EFLM SYMPOSIUM
Education in Clinical Chemistry and Laboratory Medicine
Prague April 24 – 26, 2015

EFLM — EUROPEAN FEDERATION OF CLINICAL CHEMISTRY AND LABORATORY MEDICINE

CZECH SOCIETY OF CLINICAL BIOCHEMISTRY

VERIFICATION OF IVD METROLOGICAL TRACEABILITY: ROLE AND RESPONSIBILITIES OF LABORATORY MEDICINE SPECIALISTS IN THE EU CONTEXT

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Director: Prof. Mauro Panteghini

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

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Presentation Outline

Background

Role of IVD manufacturers
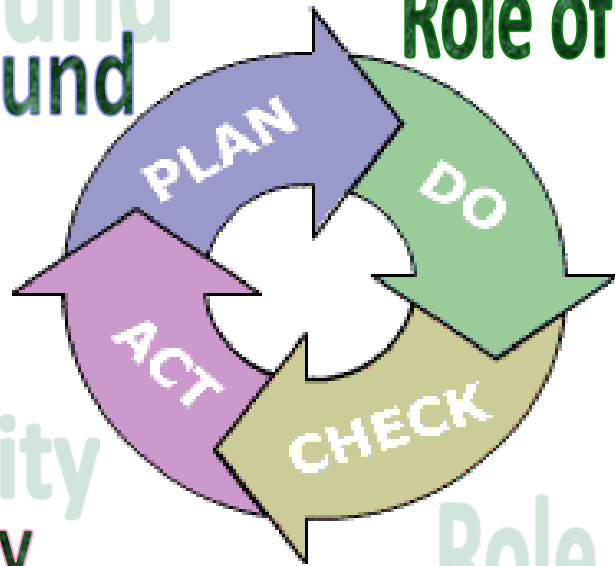
The "traceability manifesto"

Role of the Profession

PLAN

DO

CHECK

ACT

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Laboratory measurement paradigm:

•Assays that claim to measure the same analyte should give equivalent measurement results (for long term and within clinically meaningful limits)

Measurement results should be independent of:

− Time

− Location/laboratory

− Assay system

Laboratory results should be equivalent no matter where they are performed

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Potential impacts of the issue

- **CLINICAL**

- **ECONOMICAL**

- **ETHICAL**

Clinical impact

Interchangeability of results over time and space would significantly contribute to improvements in healthcare by allowing results of clinical studies undertaken in different locations or times to be universally applied

Standardize clinical decision limits (i.e., cutpoints for intervention)

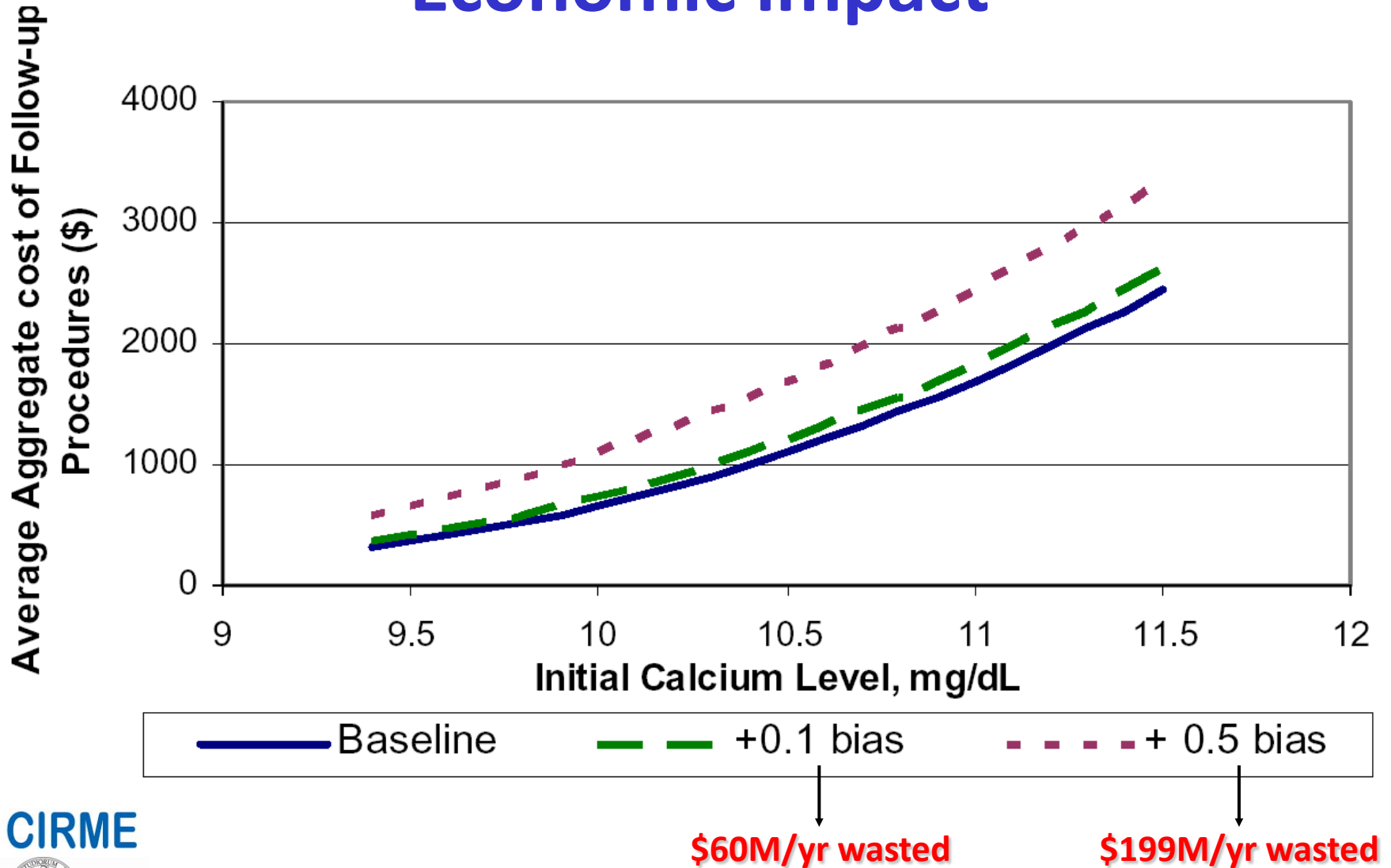**Effective application of evidence-based medicine**

EVALUATING DIAGNOSTIC TESTS

Economic impact

In short: the lack of standardization may become an ethical issue

"Standardization of laboratory tests has an ethical dimension as it aims to affect the way diagnostic tests are used in order to guarantee optimal care for patients in a global world."

Bossuyt X et al., Ann Rheum Dis 2008;67:1061

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→ **To become *equivalent for long term*, results must be traceable to higher-order references.**

Objective of traceability implementation:

