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Centre for Metrological Traceability in Laboratory Medicine (CIRME)

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

13th International Scientific Meeting

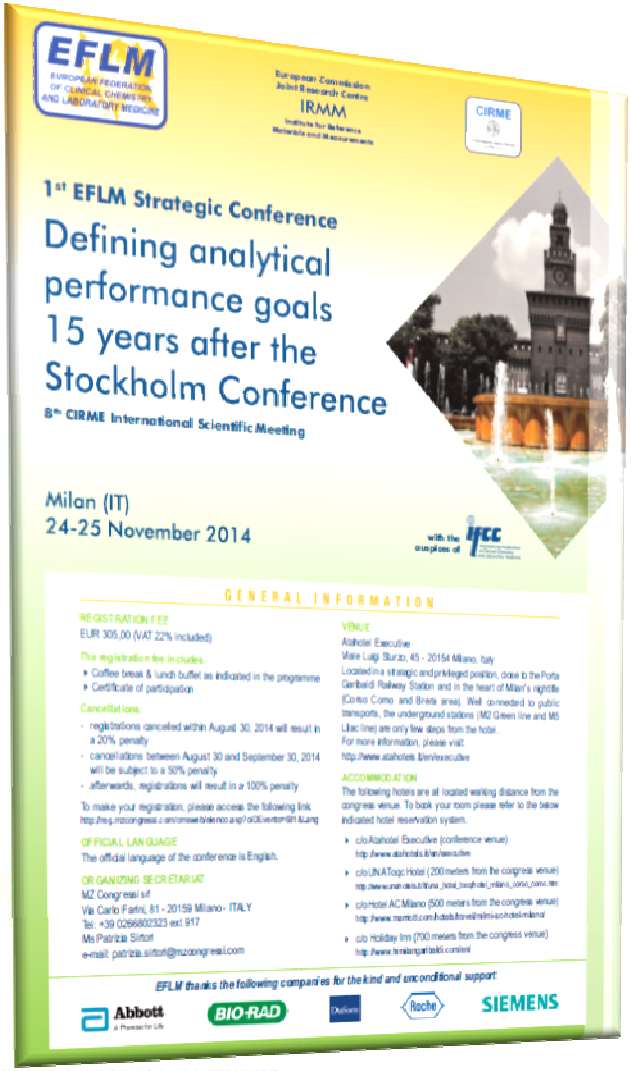
THE INTERNAL QUALITY CONTROL IN THE TRACEABILITY ERA

MILANO, ITALY
November 28th, 2019

Defining performance specifications for IQC

Federica Braga
Research Centre for Metrological Traceability in Laboratory Medicine (CIRME)

OBJECTIVE REDEFINITION OF ANALYTICAL PERFORMANCE SPECIFICATIONS



Model 1: Based on the effect of analytical performance on clinical outcome

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)

Clin Chem Lab Med 2015; 53(6): 833–835

DE GRUYTER

Clin Chem Lab Med 2015; 53(6): 829–832

Editorial

Mauro Panteghini and Sverre Sandberg

Defining analytical performance specifications 15 years after the Stockholm conference

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.

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The importance of grading different quality levels for APS

To move, in case, from desirable to minimum quality goals and, in the meantime, ask reference providers/IVD manufacturers to work for improving the quality of assay performance

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

INTERNAL QUALITY CONTROL (IQC)

Set of procedures and specified materials used by laboratory staff for the repetitive monitoring of analytical performance of measuring systems

- **Estimate of the random source of measurement uncertainty**
- **Check the alignment of measuring systems**

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Set of procedures and specified materials used by laboratory staff for the repetitive monitoring of analytical performance of measuring systems

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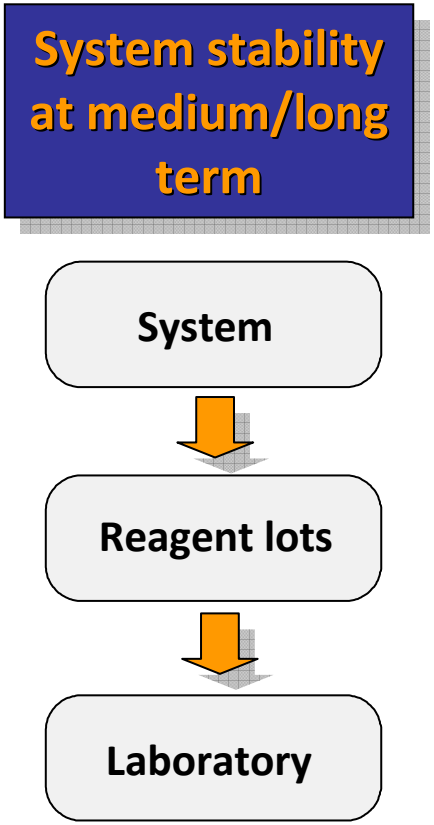
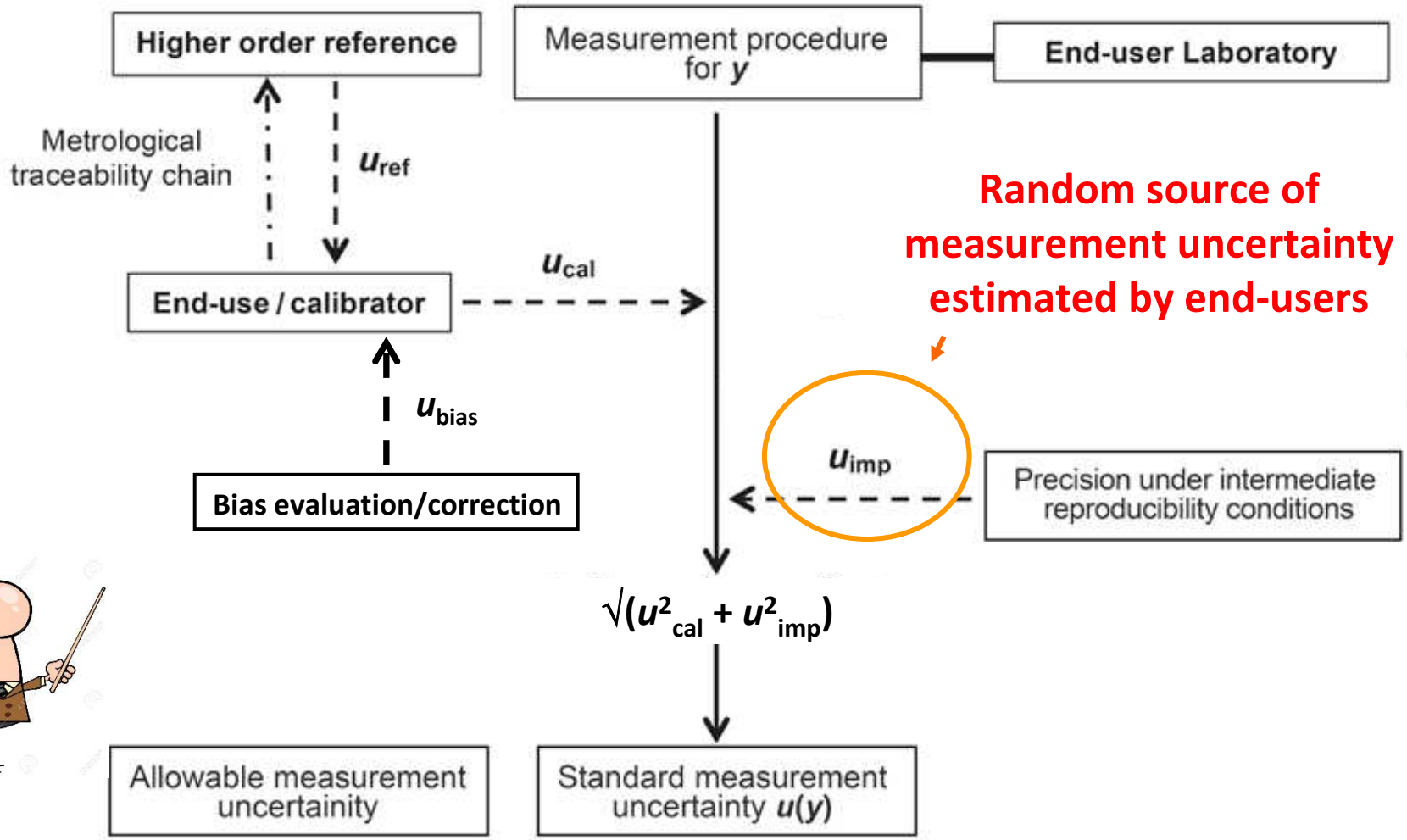
ESTIMATE OF THE RANDOM SOURCE OF MEASURING UNCERTAINTY

