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Centre for Metrological Traceability in Laboratory Medicine (CIRME)

Director: Prof. Mauro Panteghini

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

Definition of performance specifications for metrological traceability implementation

Mauro Panteghini

Accurate Results for Patient Care Workshop 2019
A JCTLM Members' and Stakeholders' meeting
2-3 December 2019, BIPM

JCTLM
Accurate results for patient care

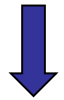
Steps of the process and different responsibilities in implementing traceability of patient results and defining their uncertainty

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

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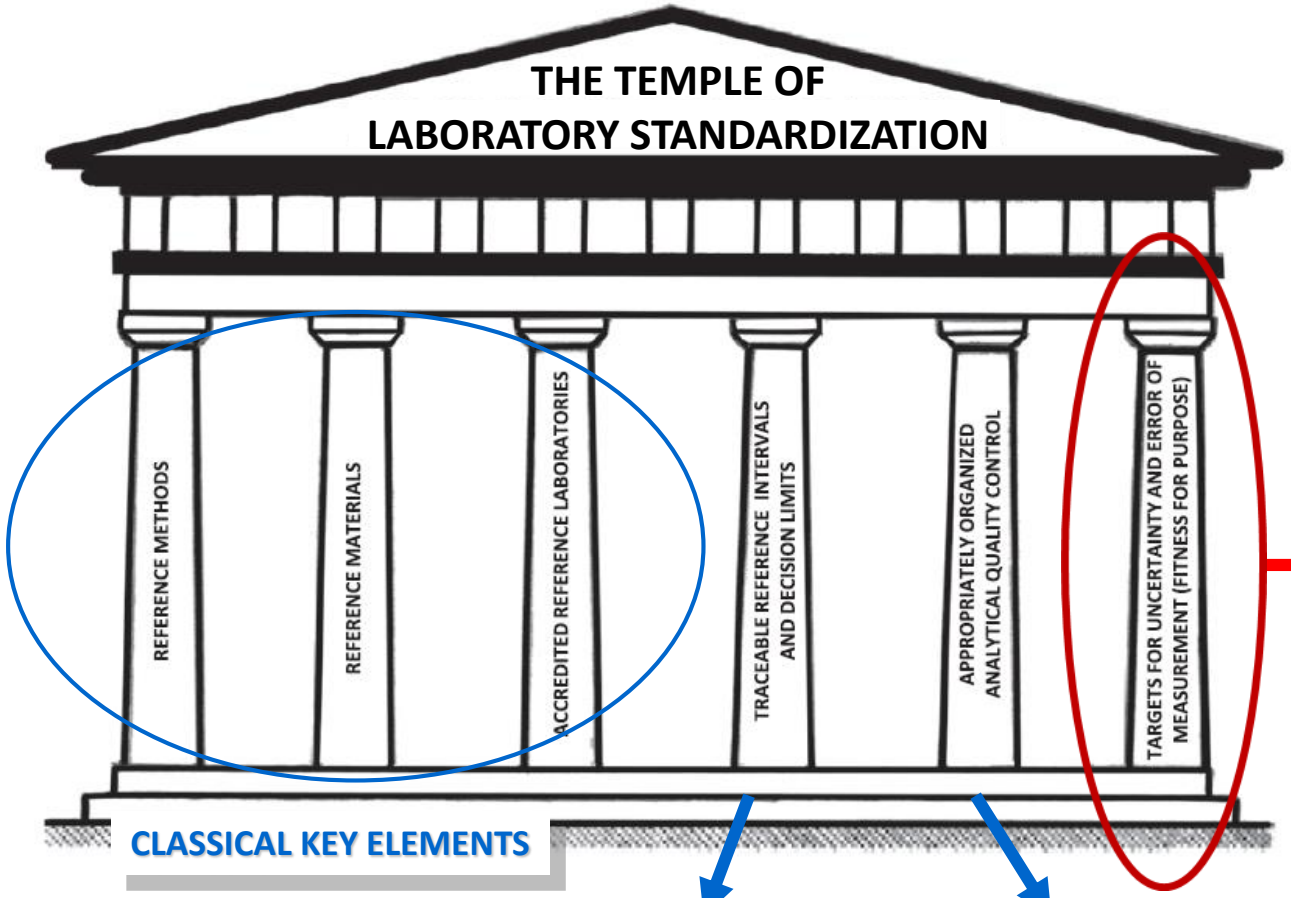
Adapted from Panteghini M, Clin Chem Lab Med 2010;48:7