to enable the results obtained by the calibrated routine procedure to be expressed in terms of the values obtained at the highest available level of the calibration hierarchy.
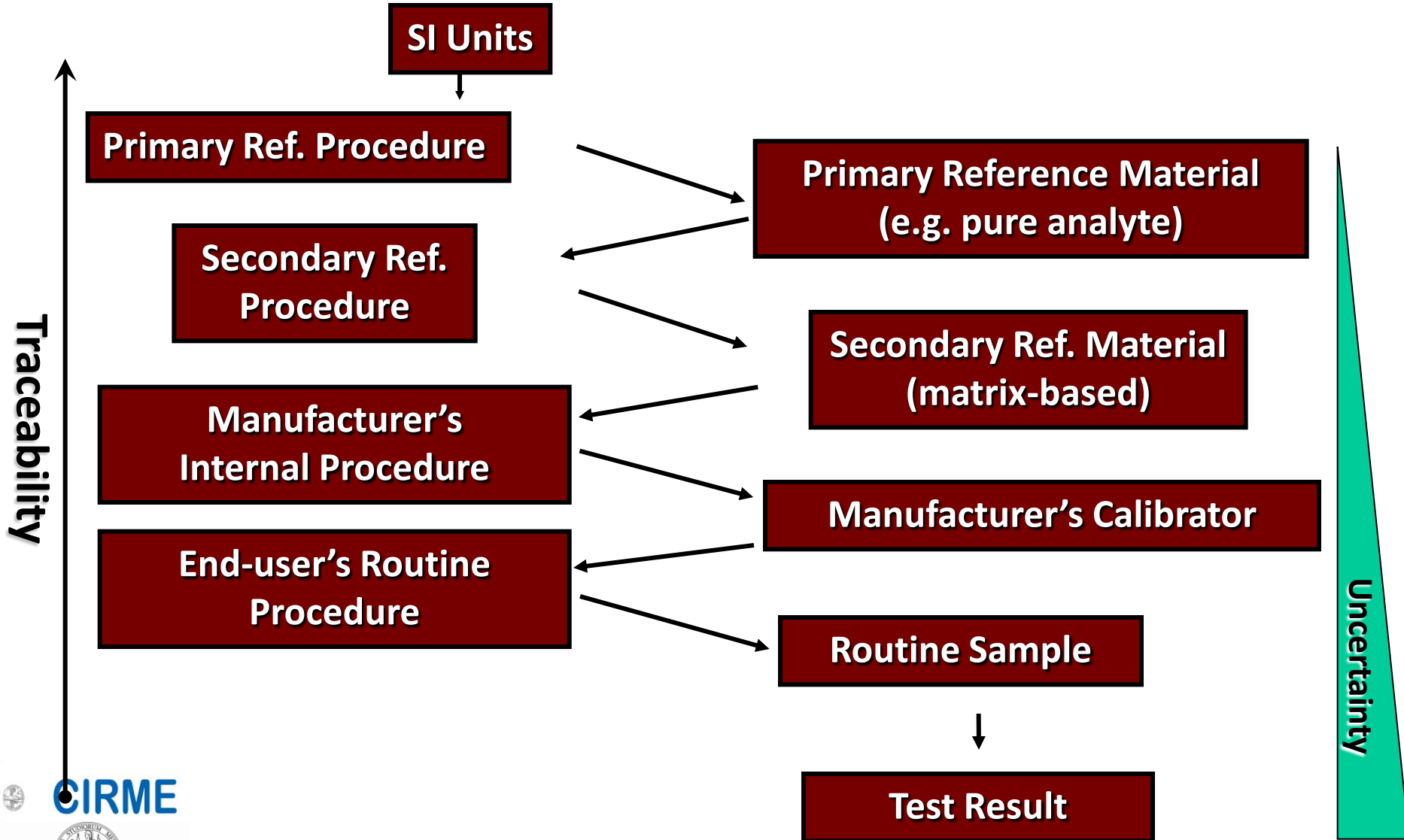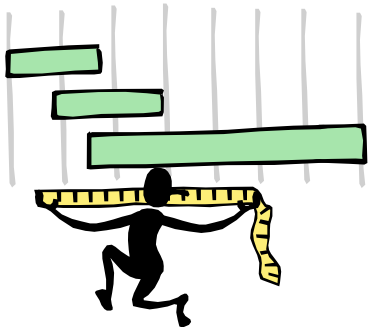
ISO/EN 17511 - Measurement of quantities in samples of biological origin - Metrological traceability of values assigned to calibrators and control materials.

Reference Measurement System

*Adapted from ISO 17511

Basic requirements to establish traceability

- **Establishment of a calibration hierarchy**

- **Establishment of the metrological traceability for the measurement results (understand the measurements)**

- **Elimination of measurement bias**

- **Adequate estimation of measurement uncertainties**

Fulfillment of the Requirements of the EU IVD Directive by Manufacturers
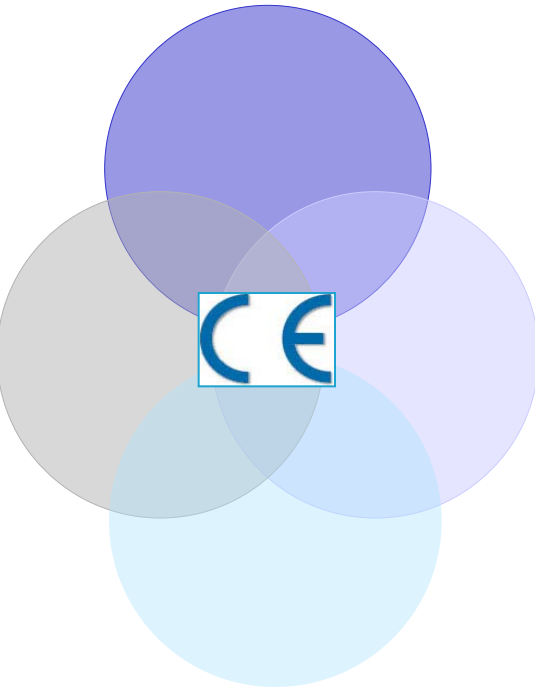
EU 98/79/EC-IVD Directive

❖ **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 (fitness for purpose)**
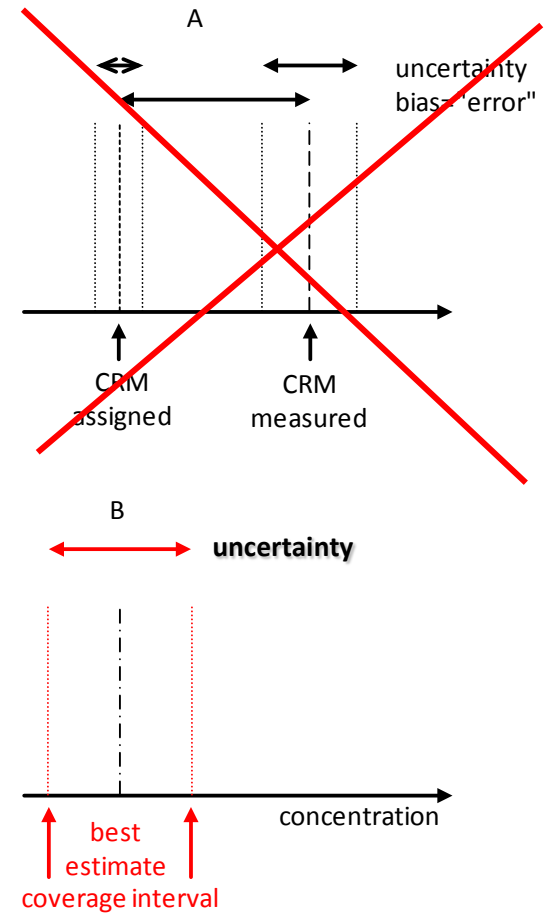
❖ **Stability testing**

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Platform

Reagents

Calibrators

Control material(s)

CE

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

A

uncertainty
bias="error"

CRM
assigned

CRM
measured

B

uncertainty

best
estimate
coverage interval

concentration

*[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 system to
the highest available level**

In theory... IVD manufacturers:

| **Identify higher order material or method** | → | **Establish traceability** | → | **Assign values (and uncertainty) to assay calibrators** | → |

In practice... IVD manufacturers:

➢ **Need to select <u>suitable</u> ref. materials and/or identify <u>who is performing</u> ref. procedures**

➢ **Need to establish the <u>acceptability</u> for the calibrator uncertainty**

Joint Committee for Traceability in Laboratory Medicine (JCTLM)

The World's only quality-assured database of:

a) **Higher Order Reference Materials**
b) **Higher Order Reference Measurement Procedures**
c) **Accredited Laboratory Reference Measurement Services**
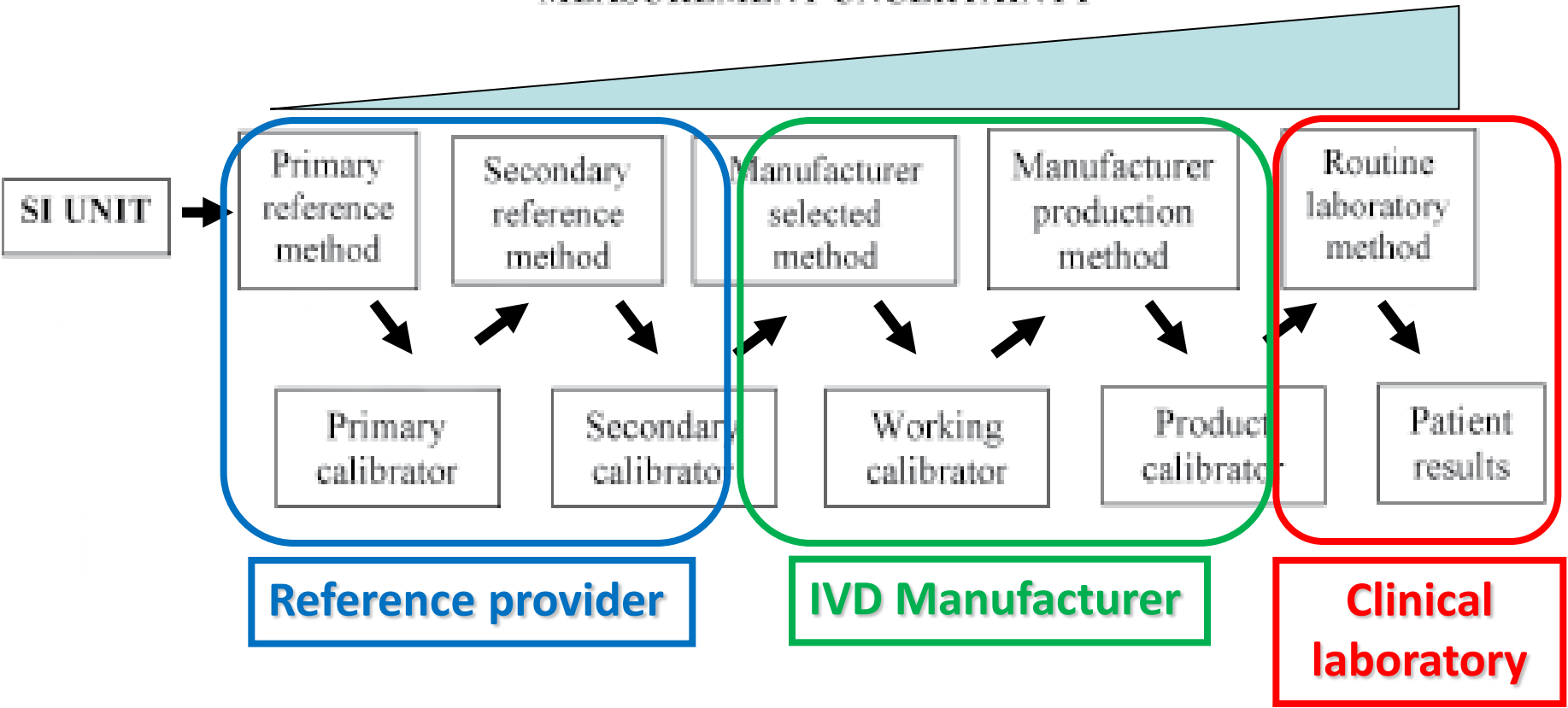
For use by (primarily):
a) IVD industry (to assist them in following the EU Directive on compliance and traceability of commercial systems)
b) Regulators (to verify that results produced by IVDs are traceable to)