- It is the evaluation, through mechanisms of retrospective evaluation, of **UNCERTAINTY CONTRIBUTION** concerning the variability due to the random effects of measuring system and of its use by the individual laboratory (u_{imp})

- **MATERIAL USED:**
  - third part
  - commutable
  - concentration appropriate to the clinical application of the analyte



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



After having derived u_{imp} from IQC, the end-user must calculate u_{result} by the formula:

$$u_{result} = (u^2_{imp} + u^2_{cal})^{1/2}$$

Combined standard uncertainty declared by manufacturer for commercial calibrator.
It must include:
-u_{ref}
-u_{bias} (if some bias has been corrected)

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The u_{result} must fulfill *clinically suitable* **Analytical Performance Specifications**

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	

The measurand has a central role in diagnosis and monitoring of a specific disease

Example MU APS from MODEL 1: OUTCOME-BASED

ANALYTICAL PERFORMANCE SPECIFICATION (APS) FOR CARDIAC TROPONIN MEASUREMENT UNCERTAINTY (MU) IN TERMS OF ALLOWABLE MISCLASSIFICATION RATES

MU	Misclassification
6.7%	0.5-0.9%
9.4%	0.9-1.2%
11.2%	1.2-1.4%
13.0%	1.4-1.8%
16.3%	1.8-3.8%
24.6%	3.8-7.7%
36.2%	7.7-15.2%

Sheehan et al.
Ann Clin Biochem. 2002 May;39:231-6.

[b] Assuming a diagnostic misclassification of 1.8%, [c] 1.0%, and [d] 0.5%.

Quality level	Outcome-based
Minimum	<13%[b]
Desirable	<10%[c]
Optimum	<6%[d]

aacb testing for health

Panteghini M, AACB Troponin Monograph 2012

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

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P-Glucose	P-Calcium ion	U-Magnesium ion
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B-Neutrophil leukocytes	B-Erythrocytes	
	B-Erythrocyte volume fraction	
	B-Erythrocyte volume	
	P-Prothrombin time	
	P-activated partial thromboplastin time	

The measurand has a high homeostatic control

Setting APS for MU from Biological Variation (BV): Concept

If the intra-individual BV is high, the analytical requirements are relatively low.

If, on the other hand, the intra-individual BV is low, it increases the necessity to reduce the analytical part of the total variation.

$$V_{TOT} = (MU^2 + CV_I^2)^{1/2}$$

Measurement uncertainty

Intra-individual biological variability

APS (quality level grading) ➡

≤0.75 x CV_I (minimum)

≤0.50 x CV_I (desirable)

≤0.25 x CV_I (optimum)

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Example MU APS from MODEL 2: BIOLOGICAL VARIATION-BASED

DE GRUYTER Clin Chem Lab Med 2019; aop

Letter to the Editor

Federica Braga*, Simona Ferraro, Simona Borille and Mauro Panteghini

Biological variation of two serum markers for preeclampsia prediction

Parameter	No. of subjects	Mean	CV_A[a]	CV_I, 95% CI	CV_G, 95% CI	II[b]	RCV[c]	n[d]	Analytical performance specifications					
									Standard measurement uncertainty[e]			Allowable bias[f]		
									M	D	O	M	D	O
sFlt-1	14	79.1 ng/L	1.6%	4.0% (1.9–5.2)	7.9% (5.5–13)	0.30	13%	1	≤3.0%	≤2.0%	≤1.0%	≤±3.3%	≤±2.2%	≤±1.1%
PlGF	14	13.0 ng/L	2.6%	7.9% (5.2–10.2)	12.9% (8.9–21.4)	0.38	21%	2	≤5.9%	≤3.9%	≤2.0%	≤±5.7%	≤±3.8%	≤±1.9%
sFlt-1/PlGF ratio	14	6.3	2.9%	8.9% (6.1–11.5)	16.1% (11.2–26.6)	0.36	29%	4	≤6.7%	≤4.4%	≤2.2%	≤±6.9%	≤±4.6%	≤±2.3%

DE GRUYTER

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

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	B-Erythrocyte volume fraction	
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	P-Prothrombin time	
	P-activated partial thromboplastin time	

Neither central diagnostic role nor sufficient homeostatic control

Example MU APS from MODEL 3: BASED ON THE STATE OF ART

Human chorionic gonadotropin (hCG)

STATE OF ART: "the highest level of analytical performance technically achievable"

Analytical system	MU (6 months)
Modular Evo (Roche)	2.3%
Architect i2000SR	5.4%
Alinity i (Abbott)	3.8%

APS FOR hCG MEASUREMENT UNCERTAINTY

NOTE: If you consider this APS as desirable, you can also modulate the quality level to, e.g., minimum goal [2.3% + ½ 2.3% = 3.5%]

