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Centre for Metrological Traceability in Laboratory Medicine (CIRME)

Director: Prof. Mauro Panteghini

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

11th International Scientific Meeting

MEASUREMENT UNCERTAINTY IN MEDICAL LABORATORIES: FRIEND OR FOE?

MILANO, ITALY
November 30th, 2017

Measurement uncertainty: friend or foe?

Mauro Panteghini

University of Milan Medical School

Research Centre for Metrological Traceability in Laboratory Medicine (CIRME)

Practical Value of TEa in Laboratory Quality Management

Sten Westgard, MS
Westgard QC, Inc.

Westgard QC

Westgard QC

‘The real-world uncertainty’

On 2/25/2016 4:11 AM, [NAME WITHHELD] wrote:

Good day,

I am hoping that you can help me….

I am busy with the uncertainty of measurement in a… laboratory and am going to use the IQC data available….

Your help in this matter would be greatly appreciated.

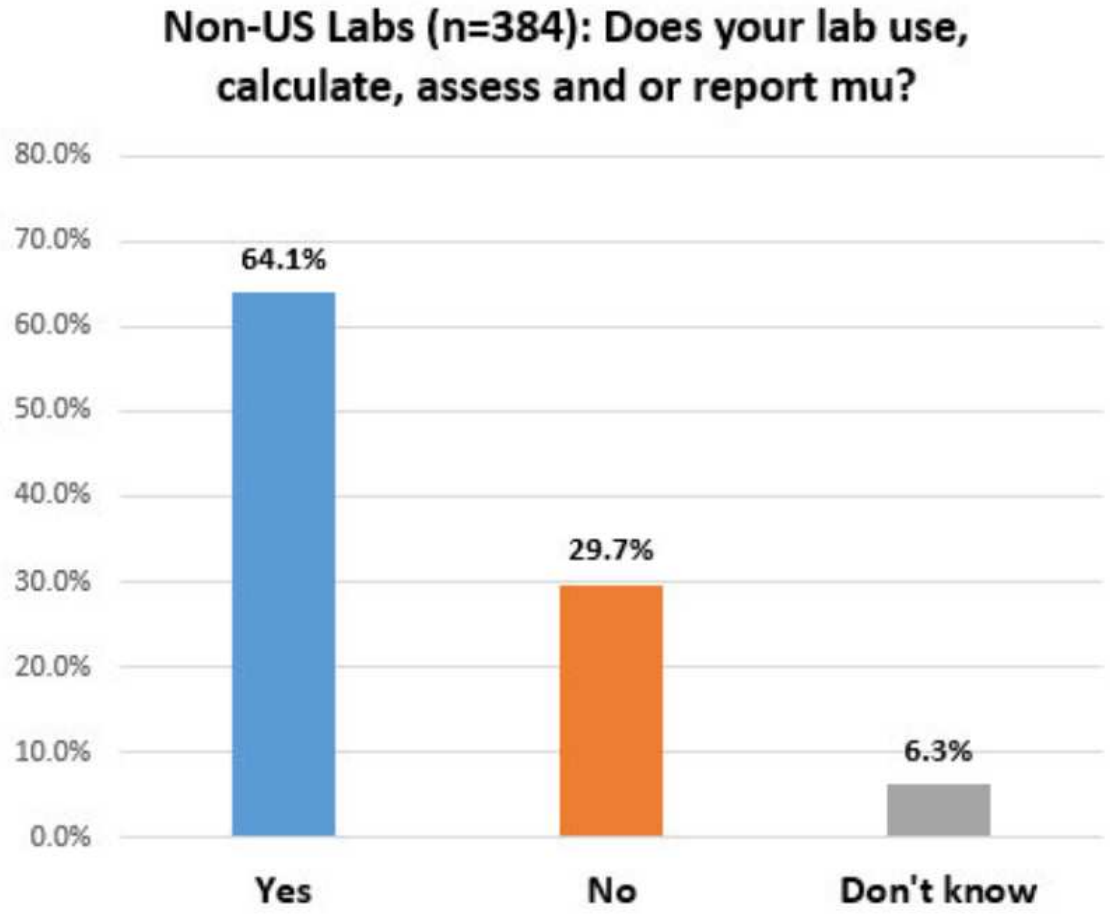
Kindest regards

….

If I may, can I ask you why you need to calculate MU? I realize this is a naive question - that it is a mandatory required calculation. But other than using it for compliance and to make inspectors happy, do you ever use it practically in the lab? Do you report it to clinicians with your results?

To answer your question – no we the laboratory do not use it and we do not report it with our results. It is as you say a requirement for accreditation. That said we have to have the data readily available if a Clinician asks for it. In all my years of practicing in the field I have not had this happen but I suppose there is always a first time for everything.

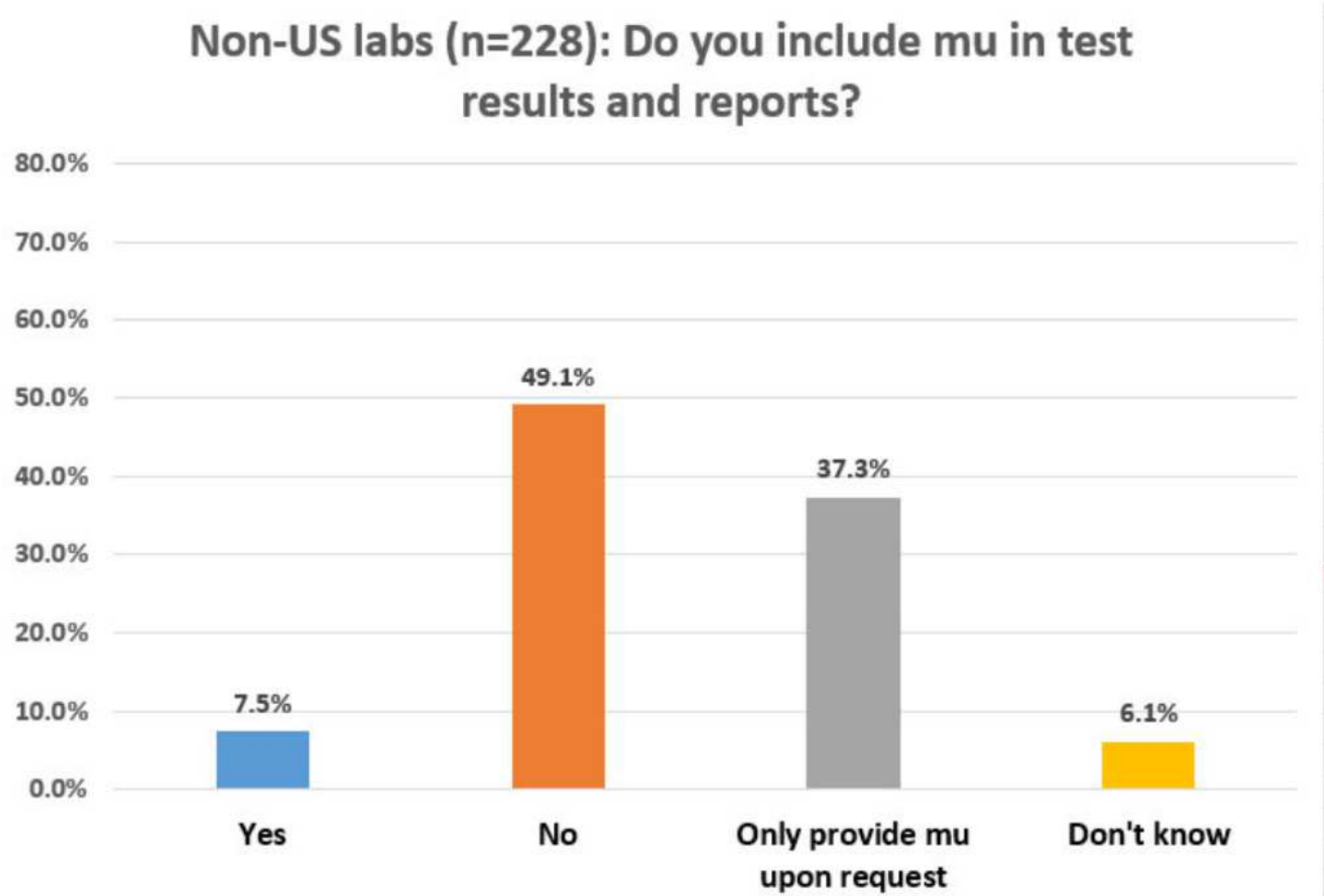
Global Survey of MU: most labs do (except for the US)



www.westgard.com/mu-global-survey.htm

Westgard QC

MU is calculated – but not used



www.westgard.com/mu-global-survey.htm

Westgard QC

Certainty of MU

- You ***must*** calculate MU, and many labs do
- Most labs do nothing with MU after that

