 15.3 |
| Finland | 1.5 | 3.1 |
| France | 5.4 | 4.6 |
| Hungary: consensus mean method | 13.5 | 19.8 |
| Russia | 15.6 | 19.8 |
| Spain 1 | 7.6 | 4.6 |
| Spain 2 | 3.1 | 2.3 |
| Switzerland: QUALAB (official for licensing) | 0.4 | 0 |
| Switzerland: CSCQ (scientific approach) | 0.8 | 2.0 |
| New York State, USA | 0.8 | 2.3 |

# Why ?

## EQA Performance Specifications

(looser)
→ Regulatory
All labs pass

(tighter)
→ Quality improvement
A portion of labs fail

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## 6. Type of model for establishing the APS

The EQA organiser must state the model used to establish the APS. It is recommended that one of the models from the Milan conference is used [1] although it is also recognised that data from different models may be used to establish a final APS, e.g. state of the art may be used to determine which category within biological variation is selected (optimal, desirable, minimal). These can be described as:

1. Outcome-based (Milan model 1a)
2. Based on clinical decision applications (Milan model 1b)
3. Derived from biological variation (Milan model 2)
4. State of the art, defined as the highest level of analytical performance technically achievable in that moment (Milan model 3)

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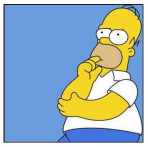
**Box 1 Factors influencing choice of External Quality Assessment (EQA) Scheme**

- Accreditation status of provider. Preference should be given to schemes accredited to ISO 17043 or equivalent (eg, those still Clinical Pathology Accreditation (CPA) accredited within the UK). If a non-accredited provider is chosen, the reason(s) should be clearly documented. Under International Laboratory Accreditation Cooperation (ILAC),[11] accreditation bodies should support the use of appropriate proficiency testing programmes which meet the essential requirements of ISO/IEC 17043, where applicable.
- Appropriateness of distribution frequency. Distributions should be at a frequency sufficient to identify performance issues in a timely manner. For core tests, this probably equates to at least monthly distributions.
- Range and number of EQA samples. Samples within the distribution cycle should cover an appropriate range of values for each analyte to verify performance across clinically relevant concentrations. Each cycle should supply sufficient samples to provide evidence of reproducibility; 3–4 samples in each distribution would probably fulfil this requirement. Samples should be 'blinded' to participants in relation to expected results.
- Scheme management and development. The scheme should be designed and overseen by appropriately competent professionals (clinical, technical and statistical). The scheme should also have an independent medical and scientific committee.[12]
- Poor performance issues. Mechanisms should be in place for reporting of poor performance to the appropriate regulatory/oversight body.
- Variety of sample provided. 'Challenging' samples should be included in selected distributions.
- Education. Educational input should be provided.
- Manufacturers. Participation of the EQA provider in postmarketing vigilance of in vitro diagnostics.[12]
- Materials. EQA providers should demonstrate use of commutable materials.[13]



*James D et al., J Clin Pathol 2014;67:651*

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## POST-MARKET SURVEILLANCE

**Requirements for the applicability of EQA results in the evaluation of the performance of participating laboratories in terms of traceability of their measurements**

| Feature | Aim |
|---|---|
| EQA materials value-assigned with reference procedures by an accredited laboratory | To check traceability of commercial system to reference measurement systems |
| Proved commutability of EQA materials | To allow transferability of participating laboratory performance to the measurement of patient samples |
| Definition and use of the clinically permissible measurement error | To verify the suitability of laboratory measurements in clinical setting |

*Panteghini M. Clin Chem Lab Med 2010;48:7*
*Infusino I et al. Clin Chem Lab Med 2010;48:301*
*Braga F, Panteghini M. Clin Chem Lab Med 2013;51:1719*
*Braga F, Panteghini M. Clin Chim Acta 2014;432:55*
*Infusino I et al. Clin Chem Lab Med 2017;55:334-40*

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DE GRUYTER Clin Chem Lab Med 2017; 55(7): 949–955

**Opinion Paper**

Graham R.D. Jones*, Stephanie Albarede, Dagmar Kesseler, Finlay MacKenzie, Joy Mammen, Morten Pedersen, Anne Stavelin, Marc Thelen, Annette Thomas, Patrick J. Twomey, Emma Ventura and Mauro Panteghini, for the EFLM Task Finish Group – Analytical Performance Specifications for EQAS (TFG-APSEQA)

## Analytical performance specifications for external quality assessment – definitions and descriptions

Basic elements that need to be considered:

a) nature of the EQA material, including commutability, which may affect the result interpretation;
b) procedure used to assign the target value;
c) data set to which APS are applied;
d) analytical property being assessed (i.e., TE, bias, imprecision);
e) rationale for the selection of the APS;
f) type(s) of model used to set APS

We need these to:

1. compare APS from EQAs
2. inform users about the APS they use
3. plan harmonization (common EQA APS would support uniform analytical performance and true quality improvement)

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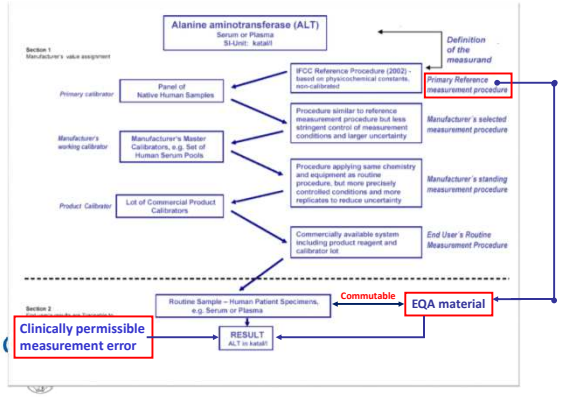