Measurement uncertainty budget

MEASUREMENT UNCERTAINTY

SI UNIT → Primary reference method → Secondary reference method → Manufacturer selected method → Manufacturer production method → Routine laboratory method

Primary calibrator — Secondary calibrator — Working calibrator — Product calibrator — Patient results

Reference provider   **IVD Manufacturer**   **Clinical laboratory**

**Uncertainty of measurement that fits for purpose must be defined across the entire traceability chain,
→ starting with the provider of reference materials,
→ extending through the IVD manufacturers and their processes for assignment of calibrator values, and
→ ultimately to the final result reported to clinicians by end users (i.e. clinical laboratories).**

*[Panteghini M, Clin Chem Lab Med 2012;50:1237]*

This approach should be applied to every analyte measured in the clinical laboratory in order to establish if the current status of the uncertainty budget of its measurement associated with the proposed metrological traceability chain is suitable for clinical application of the test.

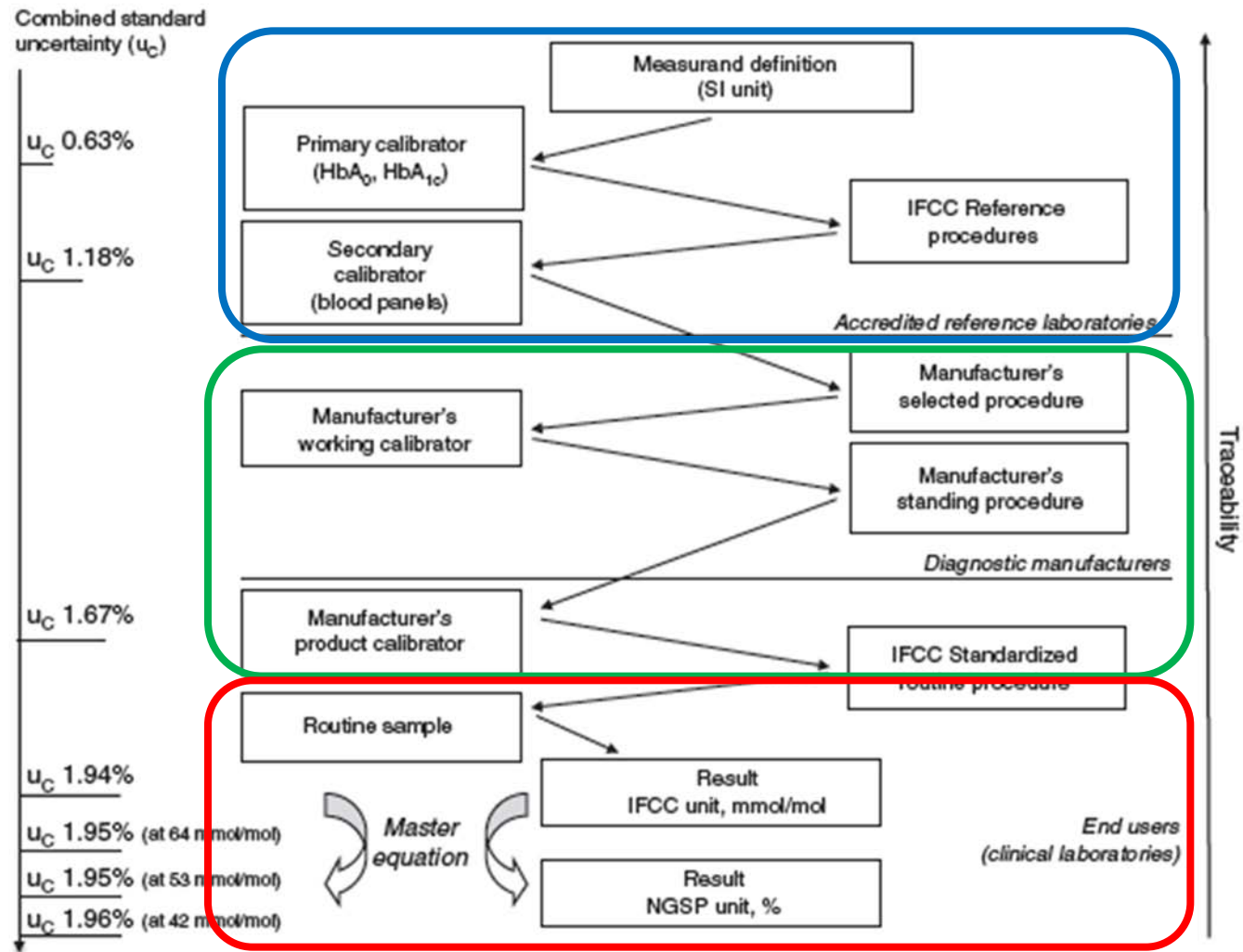*[Panteghini M, Clin Chem Lab Med 2012;50:1237]*
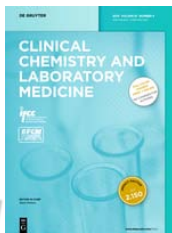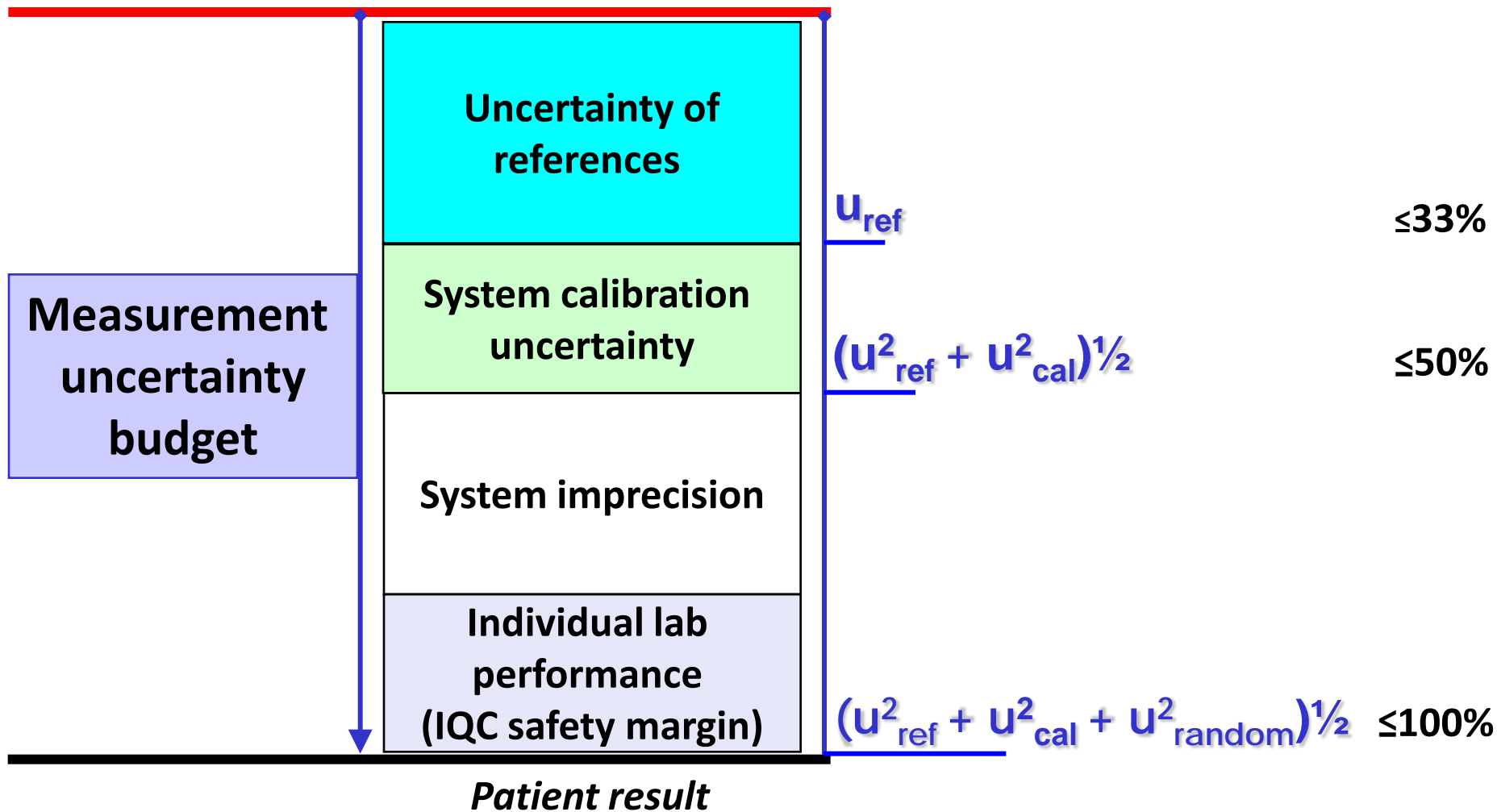
HbA$_{1c}$: Metrological traceability chain