THE TEMPLE OF LABORATORY STANDARDIZATION



CLASSICAL KEY ELEMENTS

6th pillar
TARGETS FOR UNCERTAINTY AND MEASUREMENT ERROR THAT FIT FOR PURPOSE

4th pillar
TRACEABLE REFERENCE INTERVALS AND DECISION LIMITS

5th pillar
ANALYTICAL (INTERNAL AND EXTERNAL) QUALITY CONTROL THAT MEETS METROLOGICAL CRITERIA

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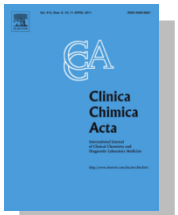


Braga F & Panteghini M, Clin Chim Acta 2014;432:55

"THE TRACEABILITY REVOLUTION MANIFESTO"

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

- 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 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 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.

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.

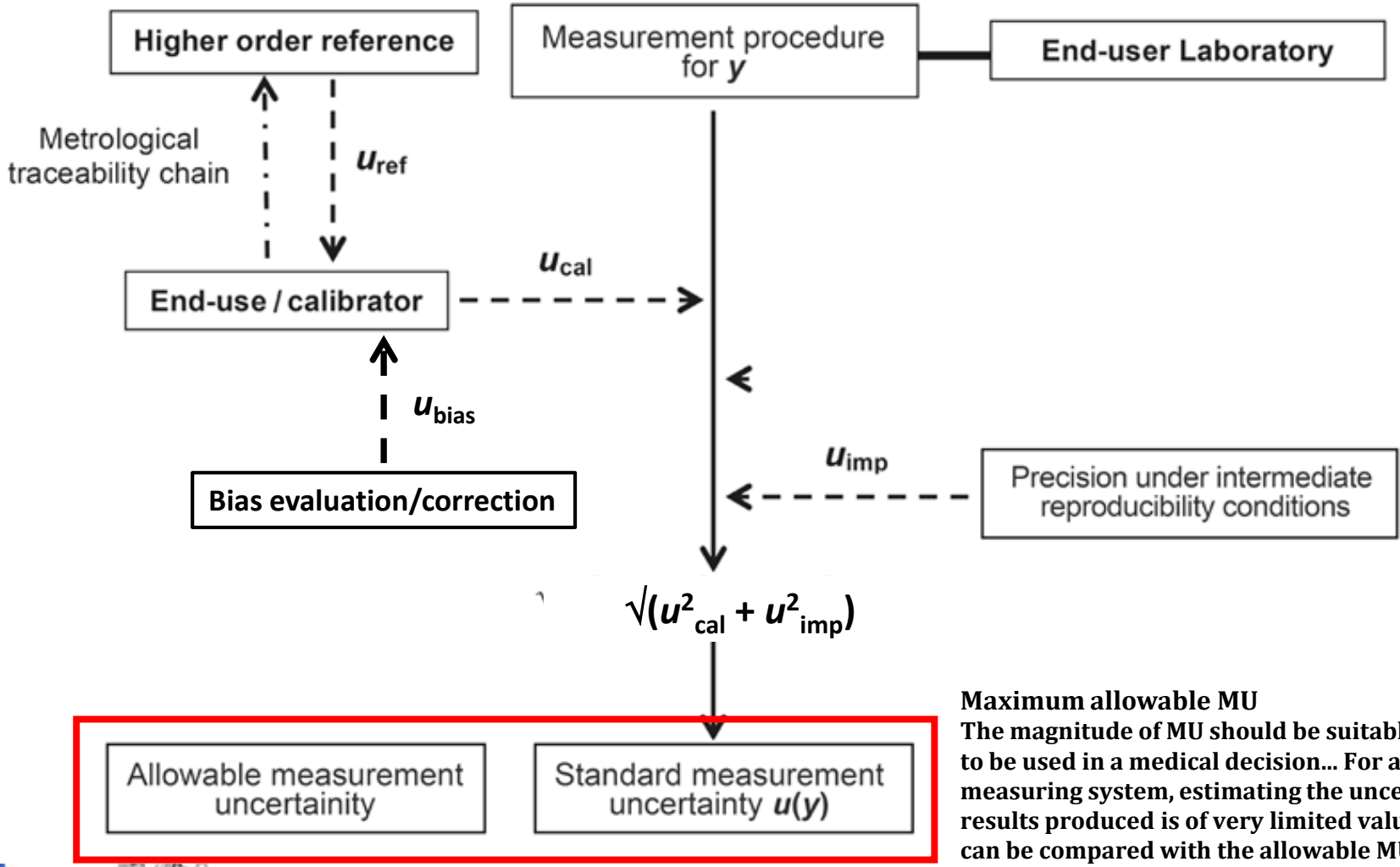
Braga F & Panteghini M, Clin Chim Acta 2014;432:55