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JCTLM Accurate results for patient care | IFCC | EFLM

Laboratory profession

PLAN DO CHECK ACT

IVD manufacturers

MedTech Europe from diagnosis to cure

All stakeholders

Clinical laboratories

EQALM

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Infusino I, Braga F, Mozzi R, Valente C, Panteghini M
Clinica Chimica Acta 412 (2011) 791–792

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/clinchim

ELSEVIER

Letter to the Editor

**Is the accuracy of serum albumin measurements suitable for clinical application of the test?**

**Probably not**

**Table 1**

Relative standard uncertainties for each contributing factor in determination of serum albumin with Roche Tina-quant immunoturbidimetric assay on Cobas c 501 platform. Data obtained by measurements of ERM-DA 470k/IFCC Human Serum Proteins reference material (certified value ± expanded uncertainty, 37.2 g/L ± 1.2 g/L).

| Factor | Result |
|---|---|
| Imprecision ($u_{Rw}$) | 1.88% |
| Bias ($u_{bias}$) | 6.42% |
| Relative combined standard uncertainty $[u_c = (u_{Bias}^2 + u_{Rw}^2)^{0.5}]$ | 6.69% |

From MILAN MODEL 2

Albumin Uncertainty

2.4% minimum
1.6% desirable
0.8% optimum

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Clinica Chimica Acta 414 (2012) 234–240

Contents lists available at SciVerse ScienceDirect

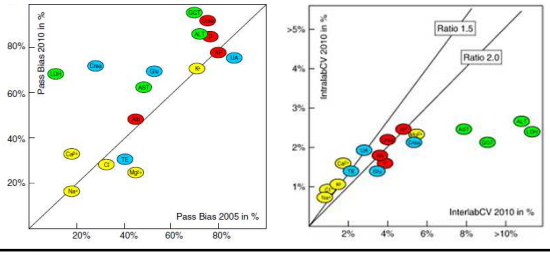
Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/clinchim

ELSEVIER

Systematic monitoring of standardization and harmonization status with commutable EQA-samples—Five year experience from the Netherlands

Christa Cobbaert [a,*], Cas Weykamp [b], Paul Franck [c], Robert de Jonge [d], Aldy Kuypers [e], Herman Steigstra [f], Jacqueline Klein Gunnewiek [g], Douwe van Loon [h], Rob Jansen [i]

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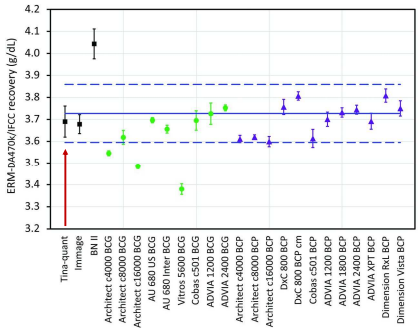
## Current State of Harmonization of Serum Albumin Measurements




Bachmann LR et al. Clin Chem 2017;63:770

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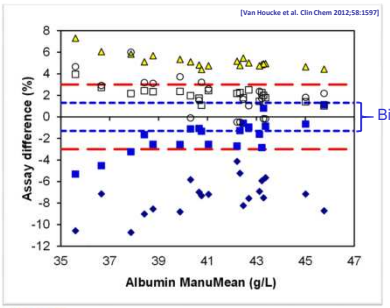
## Serum Albumin: Norwegian Survey 2011




Biological limits for bias

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**The results postulate an urgent need for improving traceability implementation of albumin assays by IVD manufacturers**

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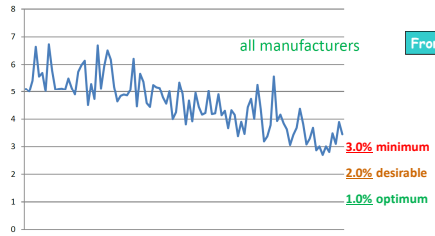
## Glucose
## EQAS results 2002 - 2015

INSTAND




3.0% minimum
2.0% desirable
1.0% optimum

target values set by RMP

Glucose Bias

From MILAN MODEL 2

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Spannagl M – Presented @ JCTLM Members' & Stakeholders' Meeting, Nov 2015

## Evaluation of Cystatin C Measurement after Assay Standardization

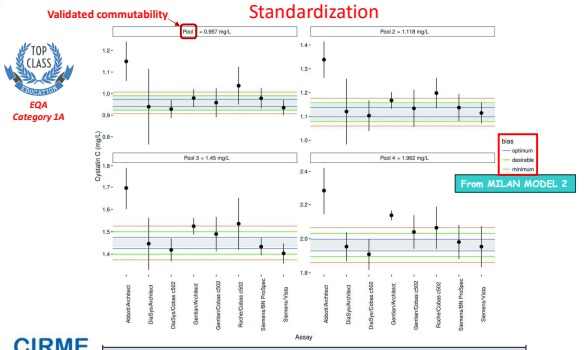
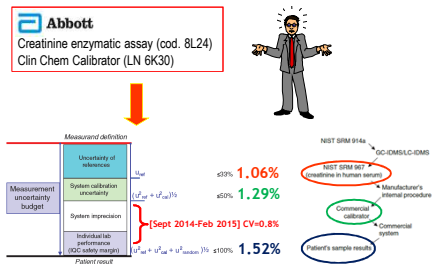



Fig. 1. Biases between the commercial assays and the IDMS target value for CysC.
The figure shows the reference material values and the areas of their uncertainty (gray zone), the mean (SD) of the results from the evaluated systems, and lines depicting the bias specifications (red, green, and blue lines correspond to the optimal, desirable, and minimum quality levels, respectively).