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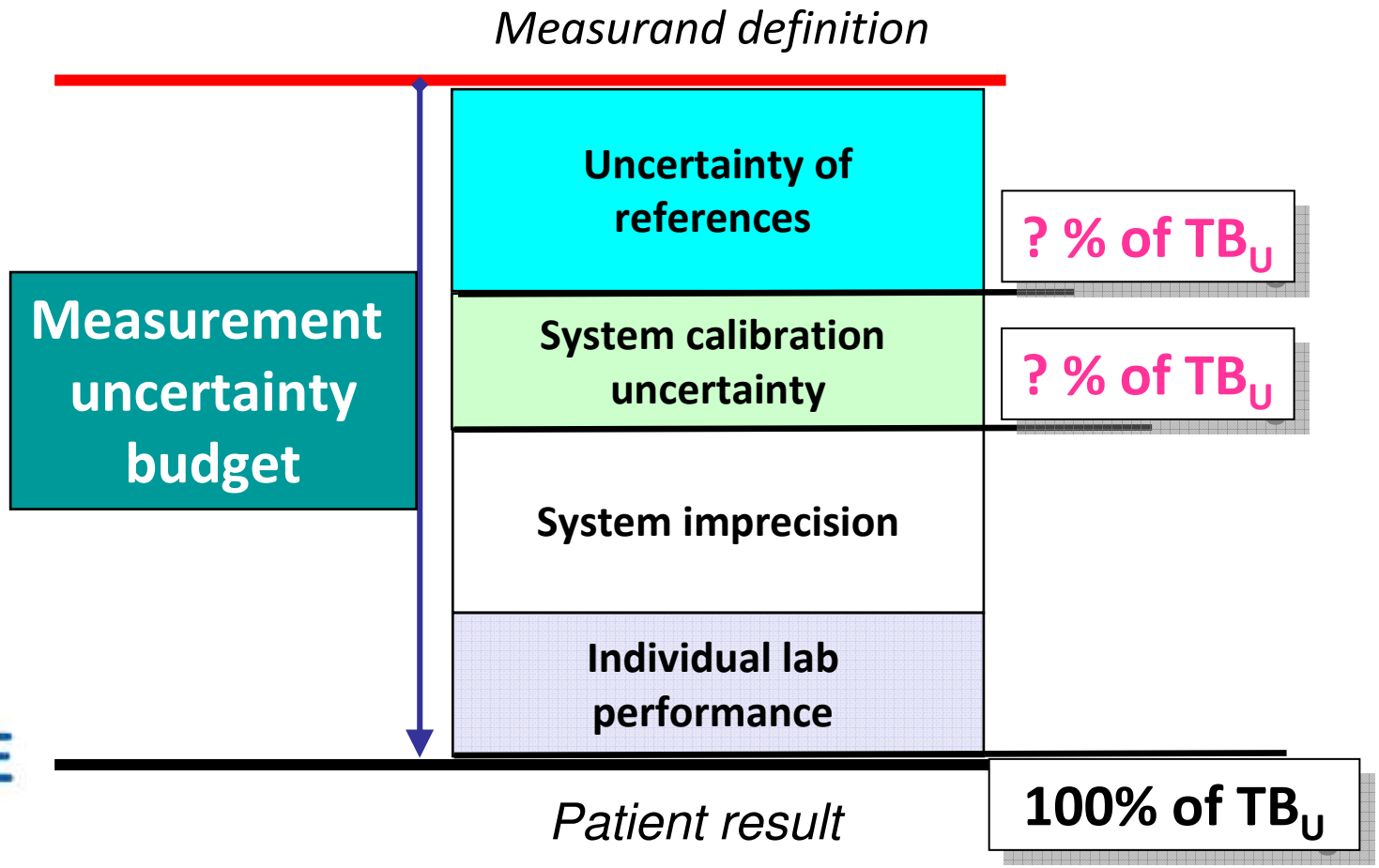
How much of the total MU budget [TB_U] should be used across the different steps of metrological traceability chain?



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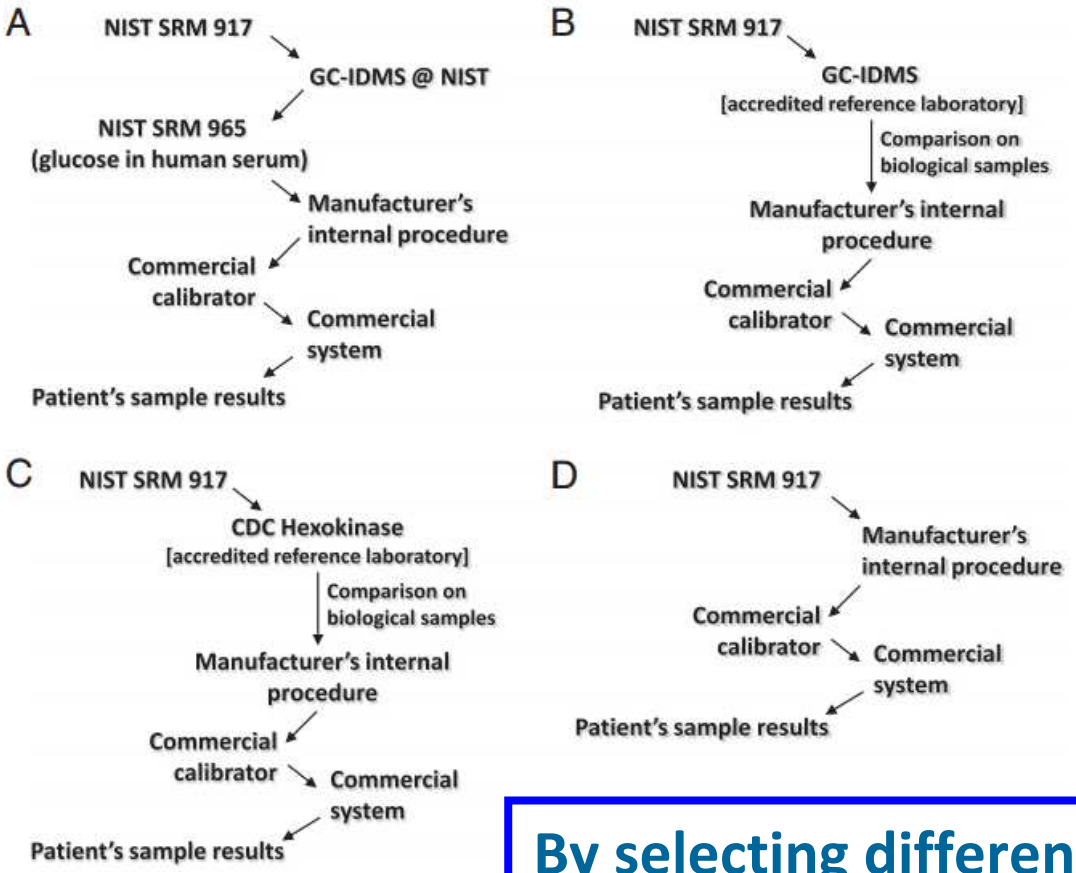
TRACEABILITY CHAINS AVAILABLE FOR IVD MANUFACTURERS FOR PLASMA GLUCOSE