The measurement uncertainty is surely a foe

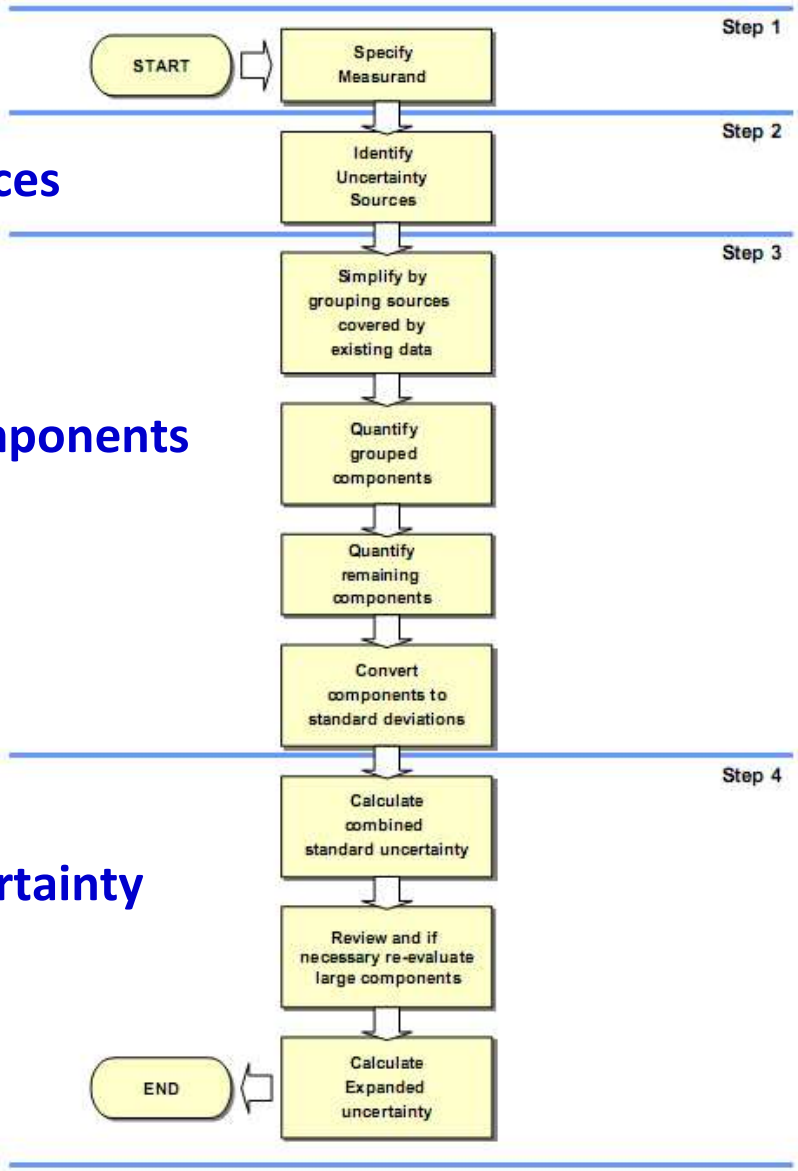
Estimation of measurement uncertainty

Step 1: Specify the measurand

Step 2: Identify uncertainty sources

Step 3: Quantify uncertainty components

Step 4: Calculate combined uncertainty



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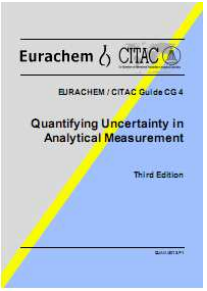
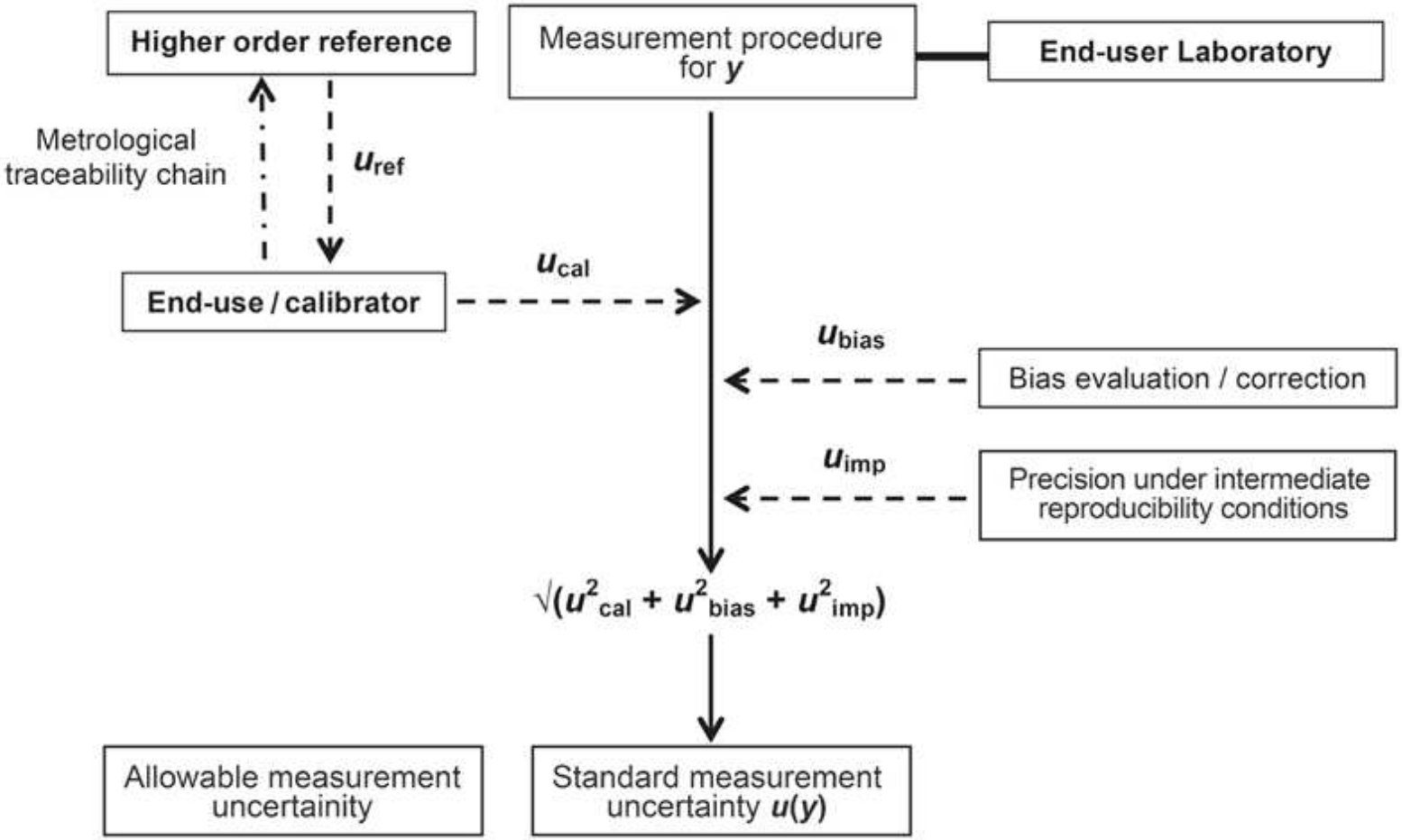


SOURCES OF MEASUREMENT UNCERTAINTY WITH THE 'TOP-DOWN' APPROACH



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CALCULATE MEASUREMENT UNCERTAINTY WITH THE 'TOP-DOWN' APPROACH

The combined standard uncertainty (u_c) is:

$$u_c = \sqrt{(u^2_{cal} + u^2_{bias} + u^2_{imp})}$$

The appropriate coverage factor should be applied to give an *expanded uncertainty (U)*:

$$U = k \times u_c$$

The choice of the factor k is based on the desired level of confidence:

Coverage probability *p*	Coverage factor *k*
90%	1.64
95%	1.96
95.45%	2.00
99%	2.58
99.73%	3.00

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WHY MEASUREMENT UNCERTAINTY IS NEEDED

ISO 15189:2012 AND MEDICAL LABORATORIES ACCREDITATION

ISO 15189:2012 introduced the estimation of measurement uncertainty as a specific requirement for the accreditation of medical laboratories

NOTE 3 Examples of the practical utility of measurement uncertainty estimates might include confirmation that patients' values meet quality goals set by the laboratory and meaningful comparison of a patient value with a previous value of the same type or with a clinical decision value.

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Why measurement uncertainty matters [with examples]

- Uncertainty of references → define their suitability
- Uncertainty of IVD calibrators → verify quality of IVD products
- Uncertainty of clinical results → evidentiate unpredictable bias and demonstrate their clinical suitability

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WHAT IS MEASUREMENT UNCERTAINTY

$$\text{Result} = x \pm u$$

quantity value — measurement uncertainty

"…In general use, the word uncertainty relates to the general concept of doubt… [however] uncertainty of measurement *does not imply doubt about the validity of a measurement*; on the contrary, knowledge of the uncertainty implies *increased confidence in the validity of a measurement result*… "

[Ellison SLR, Williams A, eds. (2012). Eurachem Guide: Quantifying Uncertainty in Analytical Measurement, Eurachem, 3rd ed.]

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If I measure my uncertainty of measurement it is no longer an uncertainty. It is now the confidence limit within which the result will fall.

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

STANDARDIZATION

Unbroken traceability chain

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

Measurement uncertainty

With definition of permissible 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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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]

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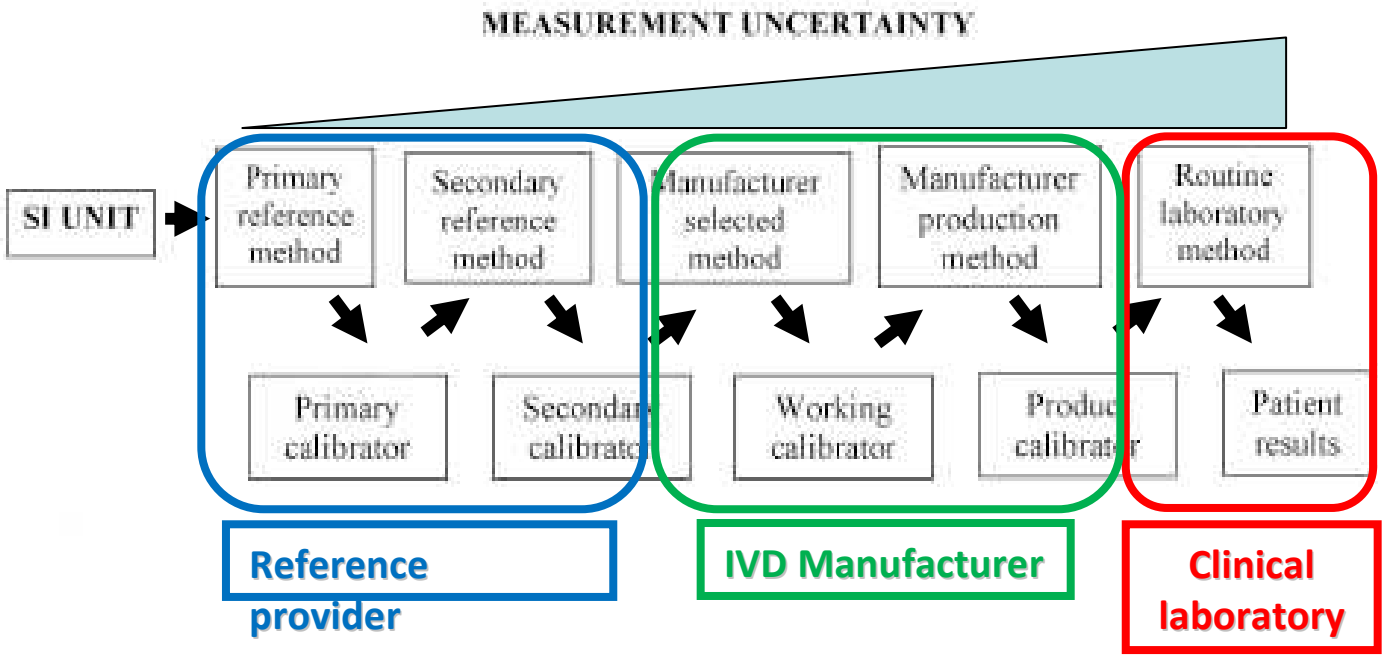
Measurement uncertainty budget