Recommended limits for sources of combined uncertainty budget (expressed as percentage of total budget uncertainty goal) in traceability implementation

Measurand definition

Uncertainty of references	u_{ref} ≤33%
System calibration uncertainty	$(u^2_{ref} + u^2_{cal})^{1/2}$ ≤50%
System imprecision	
Individual lab performance (IQC safety margin)	$(u^2_{ref} + u^2_{cal} + u^2_{random})^{1/2}$ ≤100%

Measurement uncertainty budget

Patient result

Braga F, Infusino I, Panteghini M. Clin Chem Lab Med 2015; in press

Profession (e.g., JCTLM, EFLM):

<div style="border: 2px solid red;">

Define analytical objectives: reference measurement systems (traceability chain) and associated clinically acceptable uncertainty (fitness for purpose)

</div>

↓

Diagnostic manufacturers:

Implement suitable analytical 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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The definition and use of the reference system concept for standardization of measurements must be closely associated with the setting of targets for uncertainty and error of measurement in order to make it clinically acceptable

If these goals are not objectively defined and fulfilled, there is a risk of letting error gain the upper hand, thus obscuring the clinical information supplied by the result and possibly nullifying the theoretical advantages of metrological traceability and even causing negative effects on patients' outcome.

L Thienpont et al., Clin Chem Lab Med 2004;42:842
Braga F & Panteghini M, Clin Chim Acta 2014;432:55

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EFLM Strategic Conference

Defining analytical performance goals 15 years after the Stockholm Conference

Milan, IT – 24-25 Nov 2014

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

Although the essence of the hierarchy established in Stockholm was supported, new perspectives have been forwarded prompting simplification and explanatory additions.

According to the new consensus statement, the recommended approaches for defining analytical performance goals should rely on:

- **the effect of analytical performance on clinical outcomes or**

- **on the biological variation of the measurand.**

The most innovative aspect of the new consensus is that it is recognized that some models are better suited for certain measurands than for others; the attention is therefore primarily directed towards the measurand and its biological and clinical characteristics.

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

↓

Diagnostic manufacturers: **Implement suitable analytical 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**

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

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Role of IVD manufacturers: "do"

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.

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

- Does *not* mean that comparators (e.g., similar assays) are also traceable

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Successful implementation of calibration traceability does not ensure accuracy for an individual patient's sample

➢ **Selection of different types of traceability chains**

➢ **Uncertainty (including imprecision) of the analytical system may be too large**

➢ **Commercial assay may not be specific for the measurand → Interfering substances may influence the result**

The role of the Profession: "check"

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

2. Daily surveillance of IVD system traceability

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

Houston we have a problem.

Currently, the full information about calibration is usually not available
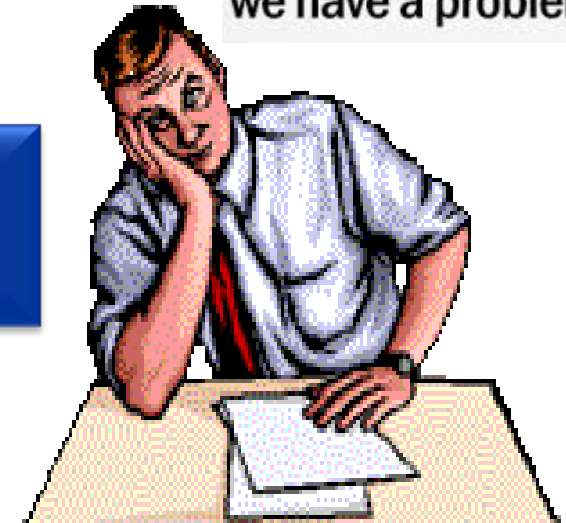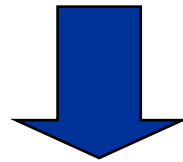
Manufacturers only provide the name of higher order reference material or procedure to which the assay calibration is traceable, without any description of implementation steps and their corresponding uncertainty.

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Some organisations are frequently mentioned (often without explanation): used as a "trusted brand"

• **NIST, IRMM, IFCC, CLSI (protocols)**

It's from NIST: it must be good

In principle, laboratory users should be able to access the following (ideally all this information should be available in the assay or calibrator package inserts):

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.

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

A

NIST SRM 917 →

GC-IDMS @ NIST

(NIST SRM 965 (glucose in human serum)) ←

Manufacturer's internal procedure →

Commercial calibrator →

Commercial system →

Patient's sample results

B

NIST SRM 917 →

(GC-IDMS [accredited reference laboratory])

Comparison on biological samples →

Manufacturer's internal procedure →

Commercial calibrator →

Commercial system →

Patient's sample results

C

NIST SRM 917 →

(CDC Hexokinase [accredited reference laboratory])

Comparison on biological samples →

Manufacturer's internal procedure →

Commercial calibrator →

Commercial system →

Patient's sample results

D

(NIST SRM 917) →

Manufacturer's internal procedure →

Commercial calibrator →

Commercial system →

Patient's sample results

*all JCTLM recognized

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Clinica Chimica Acta

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

INVITED CRITICAL REVIEW

Table 1

Metrological traceability and uncertainty information derived from calibrator package inserts of commercial systems measuring blood glucose marketed by four IVD 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	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		0.84%	IDMS	ND	B	1.70%
Siemens	Advia	Hexokinase	Chemistry calibrator	1.30%	Hexokinase	NIST SRM 917a	C	1.88-3.26%[f]
		GOD		0.80%	Hexokinase	NIST SRM 917a	C	1.88-3.26%[f]