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

ISO/TS 20914:2019

MEDICAL LABORATORIES -- PRACTICAL GUIDANCE FOR THE ESTIMATION OF MEASUREMENT UNCERTAINTY



Maximum allowable MU

The magnitude of MU should be suitable for a result to be used in a medical decision... For a given measuring system, estimating the uncertainty of the results produced is of very limited value unless it can be compared with the allowable MU based on the quality of results required for medical use.

How to define maximum allowable MU

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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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

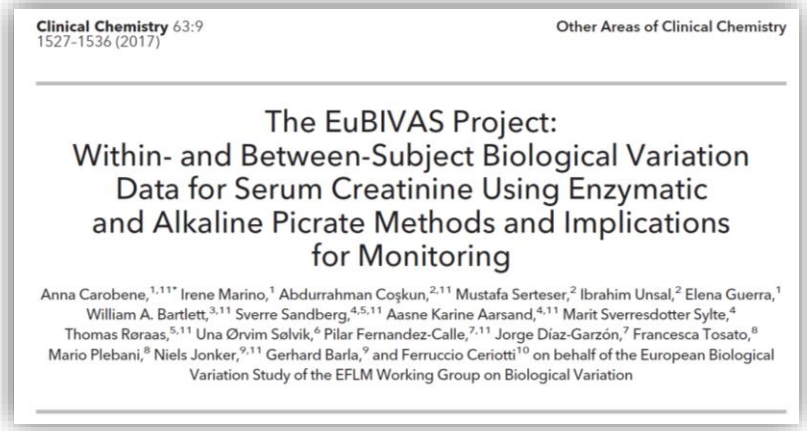
The measurand has a high homeostatic control

Neither central diagnostic role nor sufficient homeostatic control

EXAMPLE

Creatinine in serum has a strict metabolic control

Apply MILAN APS MODEL 2



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

Mean intra-individual biological variation (CV_I)
4.4%

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Setting performance specifications 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