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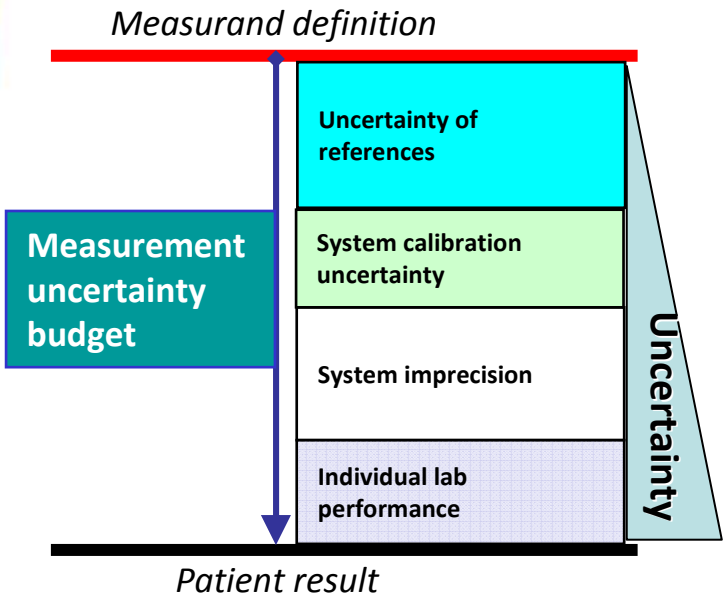

Estimate the combined uncertainty!

$$u\ result = (u^2_{ref} + u^2_{cal} + u^2_{random})^{½}$$

Avoid the common misconception that the reproducibility of a measurement result equals its overall measurement uncertainty

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Why measurement uncertainty matters [with examples]

- **Uncertainty of references → define their suitability**
- **Uncertainty of IVD calibrators → verify quality of IVD products**
- **Uncertainty of clinical results → evidentiate unpredictable bias and demonstrate their clinical suitability**

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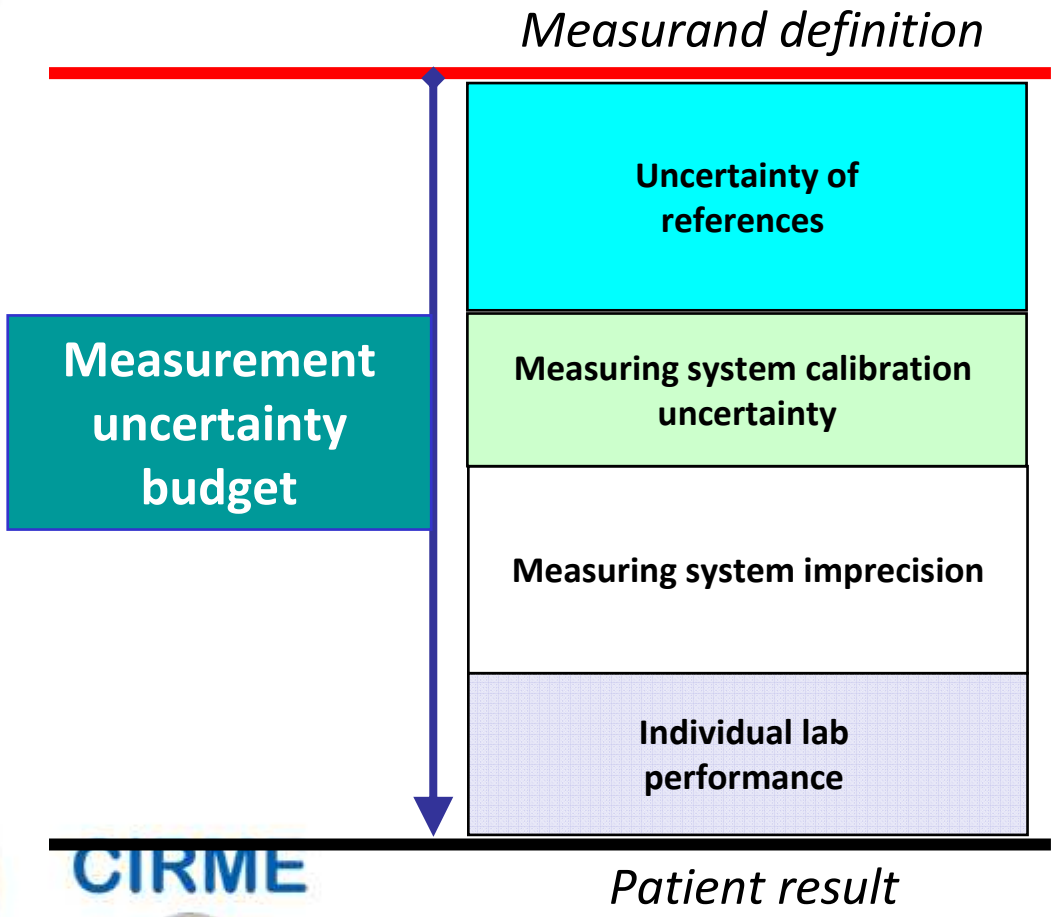
REFERENCE PROVIDER contribution to the measurement uncertainty budget



→ **Reference provider**

↓

Due to error propagation in the calibration hierarchy the uncertainty of the certified value should be significantly lower than the analytical performance goals for routine procedures.

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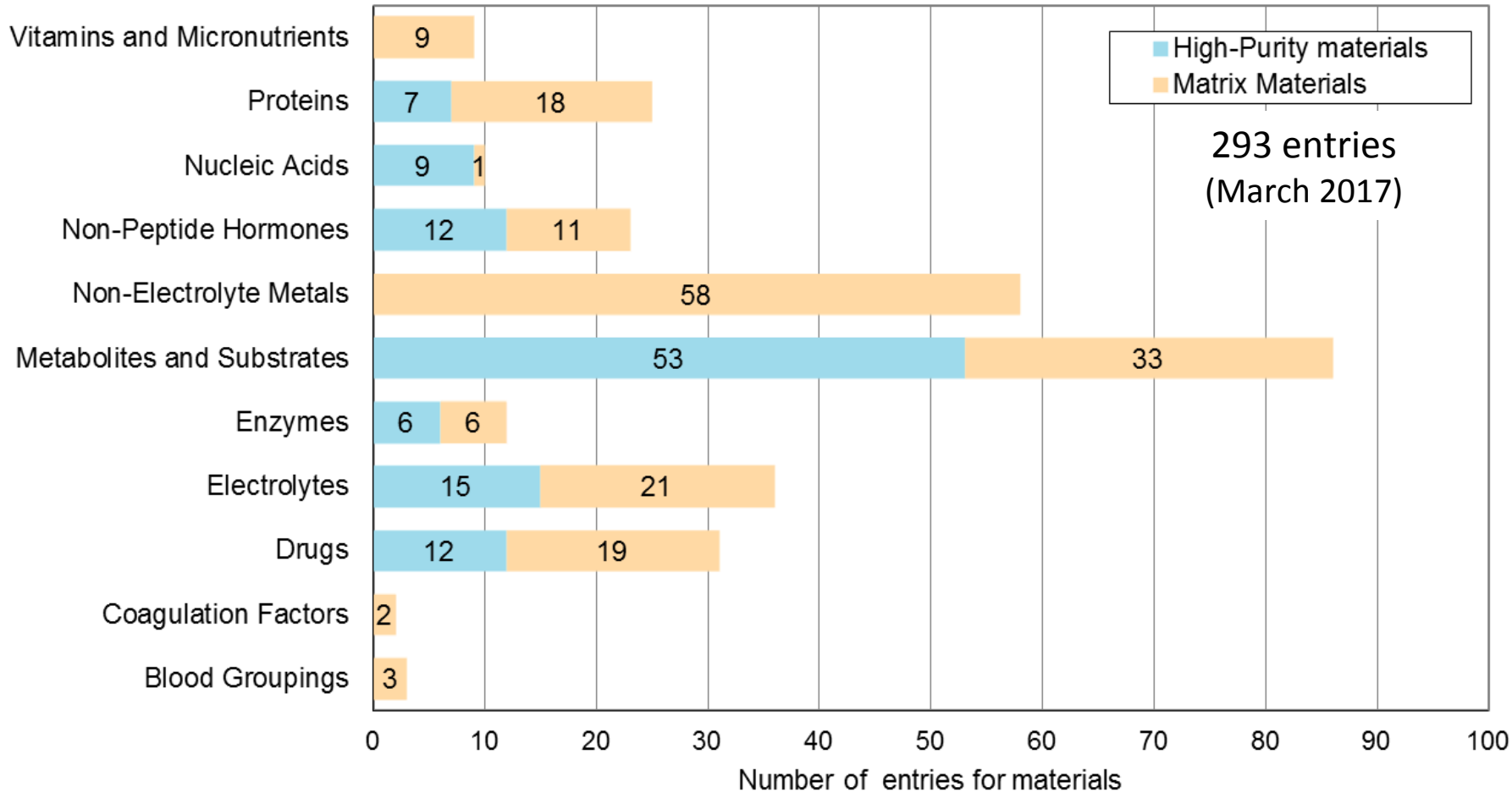
JCTLM Database Reference Materials