Note: For plasma glucose measurements on patient samples, the acceptable limits for expanded uncertainty derived from its CVI are 2.8% (desiderable) and 4.2% (minimum quality level), respectively
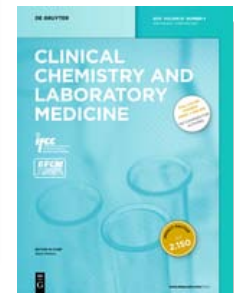
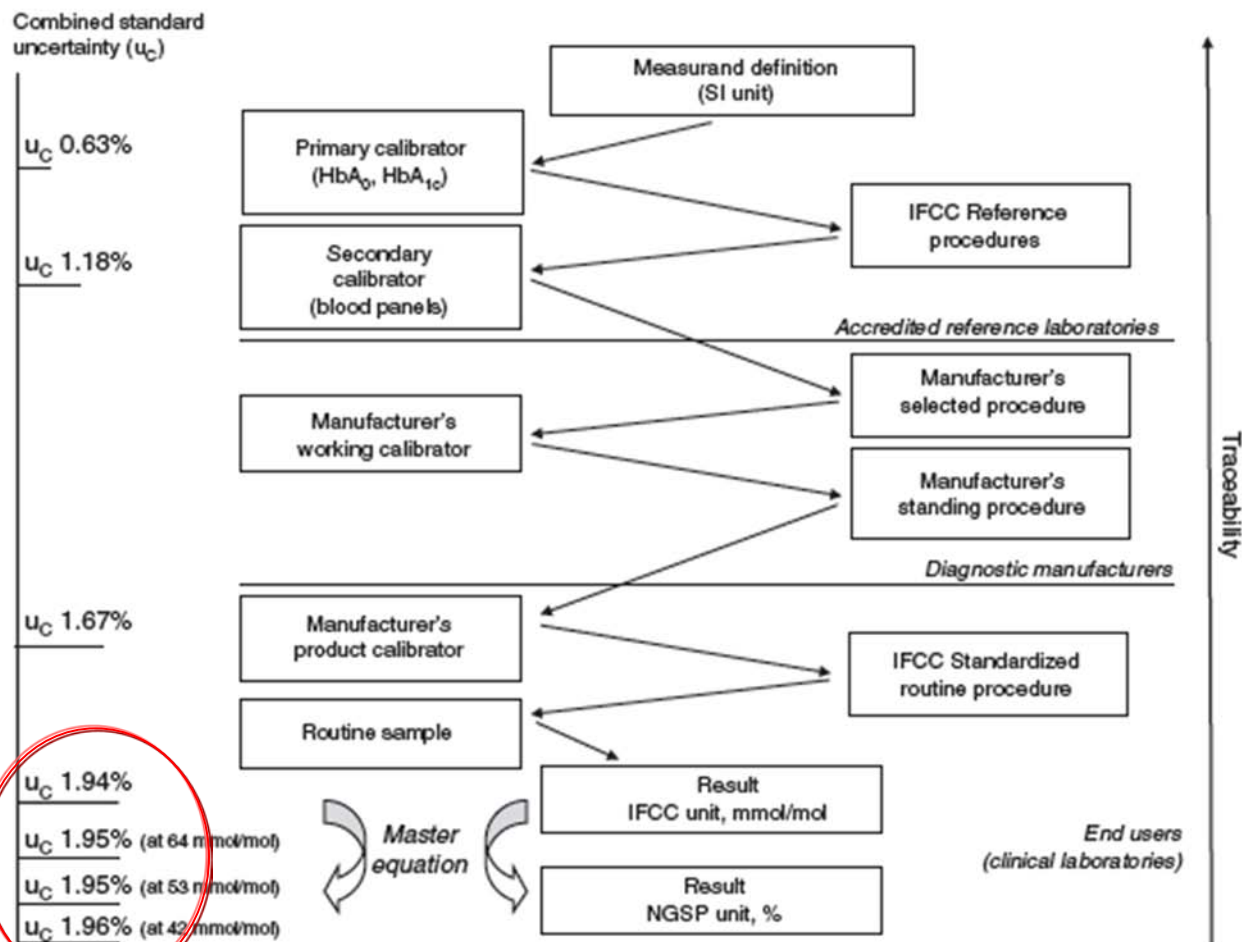Federica Braga* and Mauro Panteghini

Standardization and analytical goals for glycated hemoglobin measurement

Clin Chem Lab Med 2013;51:1719–26

HbA1c reference system and associated combined standard uncertainty

By analyzing the combined standard uncertainty of the current traceability chain for HbA1c, it is clear that the relative combined standard uncertainty associated with the measurement of a biological sample (~2.0%), which corresponds to an expanded uncertainty equal to ~4.0%, is still >2 times the minimum acceptable target that, for unbiased results, would be ~2.0% (minimum quality level goal for imprecision).

Further advances are needed, from one hand to reduce uncertainty associated with higher-order metrological references (reference materials and procedures) and on the other hand to increase the precision of commercial HbA1c assays.

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

International Federation of Clinical Chemistry and Laboratory Medicine (IFCC)[3]

IFCC Scientific Division

Mauro Panteghini* on behalf of the IFCC Scientific Division

The analytical non-specificity issue: the case of serum creatinine

- **The alkaline picrate method is unable to measure solely creatinine**

- **Endogenous and exogenous substances may significantly interfere**

- **Interfering substances in serum, particularly proteins, can lead to significant overstimation with various alkaline picrate methods**

- **Interference from glucose and ketones particularly important in diabetics who are at high-risk for CKD**

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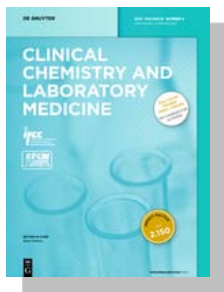
Reference System for Creatinine
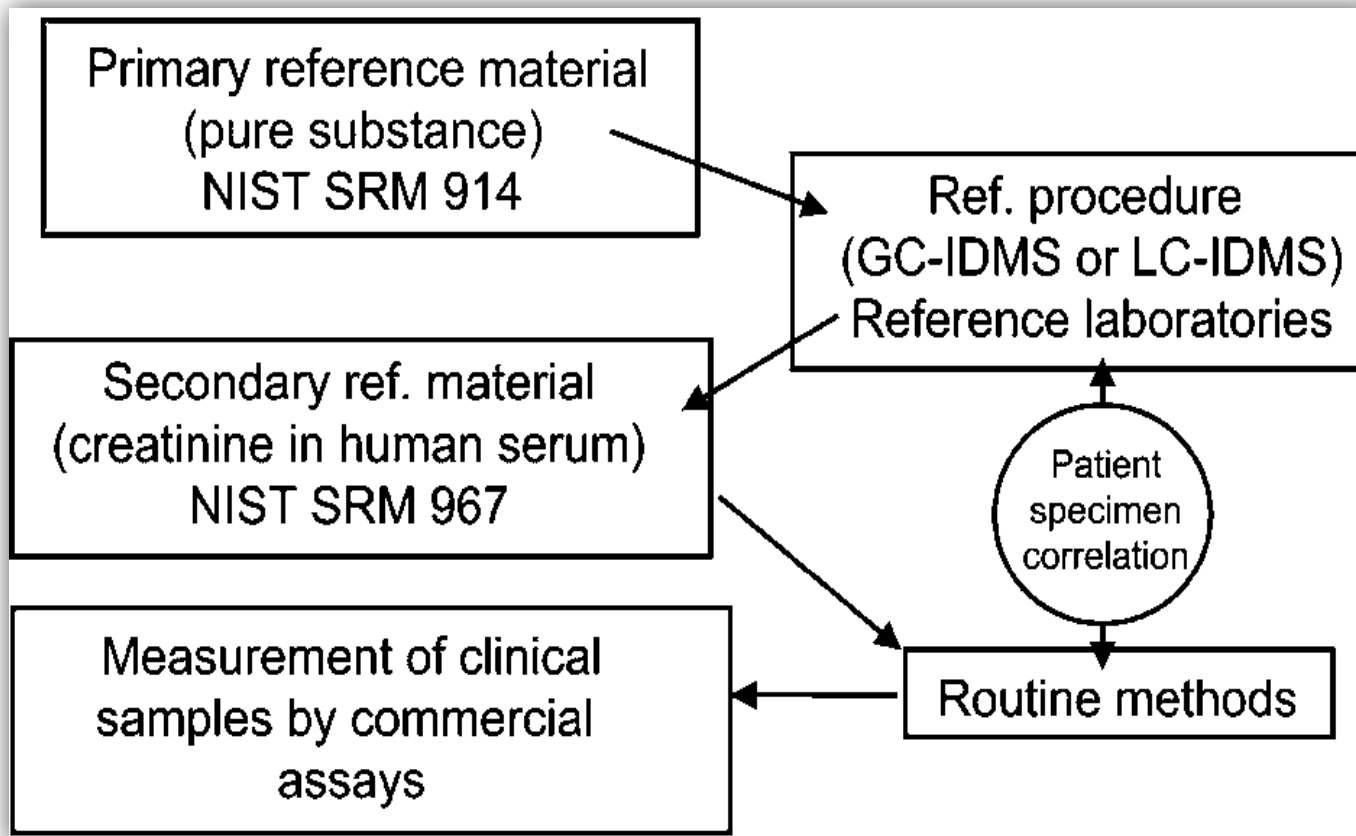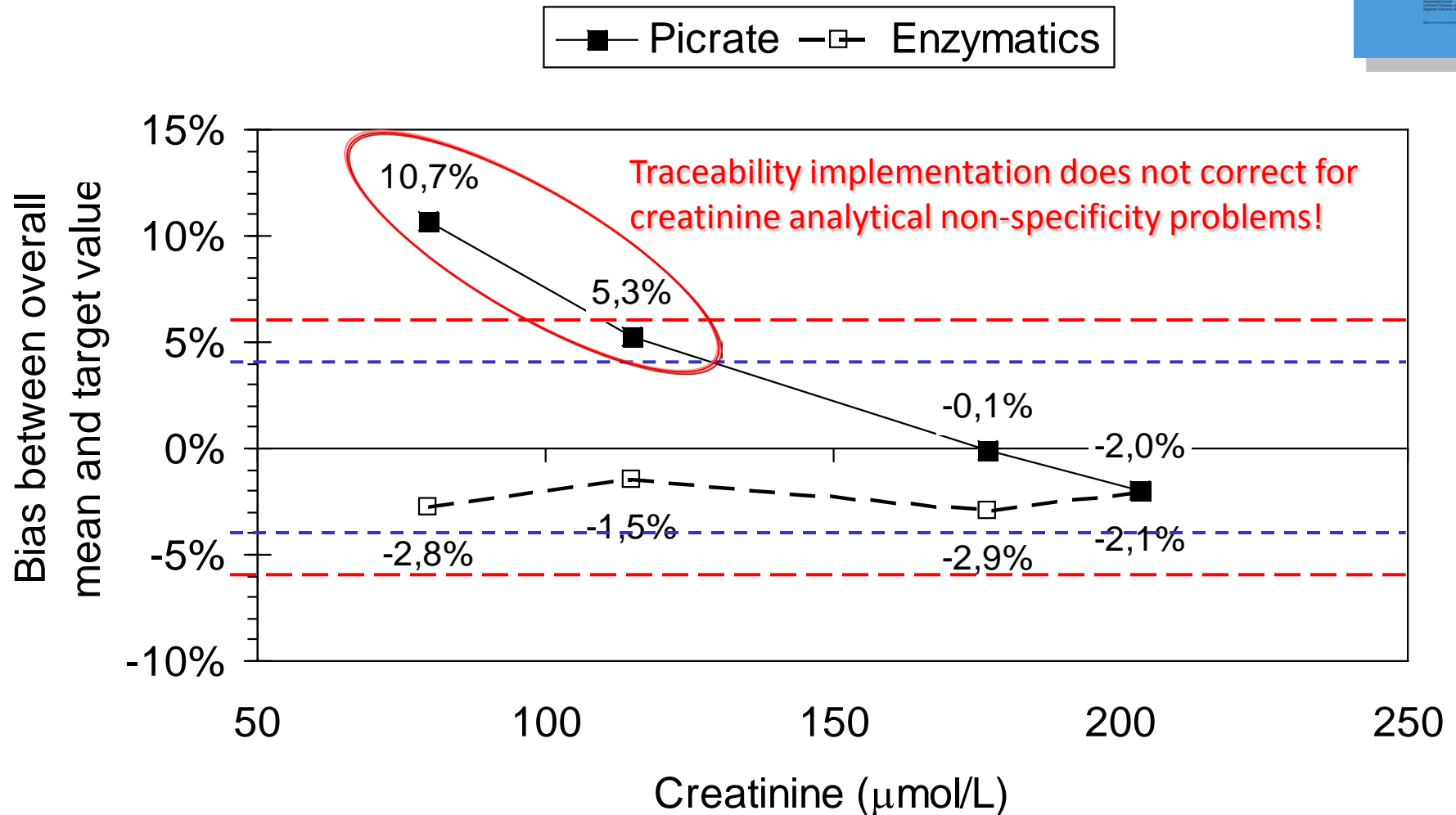
Percent bias of overall means for the two method macro-categories based on different analytic principle in post-standardization years (2010-2011). The dotted and the dashed line indicate the maximum acceptable bias at desirable (±4.0%) and at minimum quality level (±6.0%), respectively.