By selecting different traceability chains, IVD manufacturers may spend different amounts of the total MU budget in implementing traceability of their measuring systems

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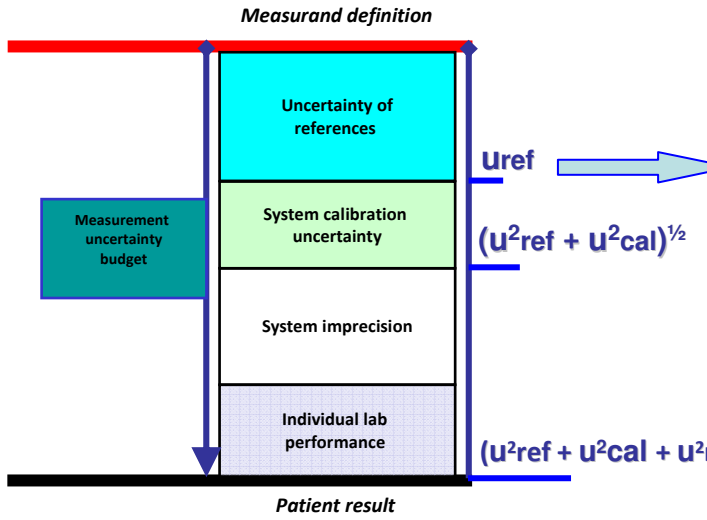
Braga F & Panteghini M, Clin Chim Acta 2014;432:55
Pasqualetti S, Braga F, Panteghini M, Clin Biochem 2017; 50:587

Company	Platform	Principle of commercial method	Calibrator	Declared standard uncertainty[a]	Higher-order reference employed		Type of traceability chain used[b]	MU associated with the selected chain
					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%

Glucose uncertainty

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 MU on clinical samples

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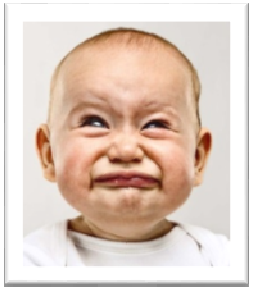
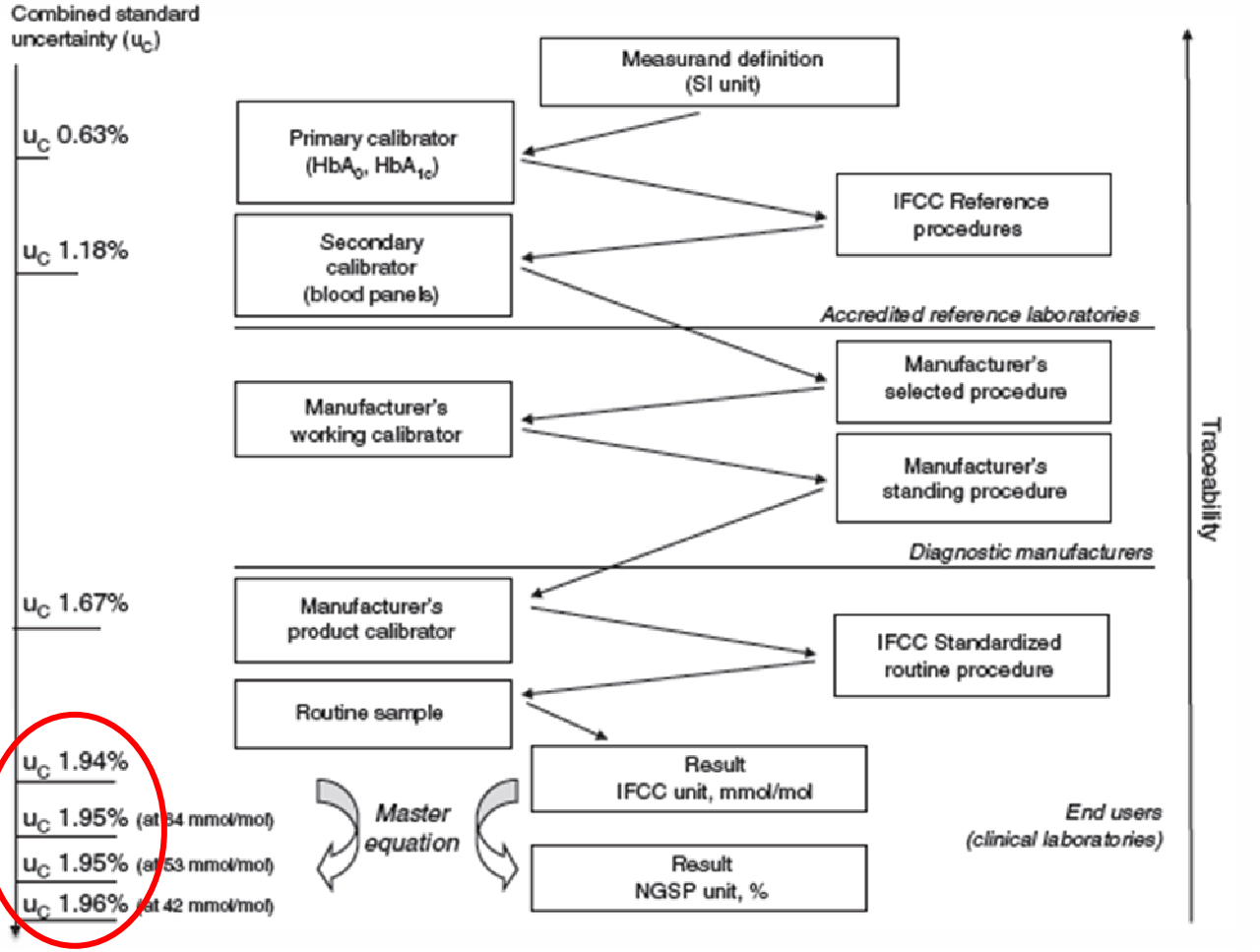
Braga F & Panteghini M, Clin Chim Acta 2014;432:55
Pasqualetti S, Braga F, Panteghini M, Clin Biochem 2017; 50:587

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. decrease the imprecision (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