JCTLM
Accurate results for patient care



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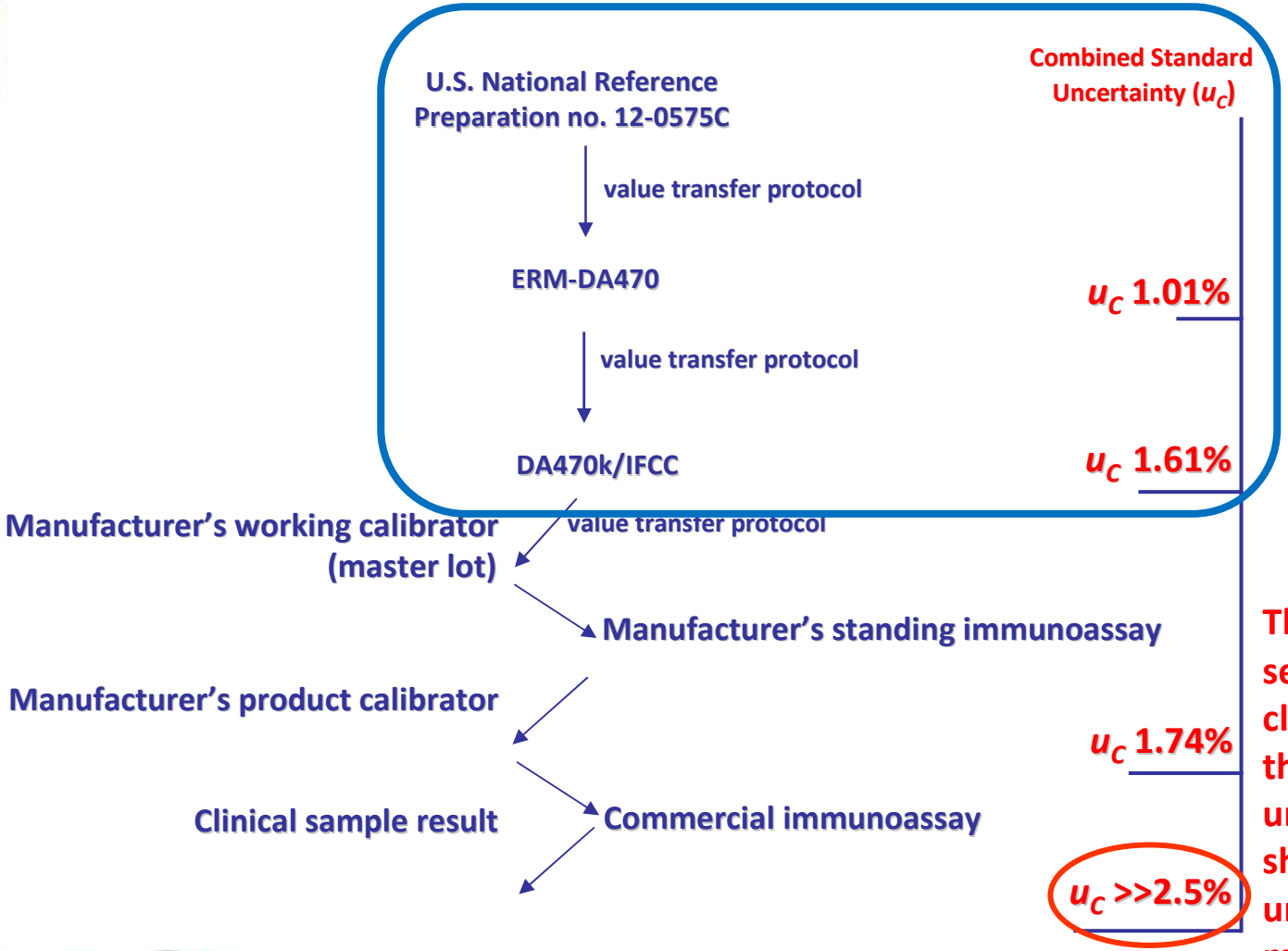
Serum albumin: An example



The u_C associated with serum albumin results on clinical samples is greater than the minimal goal for uncertainty (≤2.4%), showing that the uncertainty of albumin measurement in serum is probably too high to meet the requirements for its clinical application.

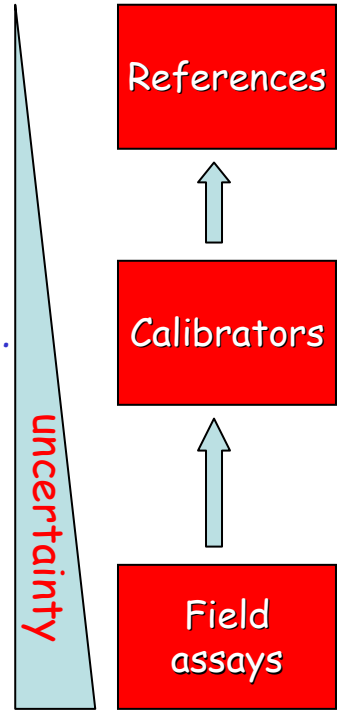
Panteghini M, Clin Chem Lab Med 2012;50:1237
Infusino I & Panteghini M, Chim Clin Acta 2013;419:15
Braga F & Panteghini M, Clin Chim Acta 2014;432:55

Turning the problem upside down
Focus first on the field assays

Specifications of higher order references defined by intended use…

…intended use is the certification of reference materials/calibrators…

…the specifications of reference materials/calibrators are defined by the performance needs of the clinical assays on patient samples.



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

Why measurement uncertainty matters [with examples]

- Uncertainty of references → define their suitability
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- Uncertainty of clinical results → evidentiate unpredictable bias and demonstrate their clinical suitability

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EU 98/79/EC-IVD Directive

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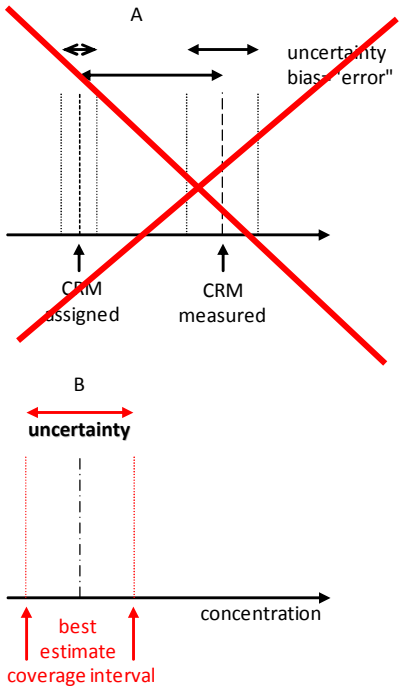
[Braga F & Panteghini M, Clin Chim Acta 2014;432:55]

EU 98/79/EC-IVD Directive

Role of IVD manufacturers



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

1) Elimination of measurement bias

2) Estimation of measurement uncertainty @ the calibrator level

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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

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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Limitations of CE mark

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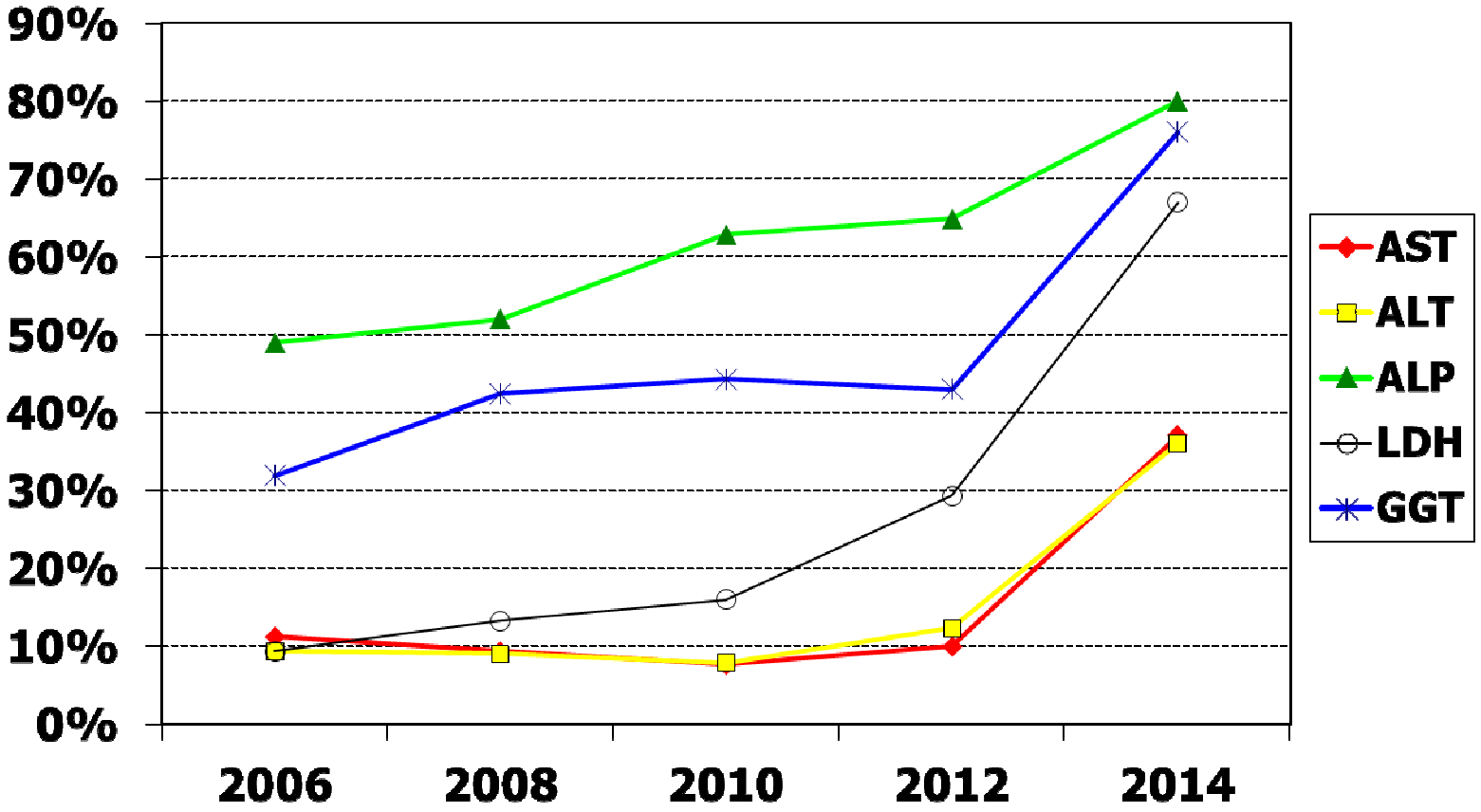
Percentage of Italian laboratories declaring to use methods for measuring enzyme employing the IFCC analytical principles