The role of the Profession: "check"

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

2. Daily surveillance of IVD system traceability

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

Diagnostic manufacturers: **Implement suitable analytical 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**

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

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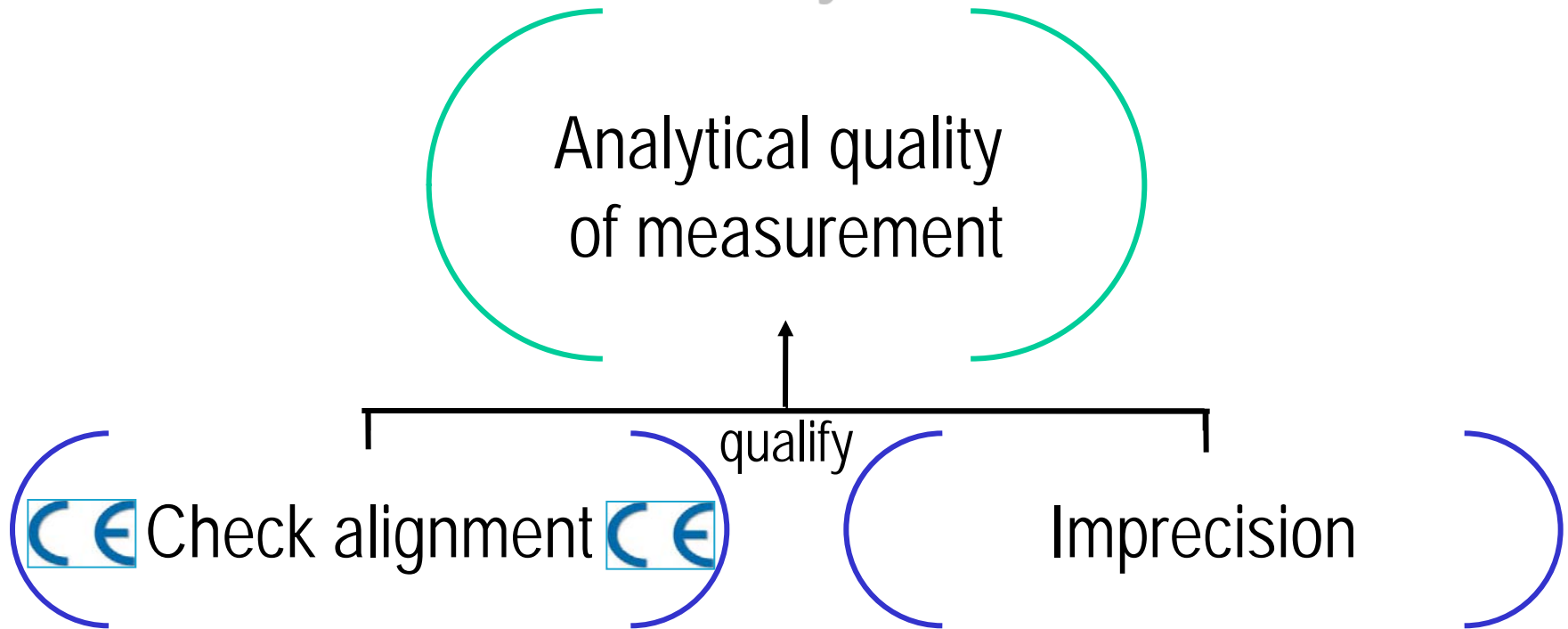
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Analytical Quality Control in the Traceability Era

External Quality Assessment

Analytical quality
of measurement

qualify

CE Check alignment CE   Imprecision

Reliability of the analytical system

Internal Quality Control

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

Monitoring the reliability of the analytical system through IQC: Component I. Check alignment ("system traceability")