Bargnoux AS et al. Clin Chem 2017;63:833

## Metrological traceability chain and measurement uncertainty of Abbott Architect enzymatic creatinine assay




4.5% minimum
3.0% desirable
1.5% optimum

## Expected consequences

1. Experts defines reference measurement systems
2. Industry implements traceability to them
3. Users (and industry) abandon non-specific methods
4. EQAs provide commutable materials and trueness-based grading
5. Professionals establish clinically allowable errors
6. Individual laboratories monitor their performance by participating to EQA and applying allowable limits

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Abbott Diagnostics in a document released on August 2014 informed customers that the internal release specification for CAL was ±5% from the target value of SRM 967a L1, which is more than two times higher than the SRM expanded uncertainty.

| | Insert Range | Lot 30410Y600 (Mean) | Lot 40043Y600 (Mean) | Lot 40150Y600 (Mean) | Lot 40252Y600 (Mean) |
|---|---|---|---|---|---|
| NIST SRM 967A | Target: 0.85* | 0.82 | 0.88 | 0.88 | 0.83 |

*Manufacturer's release specification is +/- 5% from the target.

+3.53%

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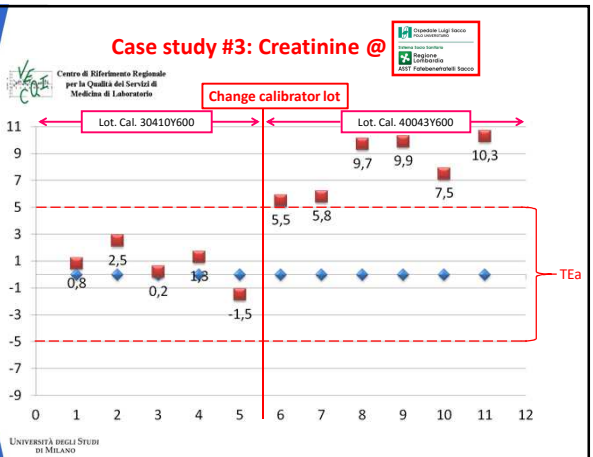
## Case study #3: Creatinine @




| | SRM 967a level 1 | SRM 967a level 2 |
|---|---|---|
| *Multigent Clin Chem Calibrator lot no. 40043Y600* | | |
| Imprecision ($u_{Rw}$) | 0.47% | 0.40% |
| Bias ($u_{bias}$) | 3.57% | 7.05% |
| Relative combined standard uncertainty [$u_c = (u_{bias}^2 + u_{Rw}^2)^{0.5}$] | 3.60% | 7.06% |
| Expanded uncertainty ($U = k \times u_c$) | 7.20% | 14.12% |

Our study shows that this validation criterion for traceability of different CAL lots adopted by the manufacturer is however too large to comply with the U goal for creatinine measurements in biological samples with an acceptable confidence. Moreover, it is also unclear why SRM 967a L1 is used for the CAL value-assignment instead of L2, whose certified value is closer to the CAL nominal value, thus increasing the risk of misalignment of the analytical system to the higher-order metrological references and to result in an unacceptable systematic error in serum creatinine measurements.

Creatinine uncertainty

4.5% minimum
3.0% desirable
1.5% optimum

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Letter to the Editor

The calibrator value assignment protocol of the Abbott enzymatic creatinine assay is inadequate for ensuring suitable quality of serum measurements

Pasqualetti S et al. CCA 2015;450:125

## Post-market surveillance of IVD medical devices: further issues

- Possibility to select different types of traceability chains by IVD manufacturers
- Uncertainty (including imprecision) of the measuring systems for certain analytes may be too large
- Commercial assay may not be selective for the measurand

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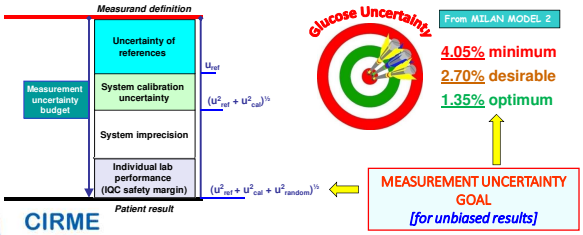
## ALLOWABLE UNCERTAINTY BUDGET FOR PLASMA GLUCOSE

Three main components of uncertainty:

1. *Uncertainty of references* - reference materials, reference procedures;
2. *Uncertainty of commercial system calibrators* - manufacturer's calibrator values [transfer process];
3. *Uncertainty of random sources* – system imprecision, individual lab performance.

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Braga F et al. Clin Chem Lab Med 2015;53:905-12

## Post-market surveillance of IVD medical devices: further issues

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- Commercial assay may not be selective for the measurand