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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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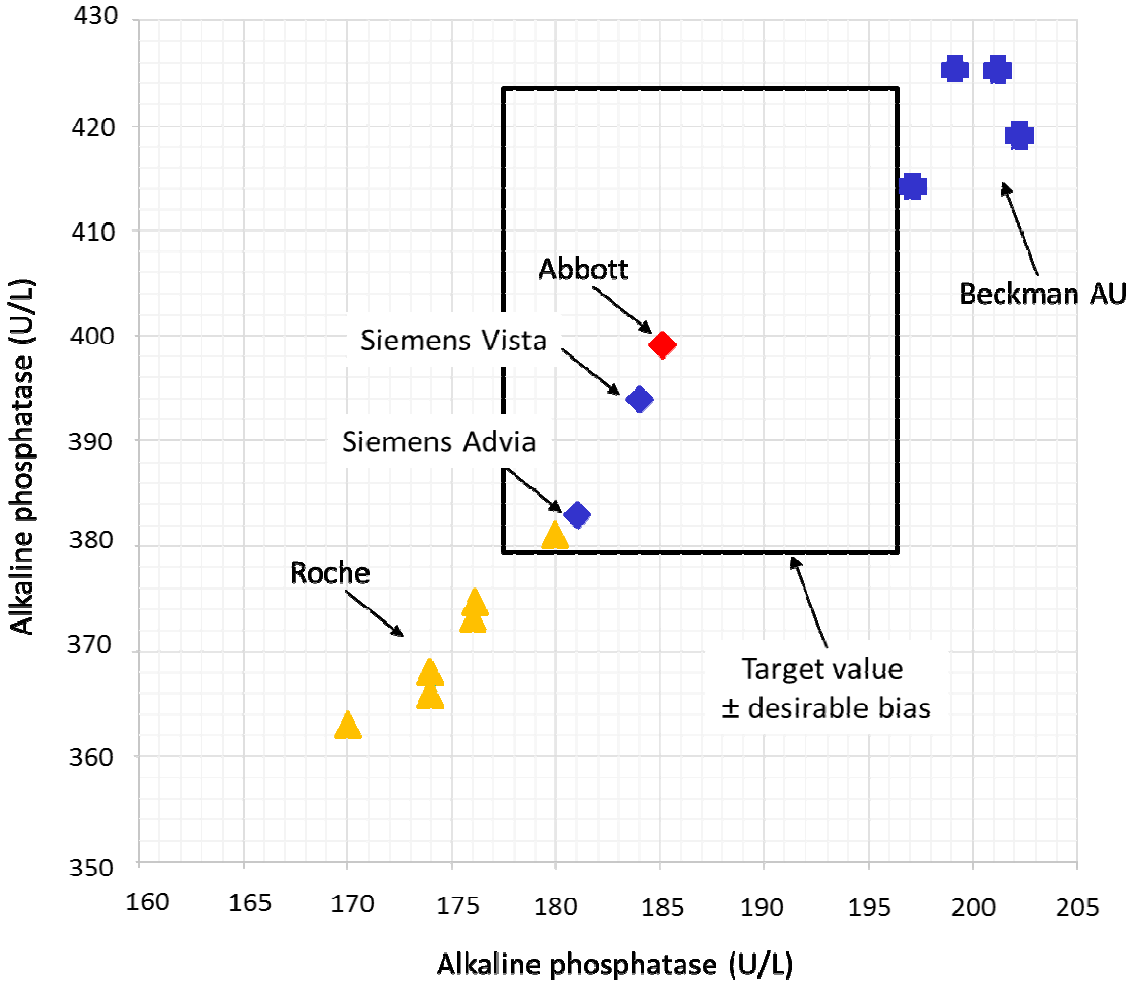
DE GRUYTER

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

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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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]

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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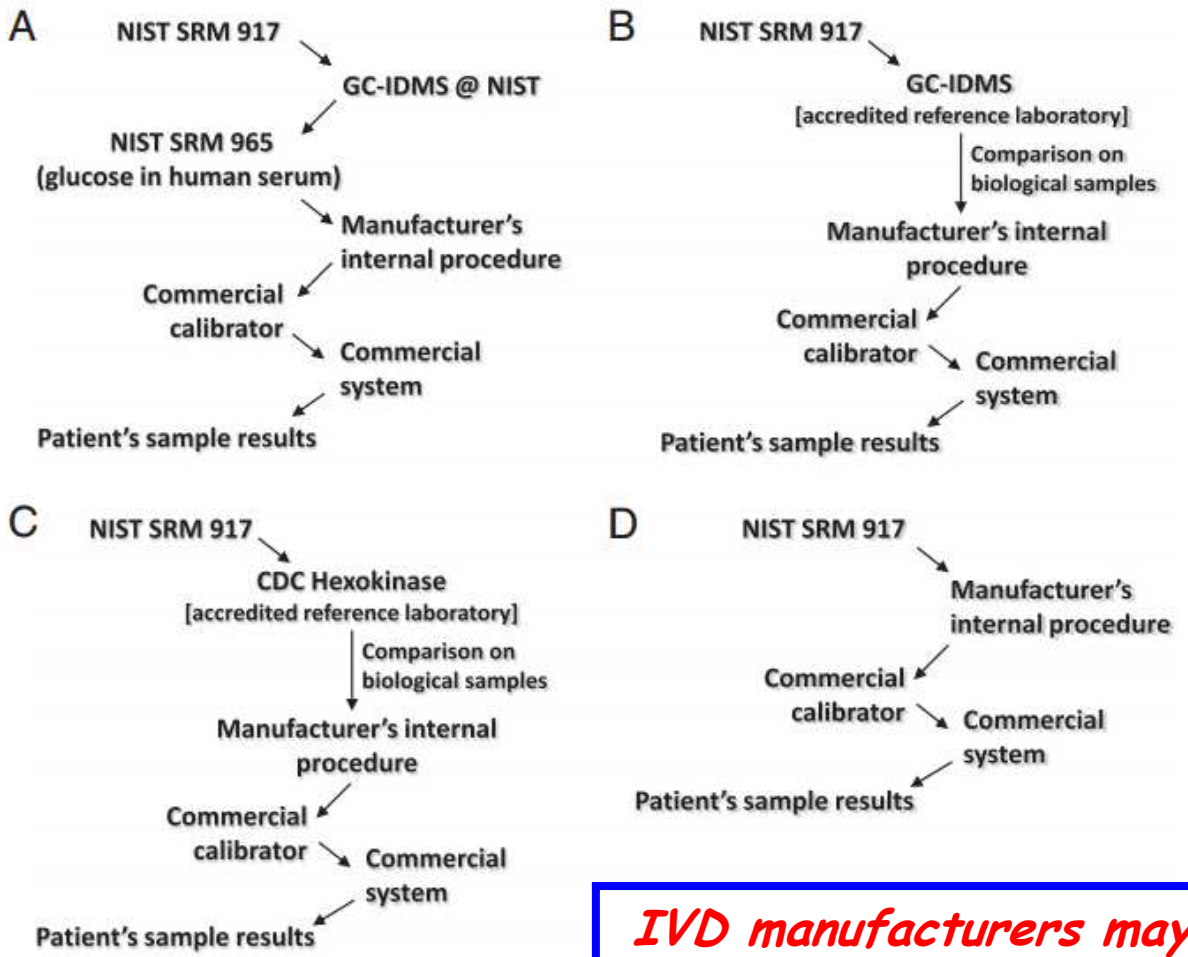
TRACEABILITY CHAINS AVAILABLE FOR IVD MANUFACTURERS FOR PLASMA GLUCOSE



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

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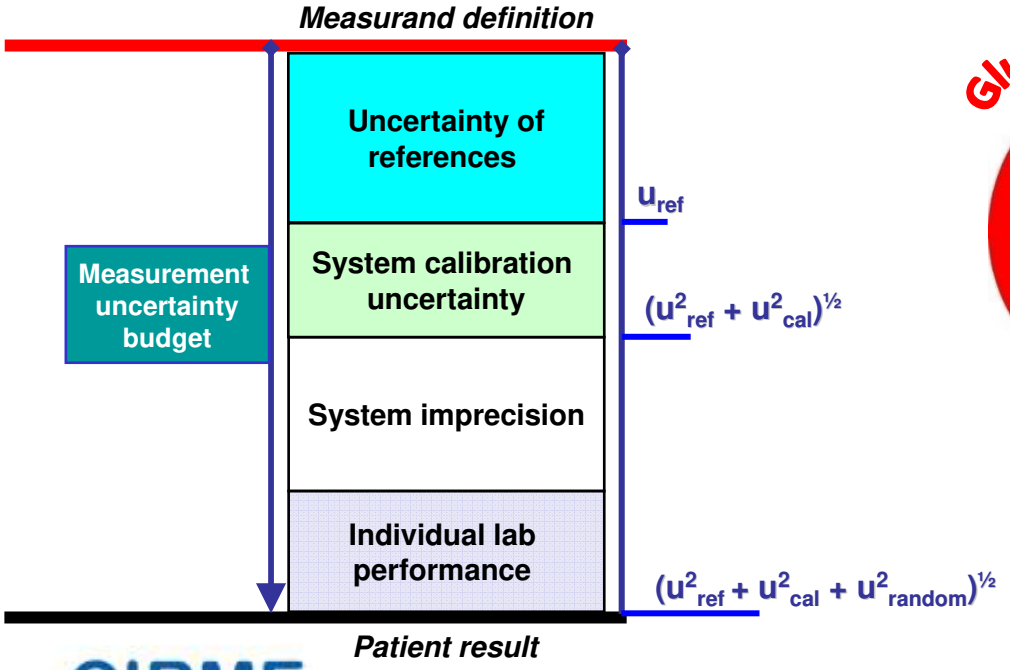
[Braga F & Panteghini M. Clin Chim Acta 2014;432:55-61]

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.