This program checks whether in the course of an analytical run the performance of an analytical system complies with the set goals, represented by the acceptable ranges of control materials.
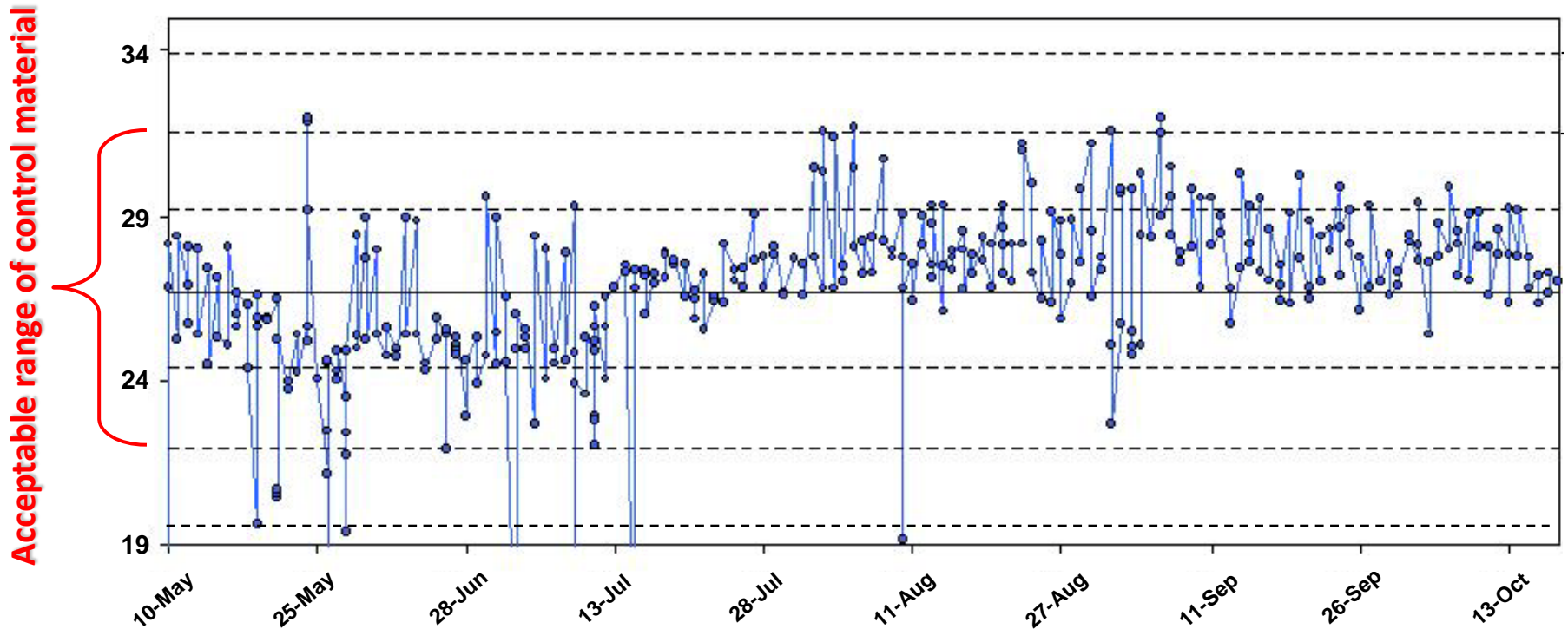
Clinical laboratories must verify the consistency of declared performance during routine operations performed in accordance with the manufacturer's instructions, by checking that values of control materials provided by the manufacturer as component of the analytical system are in the established control range, with no clinically significant changes in the assumed traceable results.

Internal Quality Control (Component I)

Acceptance/rejection of the analytical run in "real time"

→

Testing alignment ["system traceability"]

Platform

Control material(s)
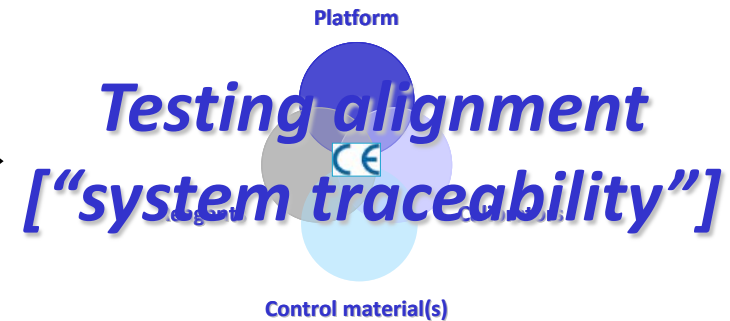
Any "out of control" signal must be made available with sufficient time to allow immediate corrective actions to bring again the situation under control (virtually "unbiased") and before reports related to the samples analyzed in the affected analytical run are issued.

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Internal Quality Control (Component II)

System stability at medium/long term ➡️ *Estimating the measurement uncertainty due to random effects ("imprecision")*

This program provides, through mechanisms of retrospective evaluation, data useful to the knowledge of variability of the analytical system and of its use by the individual laboratory.

```
System
  ↓
Reagent lots
  ↓
Laboratory
```
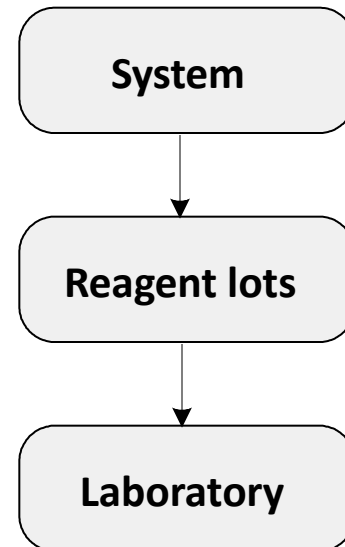
Monitoring the reliability of the analytical system through IQC: Component II. Evaluate the system + individual lab imprecision

Measurement uncertainty budget

System calibration (combined) uncertainty

System imprecision

Individual lab performance (IQC safety margin)

Cardiac troponin T high sensitive
Monthly monitoring of imprecision by IQC material

CV, %

Cumulative mean, 17 ng/L
[adopted cut-off for myocardial necrosis >15 ng/L]

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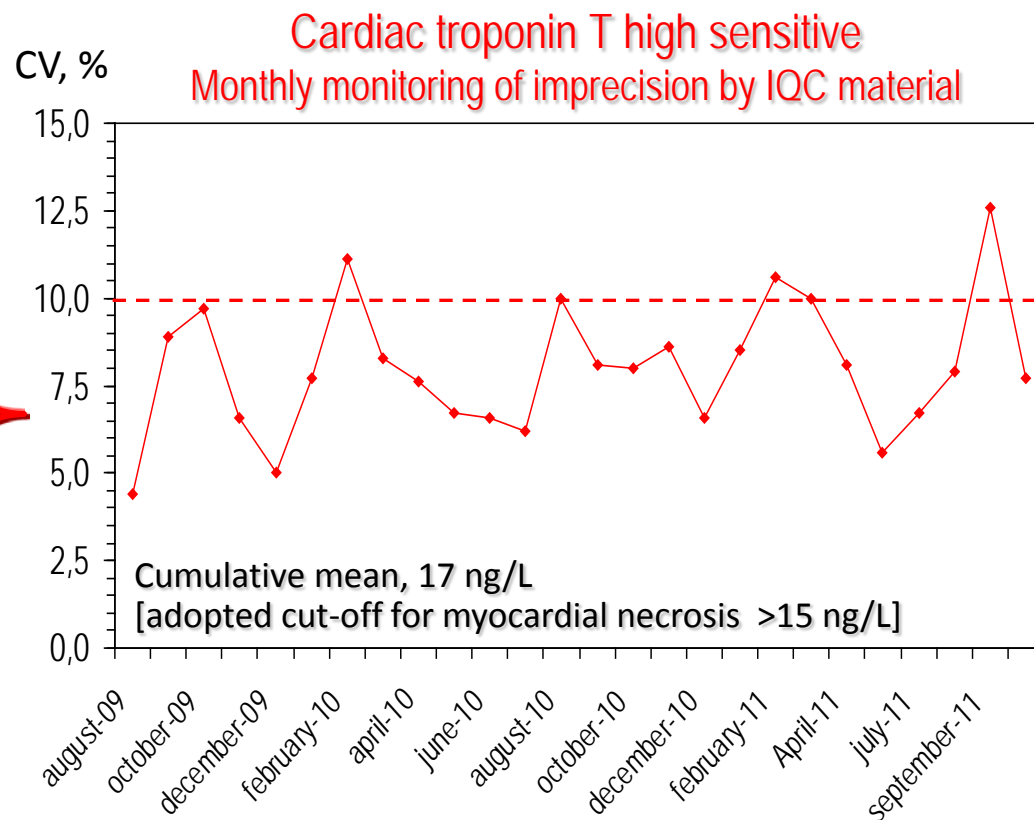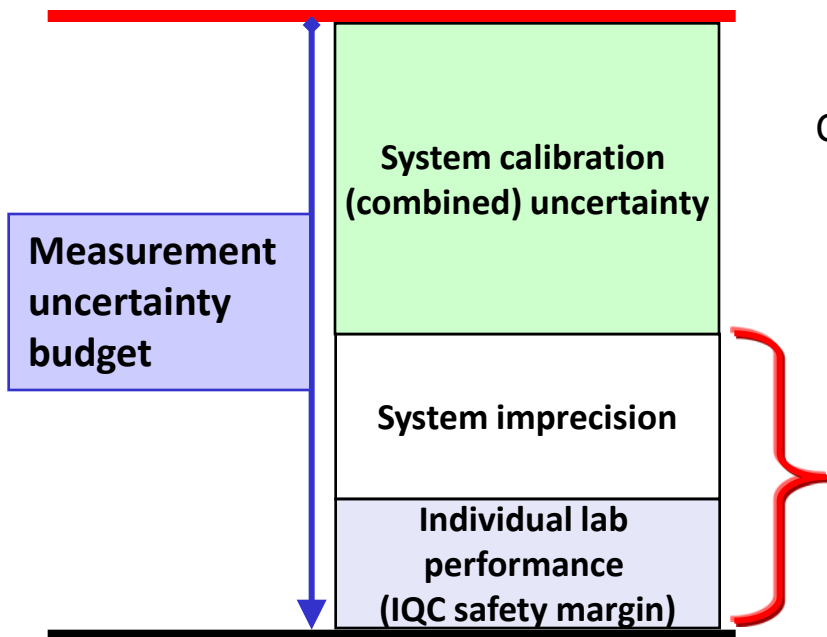
Characteristics of a material to be used for the IQC component II programme