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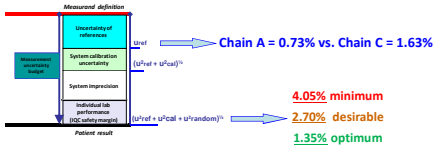
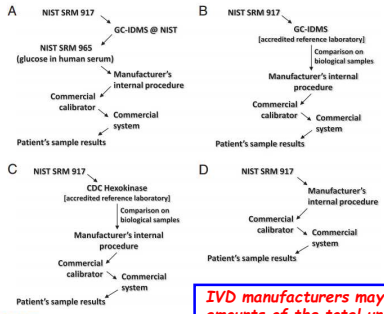
Braga F, Panteghini M. Clin Chim Acta 2014;432:55-61

| Company | Platform | Principle of commercial method | Calibrator | Declared standard uncertainty[a] | Higher-order reference employed | | Type of traceability chain used[b] | Combined standard uncertainty associated with the used chain[c] |
|---|---|---|---|---|---|---|---|---|
| | | | | | Method | Material | | |
| Abbott | Architect | ND | Multiconstituent calibrator | 2.70% | IDMS | NIST SRM 965 | A | 1.22–1.45%[d] |
| Beckman | AU | Hexokinase | System calibrator | ND | ND | NIST SRM 965 | A | 1.22–1.45%[d] |
| | Synchron | Hexokinase | Synchron multicalibrator | ND | ND | NIST SRM 917a | D | 1.60–3.00%[e] |
| Roche | Cobas c | Hexokinase | C.f.a.s. | 0.84% | IDMS | ND | B | 1.70% |
| | Integra | Hexokinase | C.f.a.s. | 0.62% | IDMS | ND | B | 1.70% |
| | Modular | Hexokinase | C.f.a.s. | 0.84% | IDMS | ND | B | 1.70% |
| | | GOD | C.f.a.s. | 0.84% | IDMS | ND | B | 1.70% |
| Siemens | Advia | Hexokinase | Chemistry calibrator | 1.30% | Hexokinase | NIST SRM 917a | C | 1.88–3.26%[e] |
| | | GOD | Chemistry calibrator | 0.80% | Hexokinase | NIST SRM 917a | C | 1.88–3.26%[e] |




The quality of glucose measurement may be dependent on the type of traceability chain selected for trueness transferring, sometimes making difficult (e.g., chain C) to achieve the acceptable limits for measurement uncertainty on clinical samples

## TRACEABILITY CHAINS AVAILABLE FOR IVD MANUFACTURERS FOR PLASMA GLUCOSE




*IVD manufacturers may spend different amounts of the total uncertainty budget in implementing traceability of their measuring systems*

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Braga F & Panteghini M. Clin Chim Acta 2014;432:55-61

## Post-market surveillance of IVD medical devices: further issues

- Possibility to select different types of traceability chains by IVD manufacturers
- Uncertainty (including imprecision) of the measuring systems for certain analytes may be too large
- Commercial assay may not be selective for the measurand

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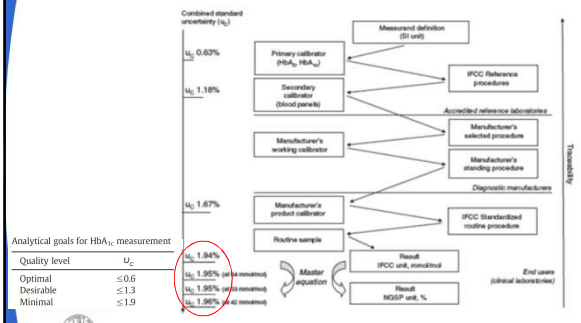
## HbA1c reference system and associated combined standard uncertainty

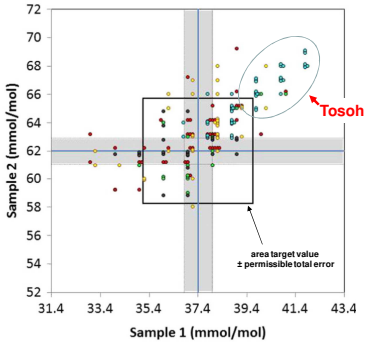



Analytical goals for $HbA_{1c}$ measurement

| Quality level | $U_C$ |
|---|---|
| Optimal | ≤0.6 |
| Desirable | ≤1.3 |
| Minimal | ≤1.9 |

[Braga F & Panteghini M, Clin Chem Lab Med 2013;51:1719]

EQA
Category 2A




Mosca A et al., Clin Chim Acta 2015;451:305

Federica Braga* and Mauro Panteghini

**Standardization and analytical goals for glycated hemoglobin measurement**

Clin Chem Lab Med 2013;51:1719–26

### Further advances are needed to:

1. reduce uncertainty associated with higher-order metrological references (reference materials and procedures)
2. increase the precision of commercial HbA1c assays

## Post-market surveillance of IVD medical devices: further issues

- Possibility to select different types of traceability chains by IVD manufacturers
- Uncertainty (including imprecision) of the measuring systems for certain analytes may be too large
- Commercial assay may not be selective for the measurand

DE GRUYTER — Clin Chem Lab Med 2016; 54(3): e71–e73

Letter to the Editor

Dominika Szőke*, Assunta Carnevale, Sara Pasqualetti, Federica Braga, Renata Paleari and Mauro Panteghini

**More on the accuracy of the Architect enzymatic assay for hemoglobin $A_{1c}$ and its traceability to the IFCC reference system**






Analytical goals for $HbA_{1c}$ measurement

| Quality level | $U_C$ |
|---|---|
| Optimal | ≤0.6 |
| Desirable | ≤1.3 |
| Minimal | ≤1.9 |

## Selectivity definition

"Property of a measuring system used with a measurement procedure, whereby it provides measured quantity value for one or more such that the values of each measurand are independent of other measurands or other quantities in the phenomenon, body, or substance being investigated."