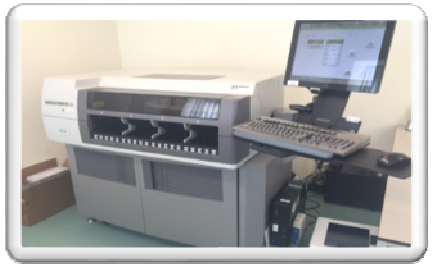
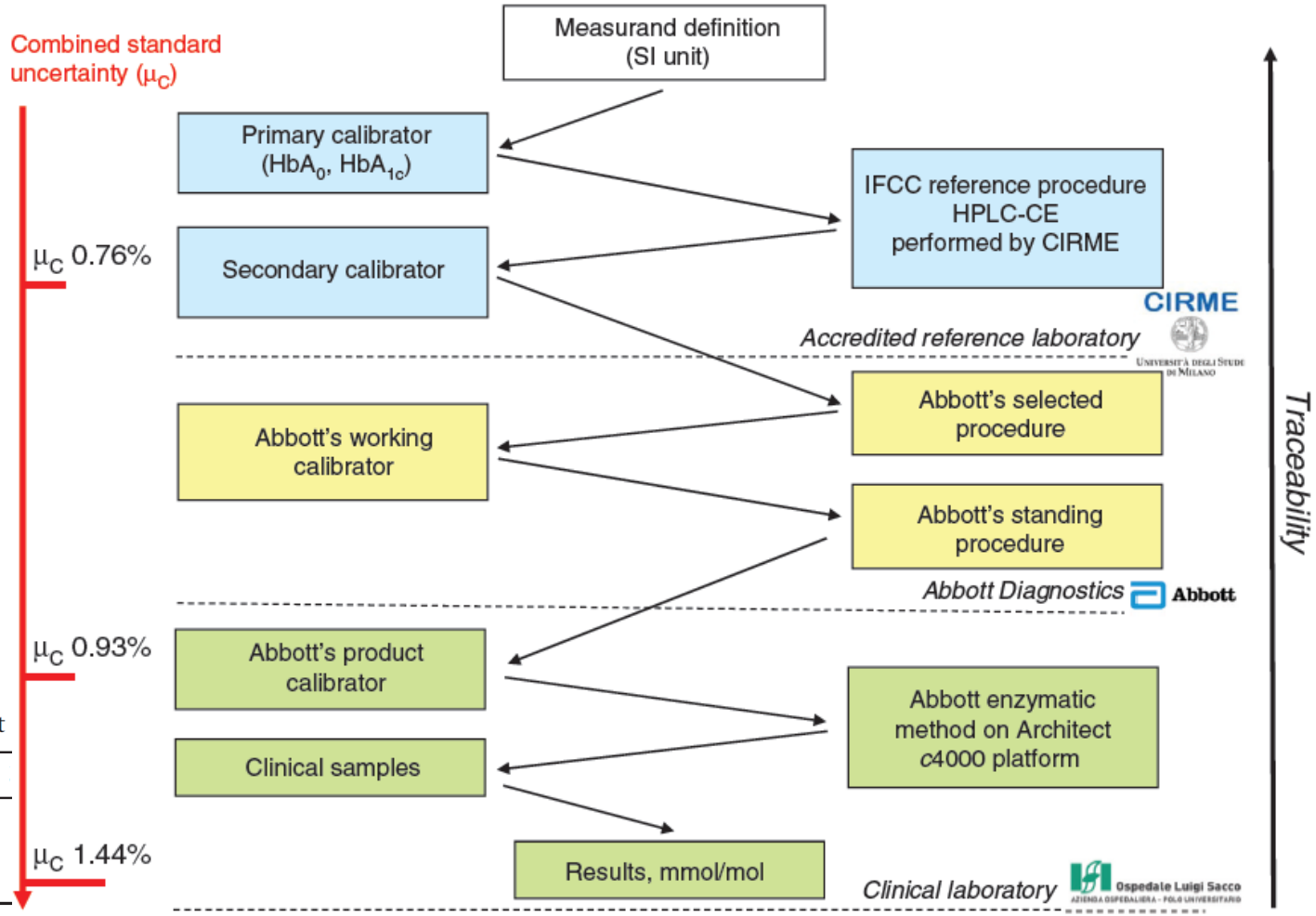


Table 3
Analytical goals for HbA_{1c} measurement

Quality level	U_C
Optimal	≤0.6
Desirable	≤1.3
Minimal	≤1.9



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Set of procedures and specified materials used by laboratory staff for the repetitive monitoring of analytical performance of measuring systems

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If the traceability of the measuring system to higher-order references is granted, the control materials from the IVD manufacturers as a part of the CE-marked measuring system have to be a good surrogate of the employed reference in order to permit checking the correct alignment to the declared reference.

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IQC Component I

THIS IS A ROLE OF IVD MANUFACTURERS

The target value of control material must be unbiased

What does it mean?

It must be calculated as mean value of replicate measurements of control material on the same measuring system calibrated to the selected reference measurement system with a negligible bias

What does it mean?

The calibrator bias becomes negligible when it permits to fulfill clinically suitable APS for MU on clinical samples

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Example BIAS APS from MODEL 1: OUTCOME-BASED