From MILAN MODEL 2

4.05% minimum

2.70% desirable

1.35% optimum

MEASUREMENT UNCERTAINTY GOAL
[for unbiased results]

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

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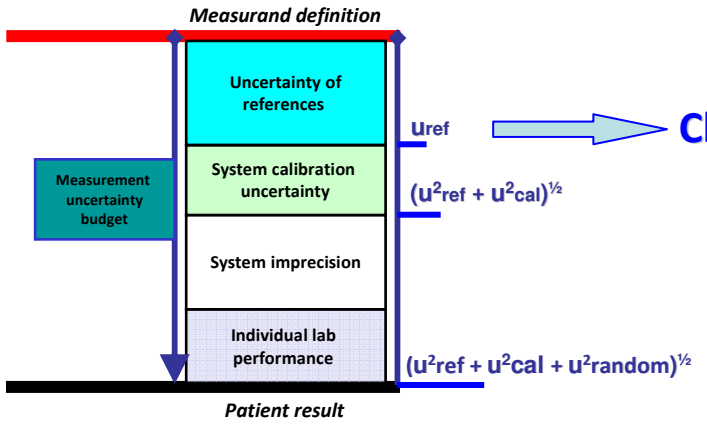
Braga F, Panteghini M. Clin Chim Acta 2014;432:55-61

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%[f]
		GOD	Chemistry calibrator	0.80%	Hexokinase	NIST SRM 917a	C	1.88–3.26%[f]



Chain A = 0.73% vs. Chain C = 1.63%

4.05% minimum

2.70% desirable

1.35% optimum

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 suitable limits for measurement uncertainty on clinical samples

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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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	3.16%[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 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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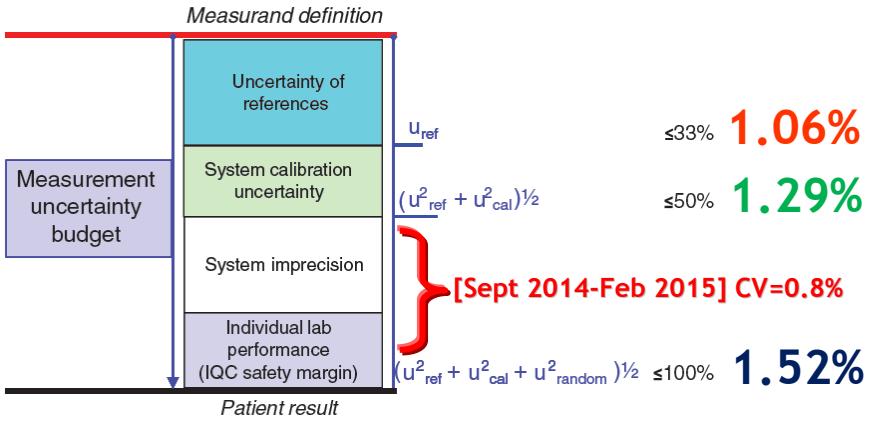
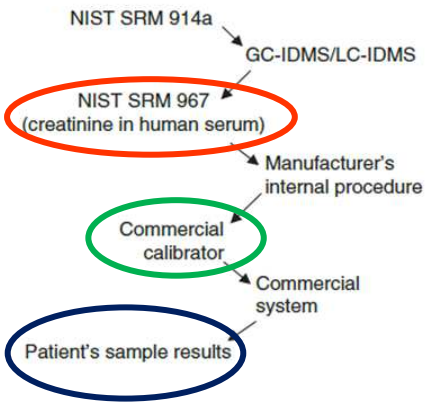
[Braga F, Infusino I, Panteghini M. Clin Chem Lab Med 2015;53:905]

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

Abbott

Creatinine enzymatic assay (cod. 8L24)
Clin Chem Calibrator (LN 6K30)





4.5% minimum

3.0% desirable

1.5% optimum

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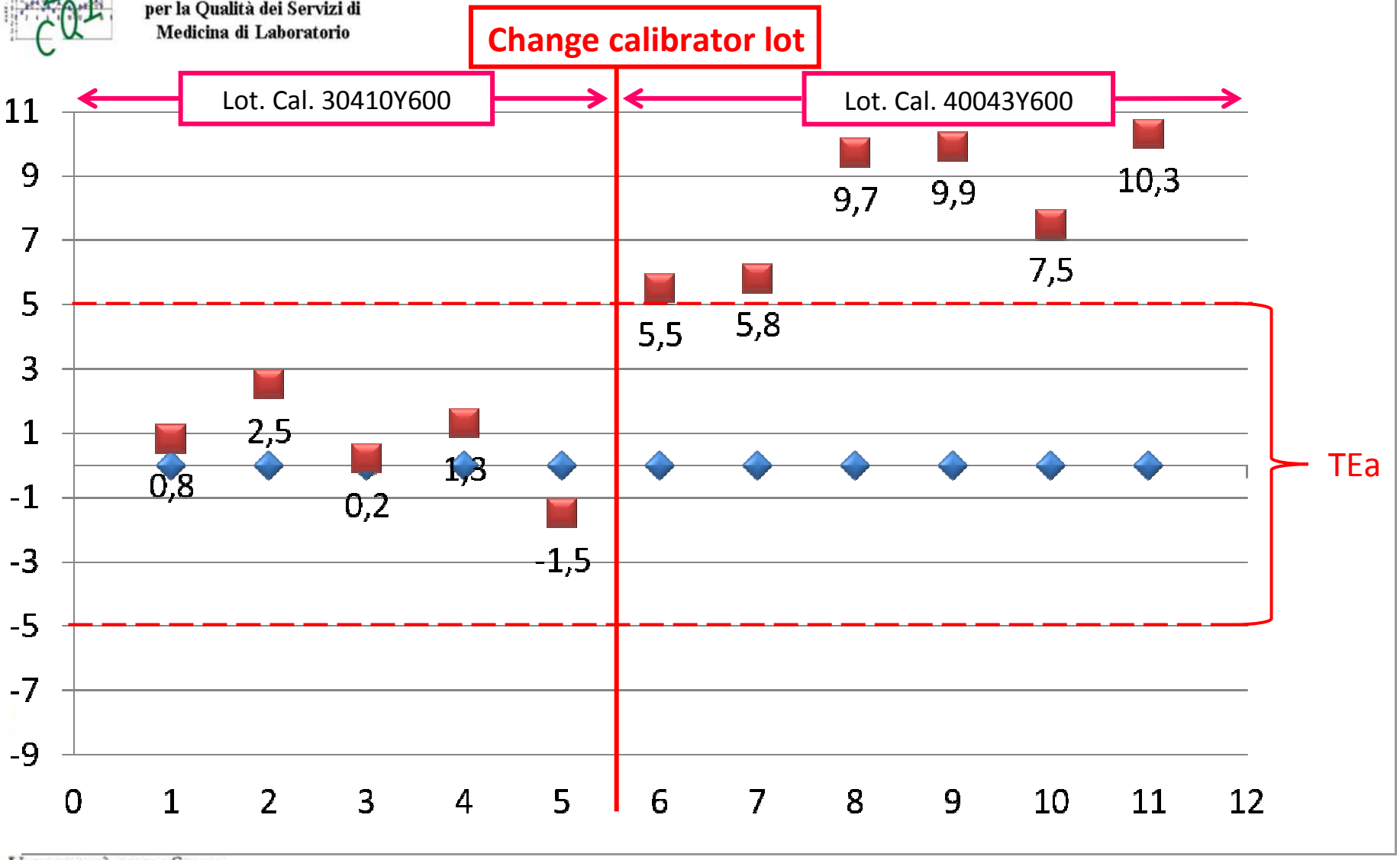
Case study #1: Creatinine @

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

Ospedale Luigi Sacco POLO UNIVERSITARIO
Sistema Socio Sanitario Regione Lombardia
ASST Fatebenefratelli Sacco



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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	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%

4.5% minimum

3.0% desirable

1.5% optimum

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.

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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

Therefore, we must improve the post-market surveillance of IVD medical devices through:

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

2. Surveillance of IVD system traceability and uncertainty

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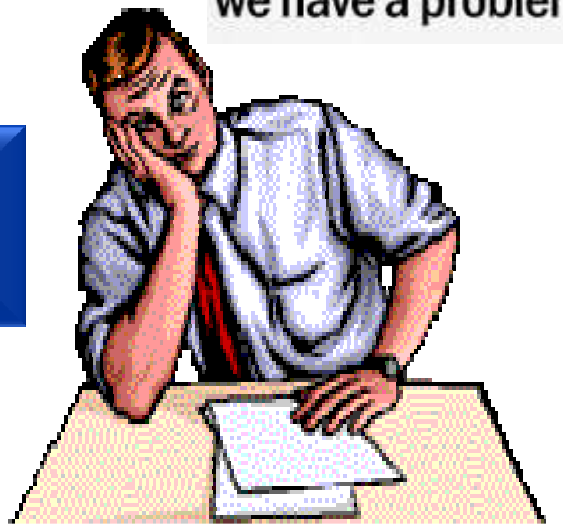
Braga F & Panteghini M, Clin Chim Acta 2014;432:55

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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Opinion Paper

Federica Braga*, Ilenia Infusino and Mauro Panteghini

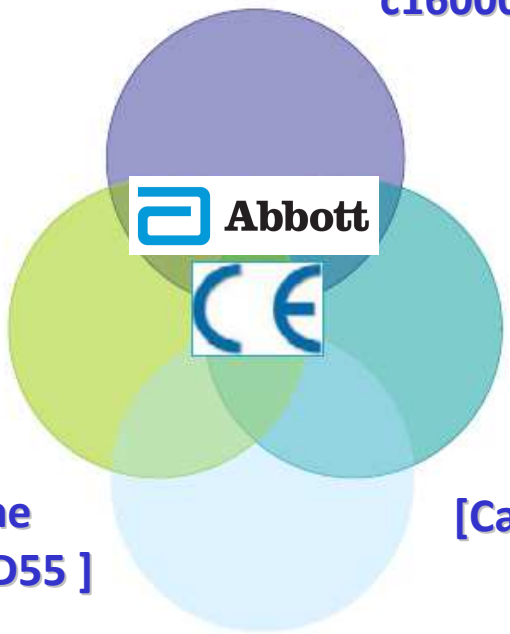
Table 2: The information that in vitro diagnostics manufacturers should provide to laboratory users about the implementation of metrological traceability of their commercial systems. Adapted from [7].

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.