Enzymatic assays for creatinine: time for action[1,2]

International Federation of Clinical Chemistry and Laboratory Medicine (IFCC)*
IFCC Scientific Division
Mauro Panteghini* on behalf of the IFCC Scientific Division

## The analytical non selectivity issue: the case of serum creatinine

- The alkaline picrate method is unable to measure solely creatinine
- Endogenous and exogenous substances may significantly interfere: particularly, proteins in serum can lead to significant overstimation with various alkaline picrate methods

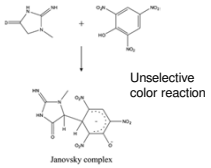



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Table 3: Metrological traceability and uncertainty information derived from calibrator package inserts of commercial systems measuring serum creatinine marketed by four in vitro diagnostics companies.

| Company | Platform | Principle of commercial method | Calibrator | Declared standard uncertainty[a] | Higher order reference employed | | Type of traceability chain used[b] | Combined standard uncertainty associated with the used chain[c] |
|---|---|---|---|---|---|---|---|---|
| | | | | | Method | Material | | |
| Abbott | Architect | Enzymatic | Multigent clin chem calibrator | 1.48% | IDMS | NIST SRM 967 | A | 2.12%–2.79%[d] |
| | | ND | Multiconstituent calibrator | 2.7% | IDMS | NIST SRM 967 | A | 2.12%–2.79%[d] |
| Beckman | AU | Enzymatic | System calibrator | ND | ND | NIST SRM 967 | A | 2.12%–2.79%[d] |
| | | Alkaline picrate | System calibrator | ND | IDMS | NIST SRM 967 | A | 2.12%–2.79%[d] |
| | | Uncompensated alkaline picrate | System calibrator | ND | ND | NIST SRM 909b L2 | B | 1.51% |
| | Synchron | ND | LX aqua calibrator | ND | IDMS | NIST SRM 914a | D | 1.5%[e] |
| Roche | Cobas c | Enzymatic | C.f.a.s. | 0.91% | IDMS | ND | D | 1.5%[e] |
| | | Alkaline picrate compensated | C.f.a.s. | 1.62% | IDMS | ND | D | 1.5%[e] |
| | | Alkaline picrate rate-blanked and compensated | C.f.a.s. | 1.42% | IDMS | ND | D | 1.5%[e] |
| | Integra/Cobas c111 | Enzymatic | C.f.a.s | 1.06% | IDMS | ND | D | 1.5%[e] |
| | Integra400/Cobas c111 | Alkaline picrate compensated | C.f.a.s | 0.30% | IDMS | ND | D | 1.5%[e] |
| | Integra800 | Alkaline picrate compensated | C.f.a.s | 0.72% | IDMS | ND | D | 1.5%[e] |
| | Modular | Enzymatic | C.f.a.s | 0.91% | IDMS | ND | D | 1.5%[e] |
| | | Alkaline picrate compensated | C.f.a.s | 1.38% | IDMS | ND | D | 1.5%[e] |
| | | Alkaline picrate rate-blanked and compensated | C.f.a.s | 0.79% | IDMS | ND | D | 1.5%[e] |
| Siemens | Dimension Vista | Enzymatic | ECREA calibrator A | 5.08%[f] | ND | NIST SRM 914a | C | NA |
| | | | ECREA calibrator B | 3.14%[f] | ND | NIST SRM 914a | C | NA |
| | | Alkaline picrate | Chemistry calibrator | 1.6% | GC-IDMS | NIST SRM 914a | D | 1.5%[e] |
| | Advia | Enzymatic | Chemistry calibrator | 0.45% | IDMS | NIST SRM 914a<br>NIST SRM 967 | A | 2.12%–2.79%[d] |
| | | Alkaline picrate rate-blanked and compensated | Chemistry calibrator | 1.6% | IDMS | NIST SRM 967 | A | 2.12%–2.79%[d] |

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[Braga F, Infusino I, Panteghini M. Clin Chem Lab Med 2015;53:905]

## Traceability implementation does not correct for analytical non-specificity problems

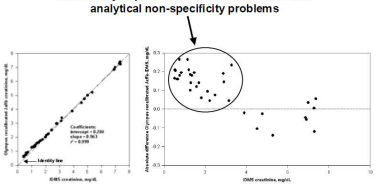

Figure 2. Regression analysis and bias plot comparing serum creatinine results obtained with Olympus alkaline picrate (Jaffé) assay (AU2700 platform) and gas chromatography-isotope dilution mass spectrometry (IDMS) reference method. The Olympus Jaffé assay is reported by the manufacturer to have been standardized ("recalibrated") against the National Institute of Standards and Technology SRM 909b, a secondary reference material with creatinine values assigned by IDMS. Note the positive intercept [0.204 mg/dL (18 μmol/L)] of the regression analysis indicating difference in analytical specificity between the two methods.

M. Panteghini, RIMeL / IJLaM 2007;3 (Suppl.)

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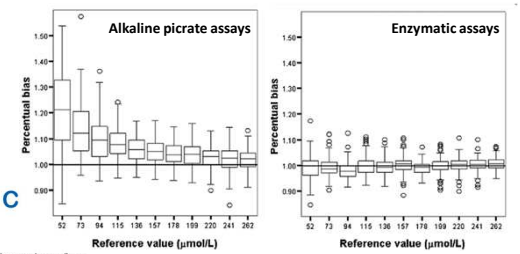
Drion et al. BMC Nephrology 2012, 13:133
http://www.biomedcentral.com/1471-2369/13/133

BMC Nephrology

RESEARCH ARTICLE Open Access

## Clinical evaluation of analytical variations in serum creatinine measurements: why laboratories should abandon Jaffe techniques

Ielke Drion[1*], Christa Cobbaert[2], Klaas H Groenier[1,3], Cas Weykamp[4], Henk JG Bilo[1,5,6], Jack FM Wetzels[7] and Nanne Kleefstra[1,5,8]