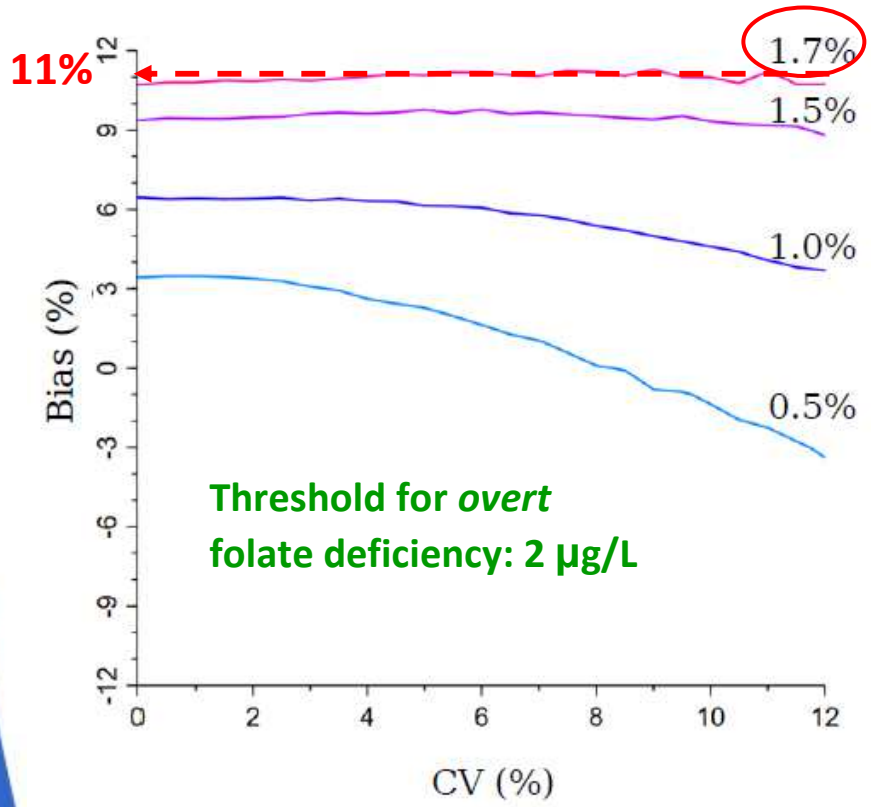
DE GRUYTER Clin Chem Lab Med 2019; aop

Letter to the Editor

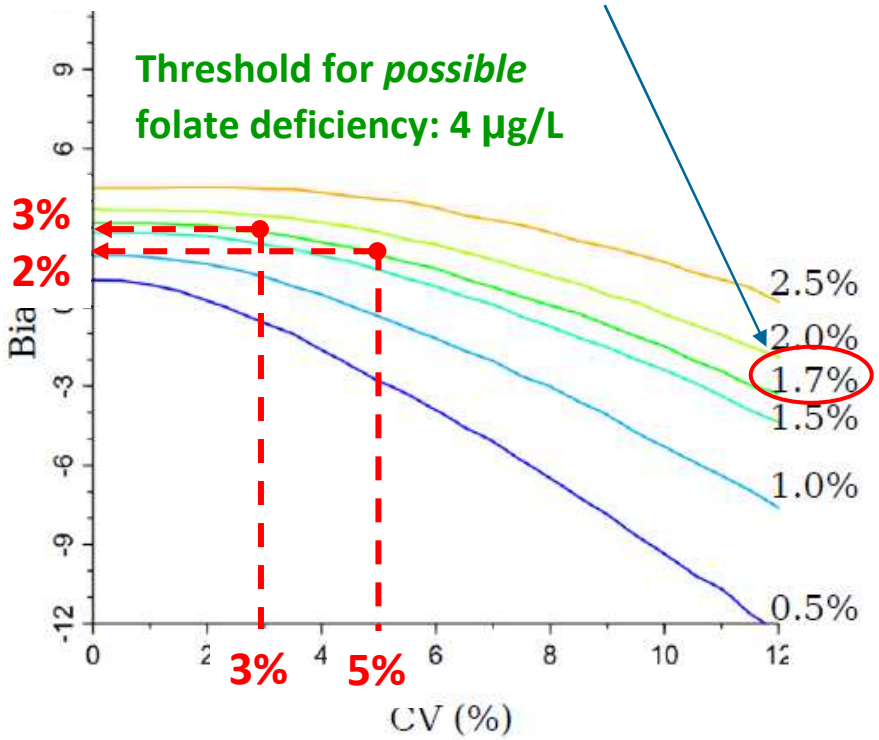
Simona Ferraro*, Andrew W. Lyon, Federica Braga and Mauro Panteghini

Definition of analytical quality specifications for serum total folate measurements using a simulation outcome-based model

Plots of the fraction of population misclassification rate [in terms of false negatives] as a function of assay bias and imprecision at mean folate of 2 & 4 µg/L



Clinically acceptable misclassification



BIAS APS from MODEL 2: BIOLOGICAL VARIATION-BASED

Analytical Performance Specifications for bias derived from biological variation of the measurand

$$\leq 0.375\ (CV_I^2 + CV_G^2)^{0.5}\ \text{(Minimum)}$$

$$\leq 0.25\ (CV_I^2 + CV_G^2)^{0.5}\ \text{(Desirable)}$$

$$\leq 0.125\ (CV_I^2 + CV_G^2)^{0.5}\ \text{(Optimum)}$$

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Example BIAS APS from MODEL 2: BIOLOGICAL VARIATION-BASED

SERUM CREATININE

Clinical Chemistry 63:9
1527–1536 (2017)

Other Areas of Clinical Chemistry

The EuBIVAS Project: Within- and Between-Subject Biological Variation Data for Serum Creatinine Using Enzymatic and Alkaline Picrate Methods and Implications for Monitoring

Anna Carobene,[1,11*] Irene Marino,[1] Abdurrahman Coşkun,[2,11] Mustafa Serteser,[2] Ibrahim Unsal,[2] Elena Guerra,[1] William A. Bartlett,[3,11] Sverre Sandberg,[4,5,11] Aasne Karine Aarsand,[4,11] Marit Sverresdotter Sylte,[4] Thomas Røraas,[5,11] Una Ørvim Sølvik,[6] Pilar Fernandez-Calle,[7,11] Jorge Díaz-Garzón,[7] Francesca Tosato,[8] Mario Plebani,[8] Niels Jonker,[9,11] Gerhard Barla,[9] and Ferruccio Ceriotti[10] on behalf of the European Biological Variation Study of the EFLM Working Group on Biological Variation

- Intra-individual BV (CV_I): 4.4%
- Inter-individual BV (CV_G): 17.1%

APS FOR CREATININE BIAS

Minimum: 6.6%
Desirable: 4.4%
Optimum: 2.2%

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Example BIAS APS from MODEL 3: BASED ON STATE OF ART

URINE SODIUM

STATE OF ART: "the highest level of analytical performance technically achievable"

Elaborato per singolo campione n. 1083326

Azienda Ospedaliero Universitaria Careggi

Centro di Riferimento Sicurezza e Qualità
Valutazione esterna di qualità
BIOCHIMICA URINA - Ciclo 2019

RegioneLombardia
Direzione Generale Welfare

Centro n. 04120

Riepilogo x Metodo risultati numerici (> 7 Centri)				Intra-assay variability
Metodo	N.	Out	M.	
I.S.E. INDIRETTA	69	1	82.566	4.4
I.S.E. IND ROCHE COBAS 6000-8000	64	1	81.222	2.9
I.S.E. INDIRETTA/ARCHITECT	20	1	81.039	2.5
I.S.E. IND. DIMENSION/VISTA	12	0	80.452	5.8

APS FOR URINE SODIUM BIAS

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NOTE: If you consider this APS as desirable, you can also modulate the quality level to, e.g., minimum goal [2.5% + ½ 2.5% = 3.8%]

THE MANUFACTURERS' SPECIFICATIONS TO VALIDATE THE CALIBRATOR TRACEABILITY TO THE SELECTED REFERENCE SYSTEM ARE SELDOM ESTABLISHED ON THE BASIS OF CLINICALLY SUITABLE BIAS GOAL!