Requirement	Comment
Material from a third-party independent source should be used	**Material must be different from the system control material used for checking alignment (IQC component I)**
Material should closely resemble authentic patient samples (fulfil commutability) (e.g., fresh-frozen pool)	**Commercial non-commutable controls may provide a different impression of imprecision performance**
Material concentration levels should be appropriate for the clinical application of the analyte measurement	**When clinical decision cut-points are employed for a given analyte, materials around these concentrations should preferentially be selected**

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The role of the Profession: "check"

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

2. **Daily surveillance of IVD system traceability**

IQC reorganized into two independent components: one devoted to checking the alignment of the analytical system and verification of the consistency of declared traceability during routine operations performed in accordance with the manufacturer's instructions (component I) and the other structured for estimating the measurement uncertainty due to random effects (component II).

Participation to appropriately structured EQAS ("meeting metrological criteria")

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

Feature	Aim
EQAS materials value-assigned with reference procedures by an accredited ref. laboratory	To check traceability of commercial system to reference systems
Proved commutability of EQAS materials	To allow transferability of participating laboratory performance to the measurement of patient samples
Definition and use of the clinically allowable 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

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EQAS materials with physiologic (88.4 µmol/L) and borderline (123.8 µmol/L) creatinine concentrations vs. the desirable goal for TE (±8.9%). Notwithstanding the marked difference in size of two groups, it was evident that the vast majority (87%) of laboratories using systems employing enzymatic assays were able to fulfill the desirable performance, while only one third of laboratories using picrate-based systems were able to meet the target.

Enzymatic assays (n=23)

Alkaline picrate assays (n=296)

area target value
± allowable total error

µmol/L
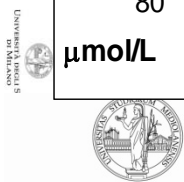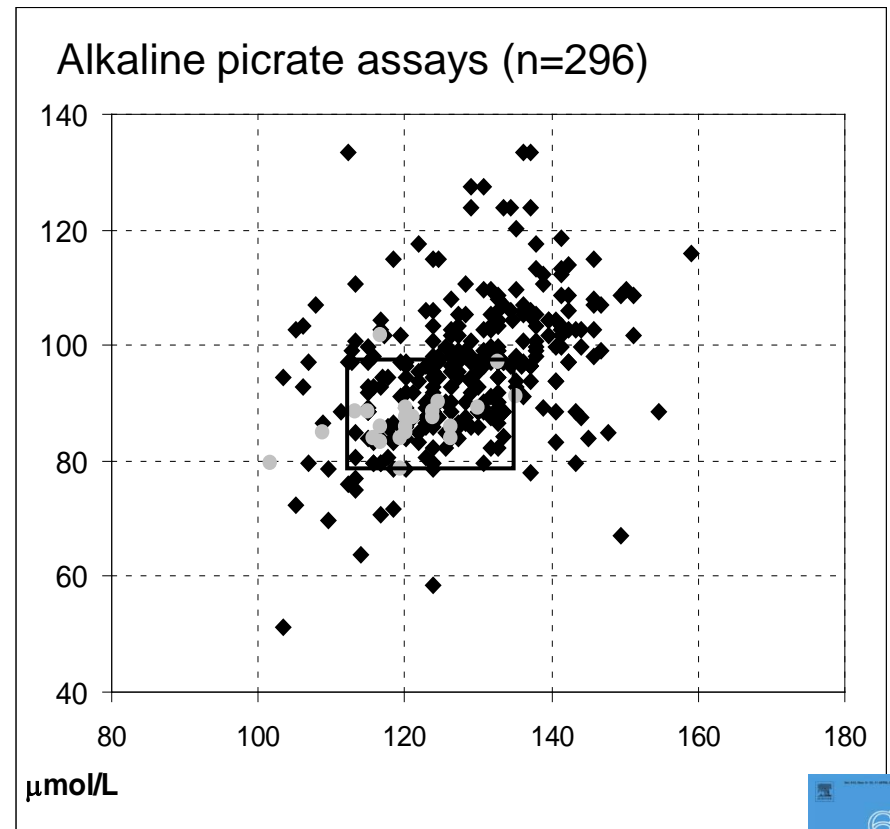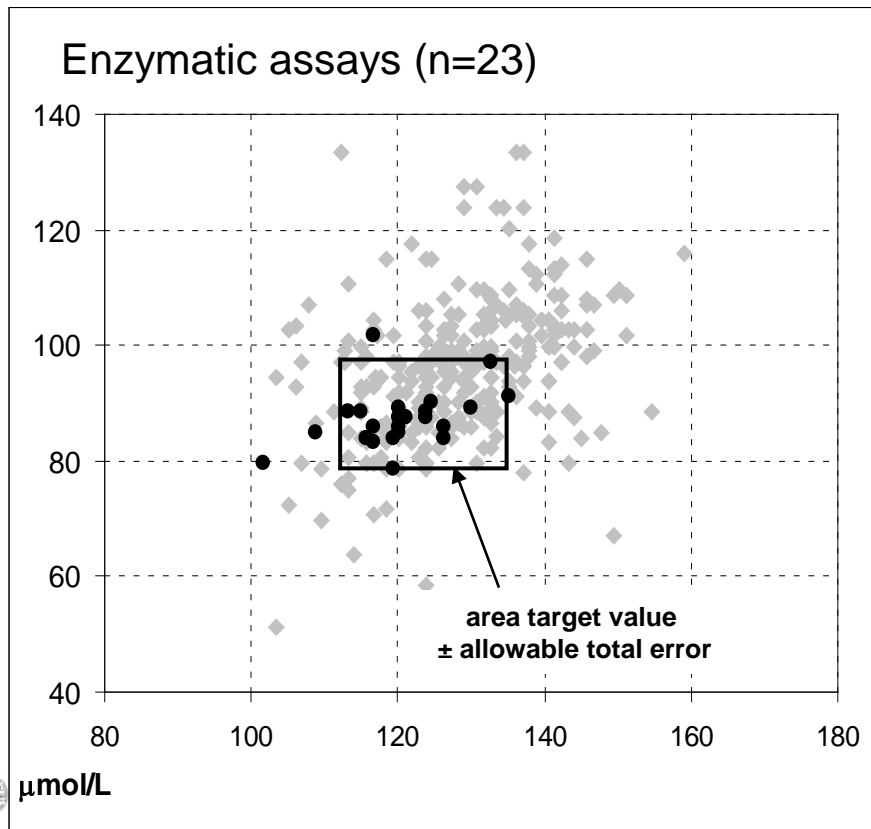
Limitations of conventional EQAS

- **Assessment of traceability (standardization) status not possible because:**

    – **Processed samples potentially non-commutable**

    – **Performance assessment restricted to consensus (peer) groups**

Constraints limiting the introduction of EQAS meeting metrological criteria

- **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 EQAS important,**

- **Economic concerns: higher costs.**

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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

Schema huius præmissæ diuisionis Sphærarum.

Equivalency-based grading

The earth is spherical and moves around the sun

Hypotyposis systematis mundani Copernicæa.

Trueness-based grading

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

Unique benefits of EQAS
meeting metrological criteria

- **Giving objective information about quality of individual laboratory performance**

- **Creating evidence about intrinsic standardization status/equivalence of the examined assays**

- **Serving as management tool for the laboratory and IVD manufacturers, forcing them to investigate and eventually fix the identified problem**

- **Helping manufacturers that produce superior products and systems to demonstrate the superiority of those products**

- **Identifying analytes that need improved harmonization and stimulating and sustaining standardization initiatives that are needed to support clinical practice guidelines**

- **Definition and approval by JCTLM 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 (error) for each of the analytes used in the clinical field;**

- **Adoption by EQAS 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 EQAS meeting 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.**

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

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ACCREDIA ACCREDITATION ACCORDING TO ISO/IEC 17025 AND ISO 15195 STANDARDS

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