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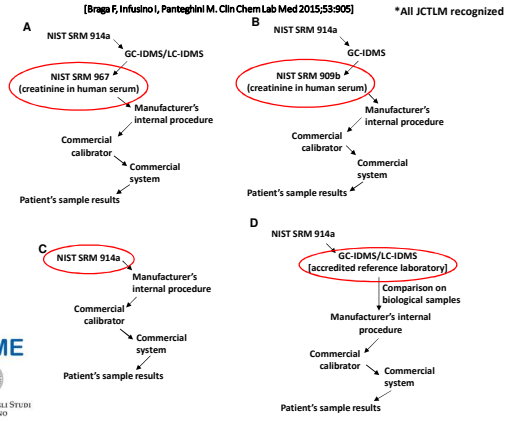
## Types of metrological chains that can be used to implement the traceability of blood creatinine results*

[Braga F, Infusino I, Panteghini M. Clin Chem Lab Med 2015;53:905] *All JCTLM recognized

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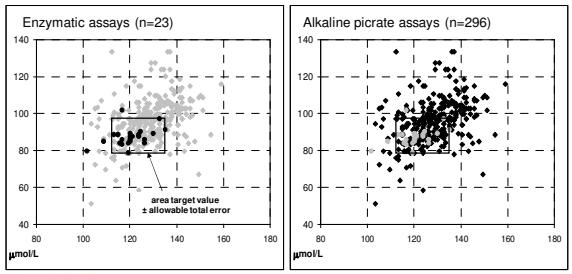
## EQA materials with physiologic (88.4 μmol/L) and borderline (123.8 μmol/L) creatinine concentrations vs. the desirable goal for total error

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[Carobene A et al., Clin Chim Acta 2014;427:100]

## EQA for quantities where no high-order reference is available

**System-dependent target values should be used to evaluate the performance of participating laboratories**

**HOWEVER**

**in this case the values assigned to the EQA materials should be determined by reference institutions (possibly including the manufacturer releasing that specific measuring system), working under strictly controlled conditions in order to maintain measurement uncertainty as low as possible, and not as a peer group mean.**

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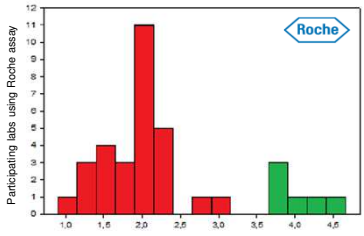
Panteghini M, Clin Chem Lab Med 2010;48:7

Centro di Riferimento Regionale per la Qualità dei Servizi di Medicina di Laboratorio

EQA exercise no. 4/2016




Roche Folate III assay code 07559992190 (traceable to NIBSC 03/178 IS)

Roche Folate III assay code 04476433190 (home-made calibration)

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At a folate concentration around the lower reference limit of the old Roche assay, a positive bias of ~50% vs. the recalibrated Roche assay can be observed

## Case study #4: Folate @

Ospedale Luigi Sacco – Polo Universitario; Regione Lombardia – ASST Fatebenefratelli Sacco

- To improve assay harmonization, in 2016 Roche folate method has undergone recalibration to the WHO NIBSC 03/178 International Standard
- After recalibration, a significant change in the average folate measured values was internally recorded

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## Do not forget the post-analytical EQA

Taking into account the ~50% difference experimentally found at the lower reference limit (LRL) level, the shift from 4.6 µg/L (Roche recommended LRL for old calibration) to 3.9 µg/L (Roche recommended LRL for recalibrated assay) appeared to be inconsistent.

Consequently, a misleading overestimate of the prevalence of folate deficiency is expected if the recalibrated Roche assay will be used together the manufacturer's newly recommended LRL.

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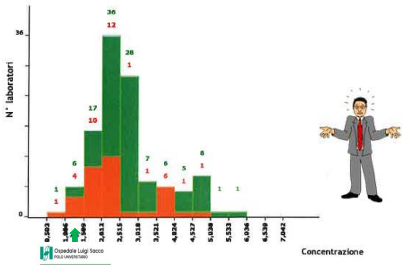
Ferraro S, Panzeri A, Panteghini M. Clin Chem Lab Med 2017;55:1262–75

## Case study #4: Folate @

Ospedale Luigi Sacco – Polo Universitario; Regione Lombardia – ASST Fatebenefratelli Sacco

Centro di Riferimento Regionale per la Qualità dei Servizi di Medicina di Laboratorio

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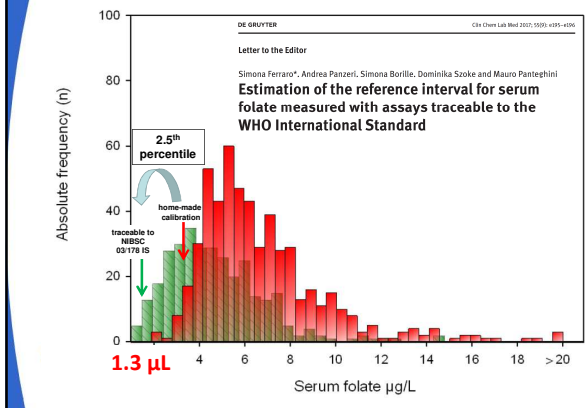