Abbott - Creatinine Enzymatic Assay -

→Manufacturer's calibrator release specification: ±5% from the target

NOTE: Desirable bias on clinical samples: ±4.4%

BECKMAN COULTER - Serum folate -

→Manufacturer's calibrator release specification: ±10% from the target

NOTE: Desirable bias on clinical samples: ±3.0%

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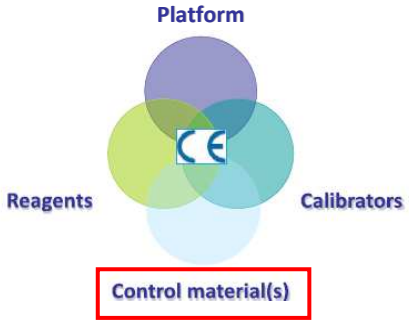
CHECK THE ALIGNMENT OF MEASURING SYSTEM

- It is the verification of the measuring system alignment over time
- **MATERIAL USED:** control material(s) provided by IVD manufacturers as a component of the whole measuring system



  - unbiased target value
  - concentrations appropriate to the clinical application of the analyte
  - assigned acceptability range permitting to fulfil APS for suitable MU on clinical samples

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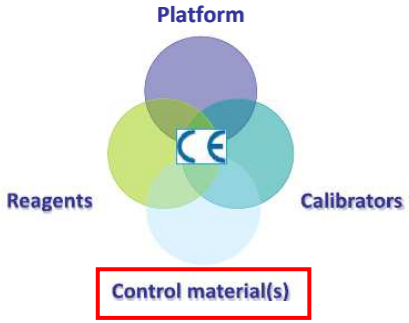

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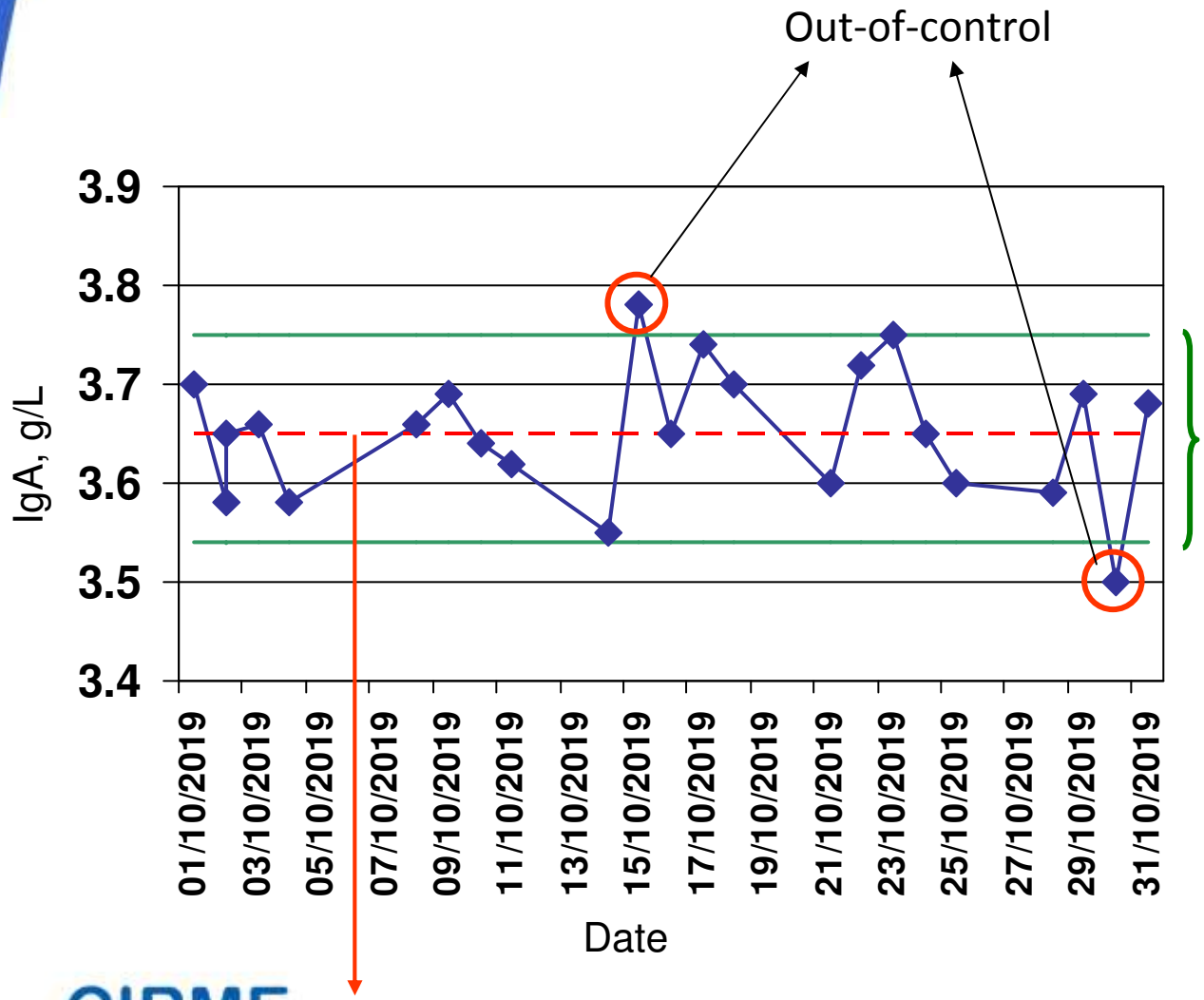

ANALYTICAL PERFORMANCE SPECIFICATION FOR MEASUREMENT UNCERTAINTY

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UNBIASED TARGET VALUE OF CONTROL MATERIAL:

mean value of replicate measurements of control material on the same measuring system calibrated to the selected reference measurement system with a negligible bias

However…

- **The acceptability range provided by manufacturers is based on the statistical dispersion of data obtained by *n* laboratories using the measuring system (e.g., ±2SD or ±20%): no relationship with clinically suitable APS.**
- **The target value of control materials is often not verified for bias: it is simply the mean value of many replicate measurements by different laboratories using the same measuring system.**
- **On many analytical systems it is only possible to set statistical dispersion parameters.**