Case study #2: Alkaline Phosphatase @

Ospedale Luigi Sacco
POLO UNIVERSITARIO
Sistema Socio Sanitario
Regione Lombardia
ASST Fatebenefratelli Sacco

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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Case study #2: Alkaline Phosphatase @

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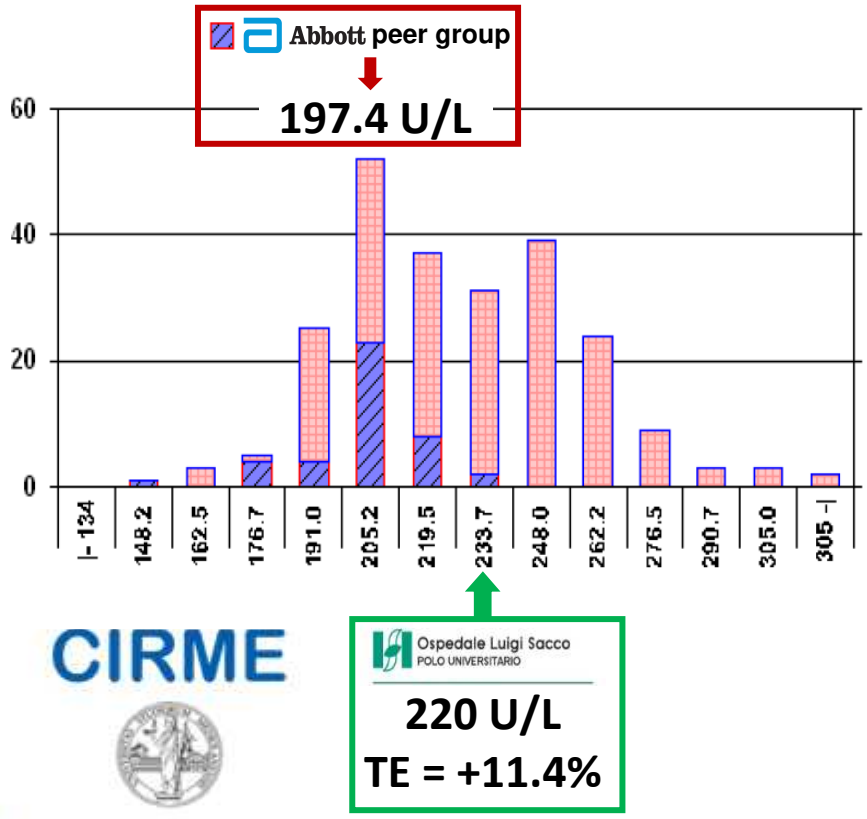
Centro di Riferimento Regionale per la Qualità dei Servizi di Medicina di Laboratorio

EQA exercise
April 2017

Tuo Metodo (Met)	Tuo Sistema (Sis)
P-NITROF.FOSF/AMP/ARCHITECT	*AUTOMATICO*



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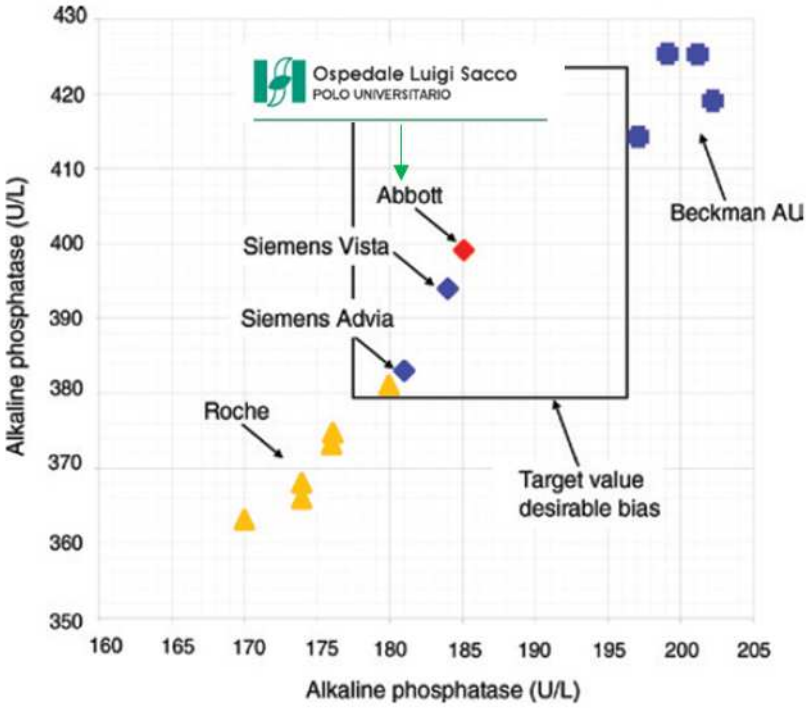

Case study #2: Alkaline Phosphatase @

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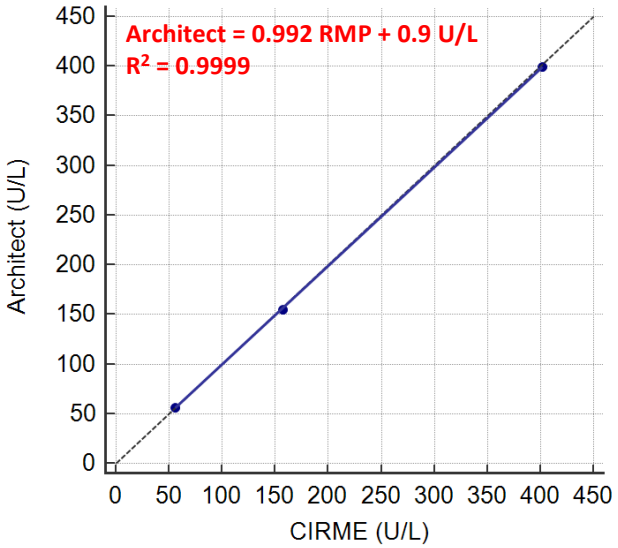
Trueness verification of ALP measurement

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



Aloisio E et al. Clin Chem Lab Med 2017;in press

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Architect ALP combined measurement uncertainty (u_c)

based on:

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

u_c = 2.0%

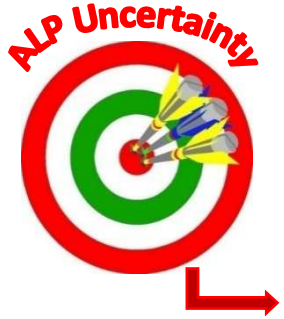

Table 2: Allowable maximum uncertainty for enzyme measurements performed by clinical laboratories.

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

Case study #2: Alkaline Phosphatase @

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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

CE

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

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

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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.

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

Why measurement uncertainty matters [with examples]

- Uncertainty of references → define their suitability
- Uncertainty of IVD calibrators → verify quality of IVD products
- Uncertainty of clinical results → evidentiate unpredictable bias and demonstrate their clinical suitability

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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

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

2.4% minimum
1.6% desirable
0.8% optimum

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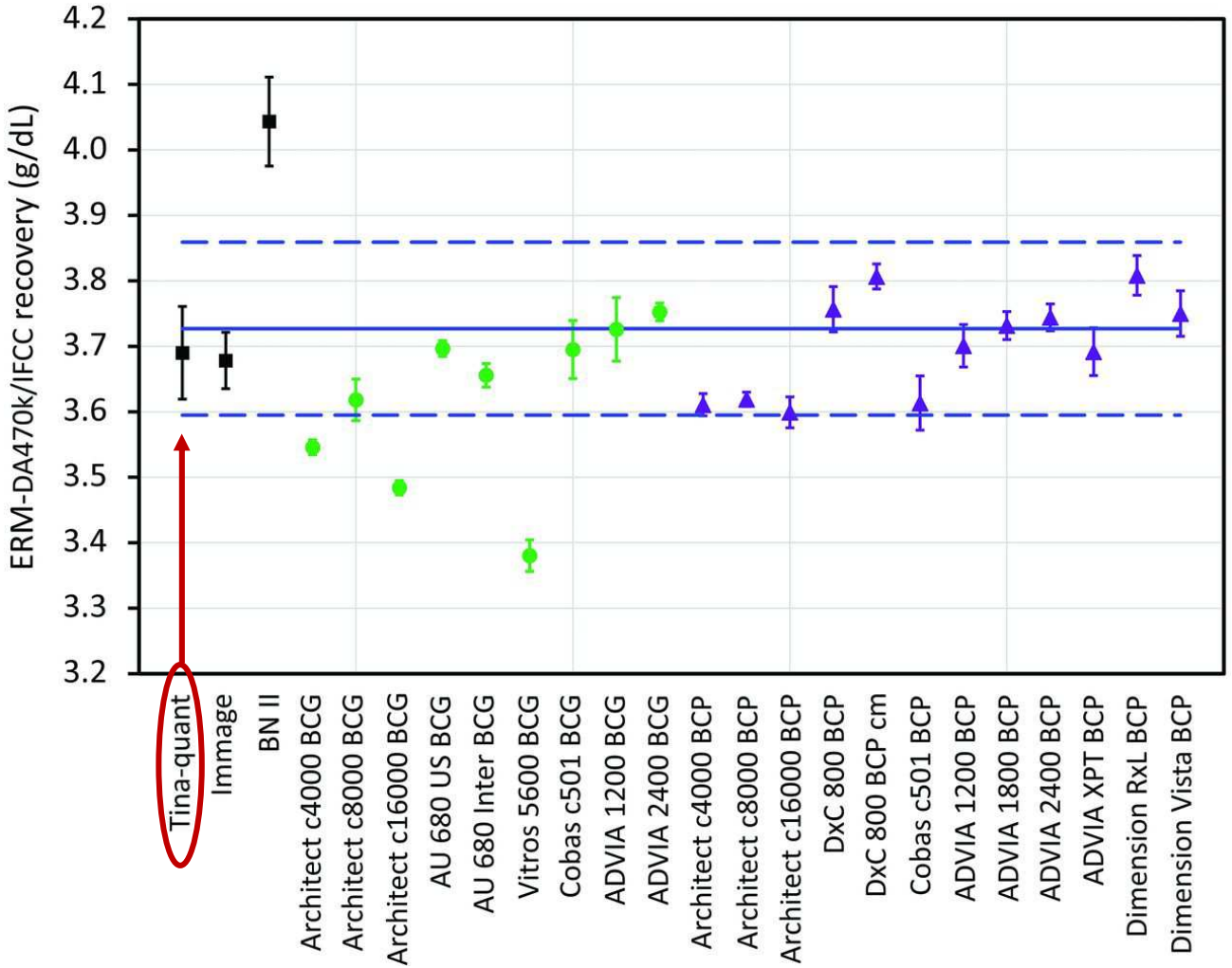
2017 State of Harmonization of Serum Albumin Measurements