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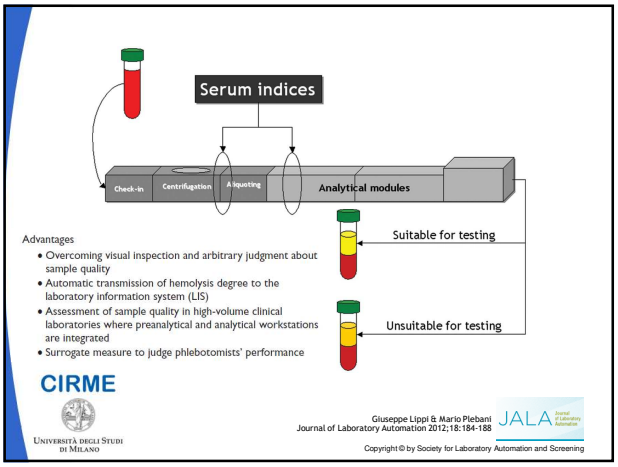


**Because of potential impact on patient outcome, determination of interference indices should be considered like any other laboratory test**

**Need to guarantee the quality of the determination through the implementation of a Quality Control**

**IMPLEMENTATION OF AN INTERNAL QUALITY CONTROL PROGRAM FOR THE PHOTOMETRIC ICTERIC INDEX DETERMINATION**

E. Aloisio[1,2], A. Carnevale[1], S. Pasqualetti[1], S. Birindelli[1], A. Dolci[1], M. Panteghini[1,2]

[1]*Clinical Pathology Unit, 'Luigi Sacco' University Hospital, Milan*

**EVALUATION OF LONG TERM IMPRECISION OF PHOTOMETRIC HEMOLYTIC INDEX DETERMINATION ON ABBOTT ARCHITECT c16000**

E. Aloisio[1,2], A. Carnevale[1], S. Pasqualetti[1], S. Birindelli[1], A. Dolci[1], M. Panteghini[1,2]

[1]*Clinical Pathology Unit, 'Luigi Sacco' University Hospital, Milan*

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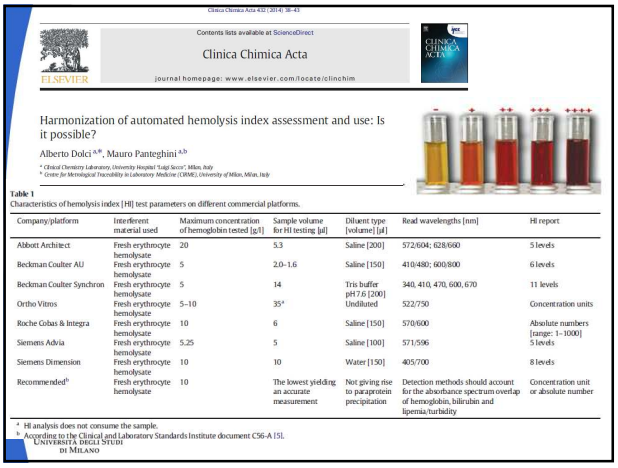

Clinica Chimica Acta 432 (2014) 38–43

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/clinchim

Harmonization of automated hemolysis index assessment and use: Is it possible?

Alberto Dolci [a,*], Mauro Panteghini [a,b]

[a] Clinical Chemistry Laboratory, University Hospital 'Luigi Sacco', Milan, Italy
[b] Centre for Metrological Traceability in Laboratory Medicine (CIRME), University of Milan, Milan, Italy

**Table 1**
Characteristics of hemolysis index [HI] test parameters on different commercial platforms.

| Company/platform | Interferent material used | Maximum concentration of hemoglobin tested [g/l] | Sample volume for HI testing [µl] | Diluent type [volume] [µl] | Read wavelengths [nm] | HI report |
|---|---|---|---|---|---|---|
| Abbott Architect | Fresh erythrocyte hemolysate | 20 | 5.3 | Saline [200] | 572/604; 628/660 | 5 levels |
| Beckman Coulter AU | Fresh erythrocyte hemolysate | 5 | 2.0–1.6 | Saline [150] | 410/480; 600/800 | 6 levels |
| Beckman Coulter Synchron | Fresh erythrocyte hemolysate | 5 | 14 | Tris buffer pH 7.6 [200] | 340, 410, 470, 600, 670 | 11 levels |
| Ortho Vitros | Fresh erythrocyte hemolysate | 5–10 | 35[a] | Undiluted | 522/750 | Concentration units |
| Roche Cobas & Integra | Fresh erythrocyte hemolysate | 10 | 6 | Saline [150] | 570/600 | Absolute numbers [range: 1–1000] |
| Siemens Advia | Fresh erythrocyte hemolysate | 5.25 | 5 | Saline [100] | 571/596 | 5 levels |
| Siemens Dimension | Fresh erythrocyte hemolysate | 10 | 10 | Water [150] | 405/700 | 8 levels |
| Recommended[b] | Fresh erythrocyte hemolysate | 10 | The lowest yielding an accurate measurement | Not giving rise to paraprotein precipitation | Detection methods should account for the absorbance spectrum overlap of hemoglobin, bilirubin and lipemia/turbidity | Concentration unit or absolute number |

[a] HI analysis does not consume the sample.
[b] According to the Clinical and Laboratory Standards Institute document C56-A [5].