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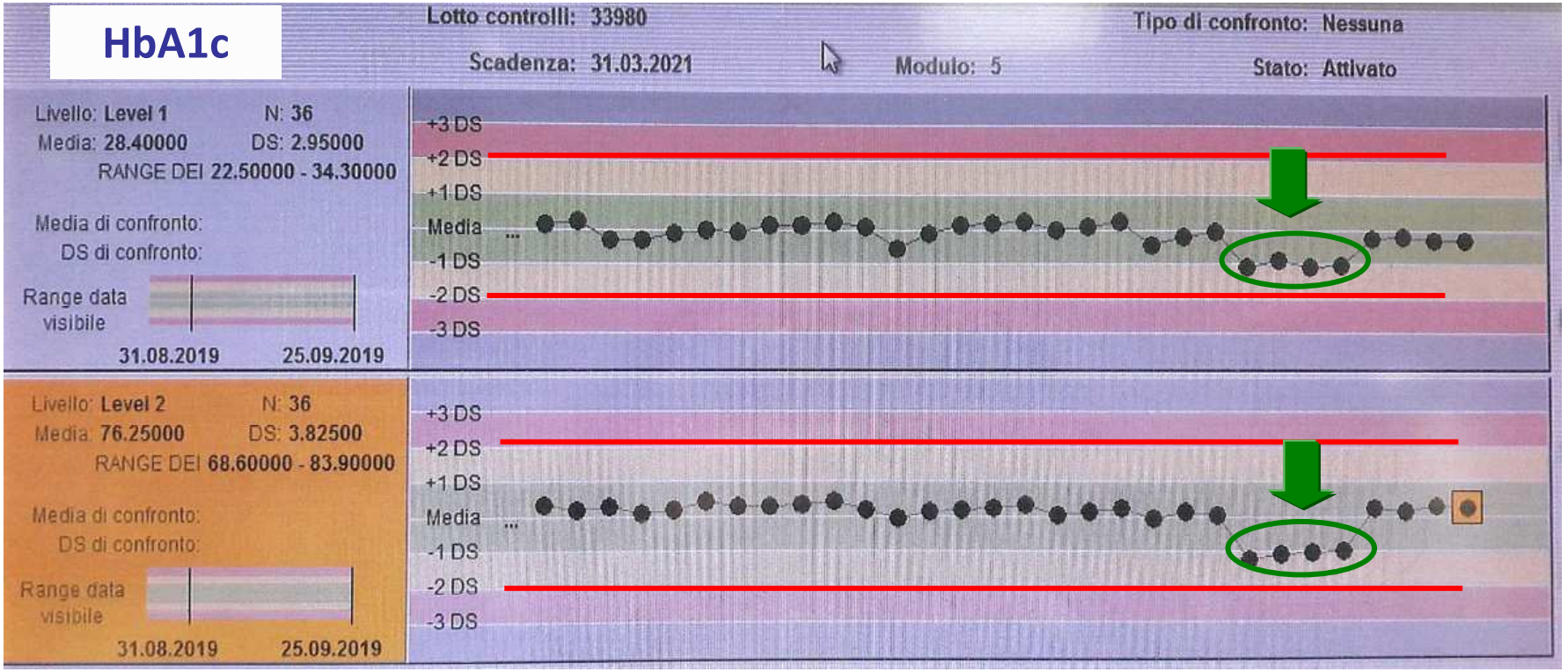
CASE STUDY



By using the acceptability range provided by the manufacturer (±2 SD), the control shift, causing an excessively elevated random MU on patient samples, was not identified.

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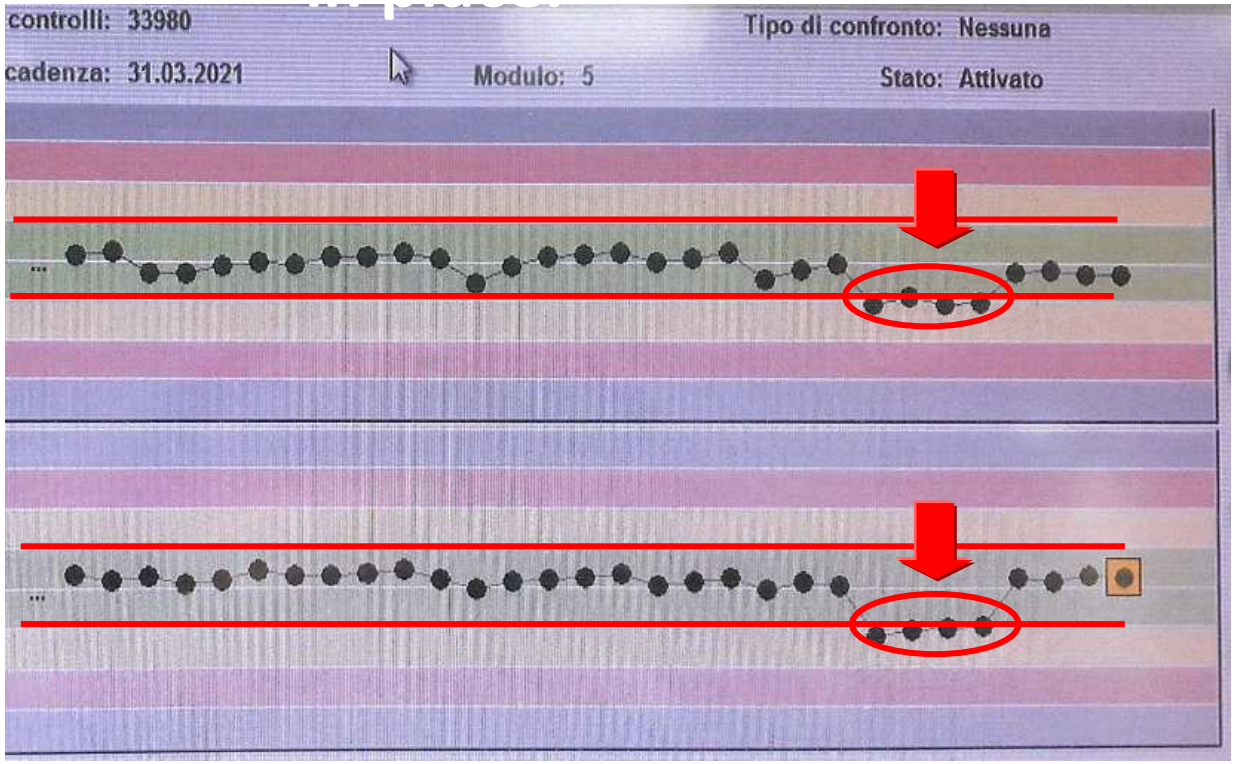
However, if the acceptability range was defined according to the appropriate MU APS, the shift of the measuring system, significantly impacting on MU of patient results, would have been identified and corrective actions immediately put

APS fulfilling MU



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Performance specifications & IQC

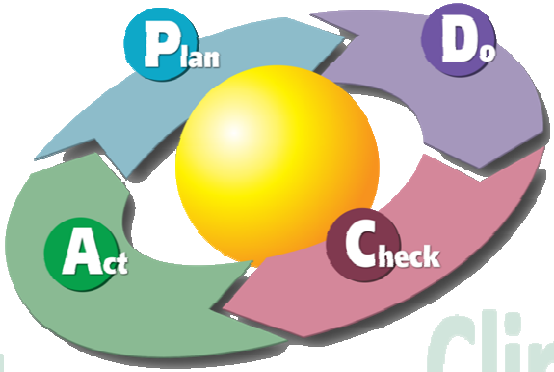
URGENT ACTIONS !

Define clinically suitable APS for MU (and bias) according to the Milan models

Validate the calibrator traceability to the selected reference system and assign unbiased target values and acceptability range to control materials permitting to fulfil APS for suitable MU on clinical samples

Laboratory profession

IVD manufacturers



All stakeholders

Clinical laboratories

Improve the IQC process and judging criteria to establish a direct link between the laboratory performance and clinically suitable APS

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Thank you for your kind attention!

F. Braga

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