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

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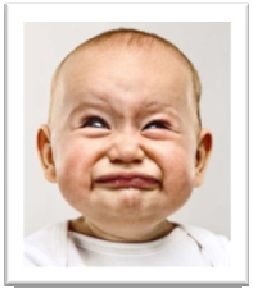
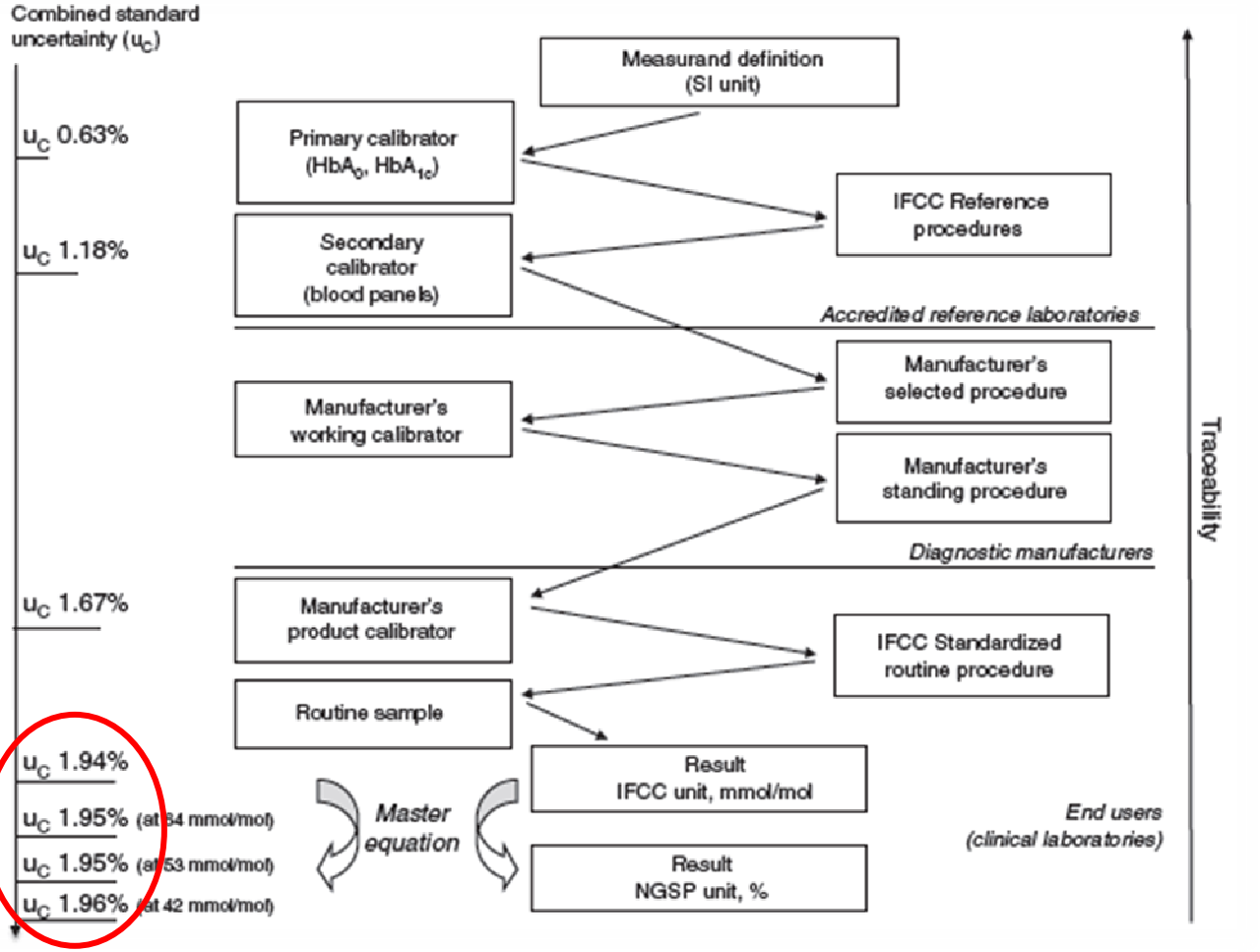
HbA1c reference system and associated combined standard uncertainty



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]

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 (i.e. random uncertainty) of commercial HbA1c assays**

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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

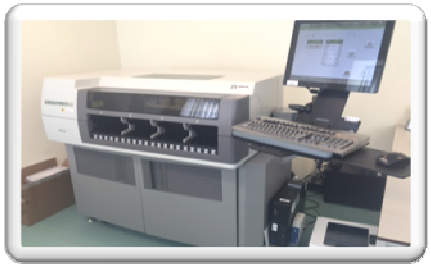

Table 3
Analytical goals for HbA_{1c} measurement

Quality level	U_C
Optimal	≤0.6
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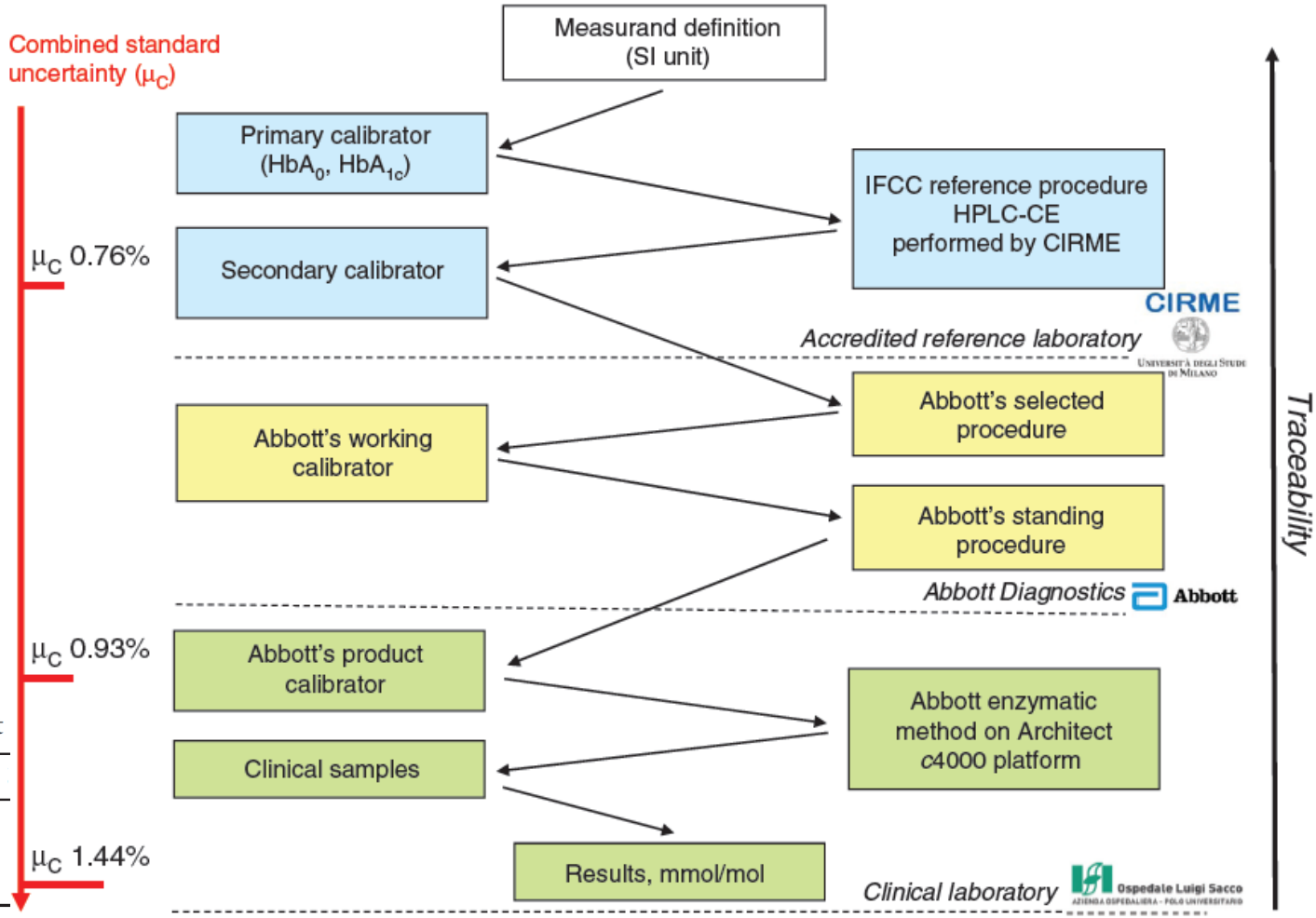
Minimal	≤1.9



Measurement uncertainty is useful for a number of reasons

- Giving objective information about quality of individual laboratory performance
- 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 measuring systems to demonstrate the superiority of those products
- Identifying analytes that need analytical improvement for their clinical use and ask IVD manufacturers to work for improving the quality of assay performance
- Abandonment by users (and consequently by industry) of assays with demonstrated insufficient quality

To estimate measurement uncertainty is not enough!

- Uncertainty of measurement is not a finding to be calculated because you should fulfil accreditation parameters and then immediately forgotten.
- Together with the measurement uncertainty, the laboratory must define the performance specifications to validate it.
- If needed, all attempts must be made to improve on the value.
- Measurement uncertainty must become a key Quality Indicator in your laboratory because it can be used to describe both the performance of an IVD measuring system and the laboratory itself.

Clinical Chemistry 63:9 (2017) 1551

the Clinical Chemist — *Unveiling the Right Side*

An Ode to "Measurement Uncertainty"

Usha Anand*

Once we learn how to calculate "measurement uncertainty" half the battle is won.
If we then ascertain if it affects the interpretation of our results, our job is almost done.

The measurement uncertainty is surely a friend

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