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**QC programs for serum interference indices are not widespread**

**Limited offer on the market of manufactured control materials**

**It is possible to organize a complete and effective IQC program for assuring accuracy of these measurements**

**What about EQA?**

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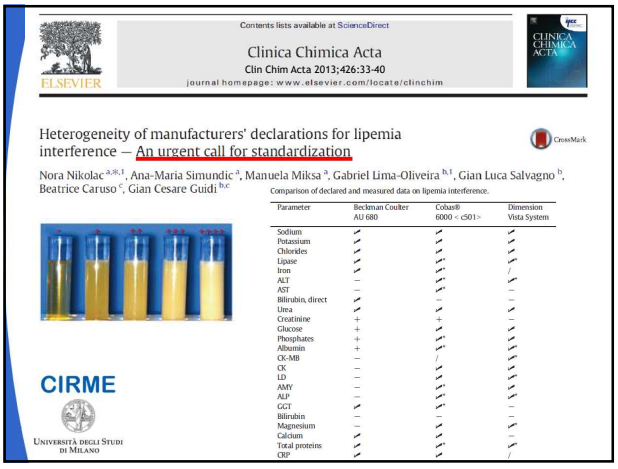

Contents lists available at ScienceDirect

Clinica Chimica Acta

Clin Chim Acta 2013;426:33-40

journal homepage: www.elsevier.com/locate/clinchim

Heterogeneity of manufacturers' declarations for lipemia interference — An urgent call for standardization

Nora Nikolac [a,*,1], Ana-Maria Simundic [a], Manuela Miksa [a], Gabriel Lima-Oliveira [b,1], Gian Luca Salvagno [b], Beatrice Caruso [c], Gian Cesare Guidi [b,c]

Comparison of declared and measured data on lipemia interference.

| Parameter | Beckman Coulter AU 680 | Cobas® 6000 < c501> | Dimension Vista System |
|---|---|---|---|
| Sodium | ✓ | ✓ | ✓ |
| Potassium | ✓ | ✓ | ✓ |
| Chlorides | ✓ | ✓ | ✓ |
| Lipase | ✓ | ✓ | ✓ |
| Iron | ✓ | ✓ | / |
| ALT | – | ✓ | ✓ |
| AST | – | ✓ | – |
| Bilirubin, direct | ✓ | – | – |
| Urea | ✓ | ✓ | ✓ |
| Creatinine | + | ✓ | – |
| Glucose | + | ✓ | ✓ |
| Phosphates | + | ✓ | ✓ |
| Albumin | + | ✓ | ✓ |
| CK-MB | – | / | ✓ |
| CK | – | ✓ | ✓ |
| LD | – | ✓ | ✓ |
| AMY | – | ✓ | ✓ |
| ALP | – | ✓ | ✓ |
| GGT | ✓ | ✓ | – |
| Bilirubin | – | – | – |
| Magnesium | – | ✓ | ✓ |
| Calcium | ✓ | ✓ | – |
| Total proteins | ✓ | ✓ | ✓ |
| CRP | ✓ | ✓ | / |

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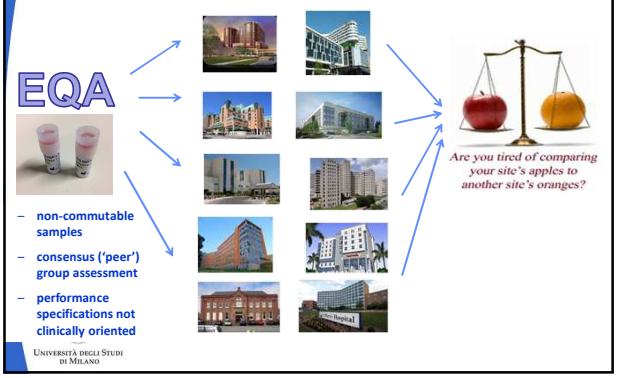
## Conventional External Quality Assessment




- non-commutable samples
- consensus ('peer') group assessment
- performance specifications not clinically oriented

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## Constraints limiting the introduction of EQA that meet metrological criteria

Miller WG et al. Clin Chem 2011;57:1670

- Technical aspects: lack of certified control materials or difficulties to prepare commutable samples
- Practical considerations: complicated logistics of distribution of frozen samples
- Educational limitations: lack of awareness of which quality factors make an EQA important
- Economic concerns: higher costs

Official Journal of the European Union L 117

## New EU regulatory framework

- **Supervision of Notified Bodies**
- **Post-market safety and surveillance activities, with enhanced involvement of healthcare professionals and patients**
- **Transparency**
  - **Summary of safety and performance data**
  - **Traceability of devices**
- **Access to external expertise (scientific experts, reference laboratories)**

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**What COPERNICUS did was take the existing 'a priori' concept of the world and pose an alternative 'a priori' concept**

**The earth is flat and fixed in space** → **The earth is spherical and moves around the sun**

**Equivalency-based grading** → **Accuracy-based grading**

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**What TRACEABILITY does is take the existing 'a priori' concept of the Quality Control and pose an alternative 'a priori' concept**

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Scand J Clin Lab Invest 1998; 58: 265–268

EDITORIAL

Is it possible to create a perfect external control system?

P. H. PETERSEN
Department of Clinical Biochemistry, Odense University Hospital, Odense, Denmark


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**Table 1:** Unique benefits of External Quality Assessment Schemes meeting metrological criteria.

- Giving objective information about quality of individual laboratory performance
- Creating evidence about intrinsic standardisation status/ equivalence of the examined assays
- Serving as management tool for the clinical laboratory and IVD manufacturers, forcing them to investigate and eventually fix the identified problem
- Helping those manufacturers that produce superior products and systems to demonstrate the superiority of those products
- Identifying analytes that need improved harmonisation and stimulating and sustaining standardisation initiatives that are needed to support clinical practice guidelines
- Abandonment by users (and consequently by industry) of nonspecific methods and/or of assays with demonstrated insufficient quality

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[Ferraro S, Braga F, Panteghini M. Clin Chem Lab Med 2016;54:523]

**"It was the acceptance of the Copernican revolution that distinguishes modern man from his medieval predecessors."**

*Robert M Pirsig – "Zen and the art of motorcycle maintenance", 1974*

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