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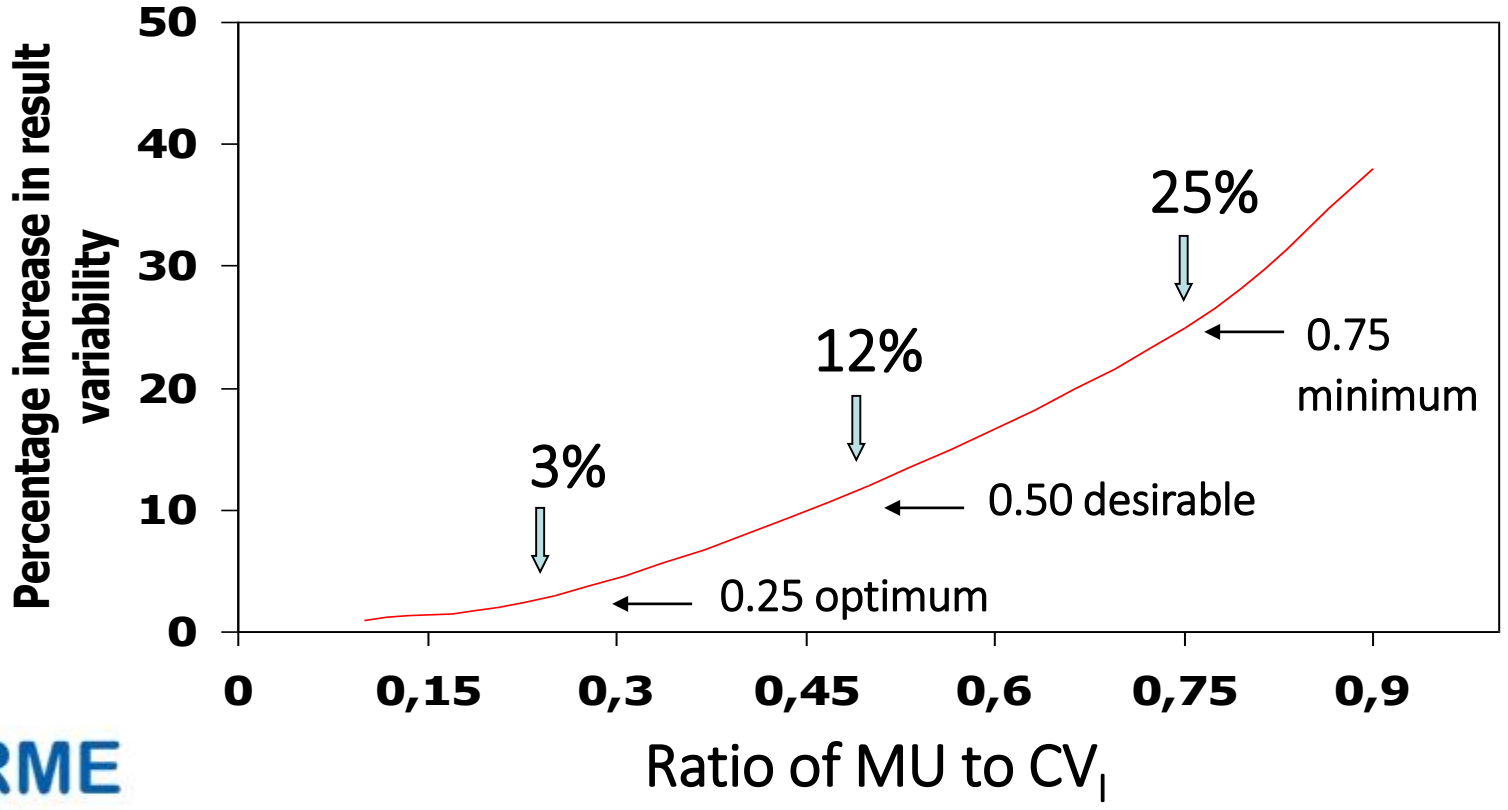
Impact of MU on total variability of results



[Adapted from Fraser CG et al. Ann Clin Biochem 1997;34:8]

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Performance specifications for MU of creatinine measurement on clinical samples

Biological variation model

Average CV_I = 4.4%

≤0.75 x CV_I (minimum) = 3.3%

≤0.50 x CV_I (desirable) = 2.2%

≤0.25 x CV_I (optimum) = 1.1%

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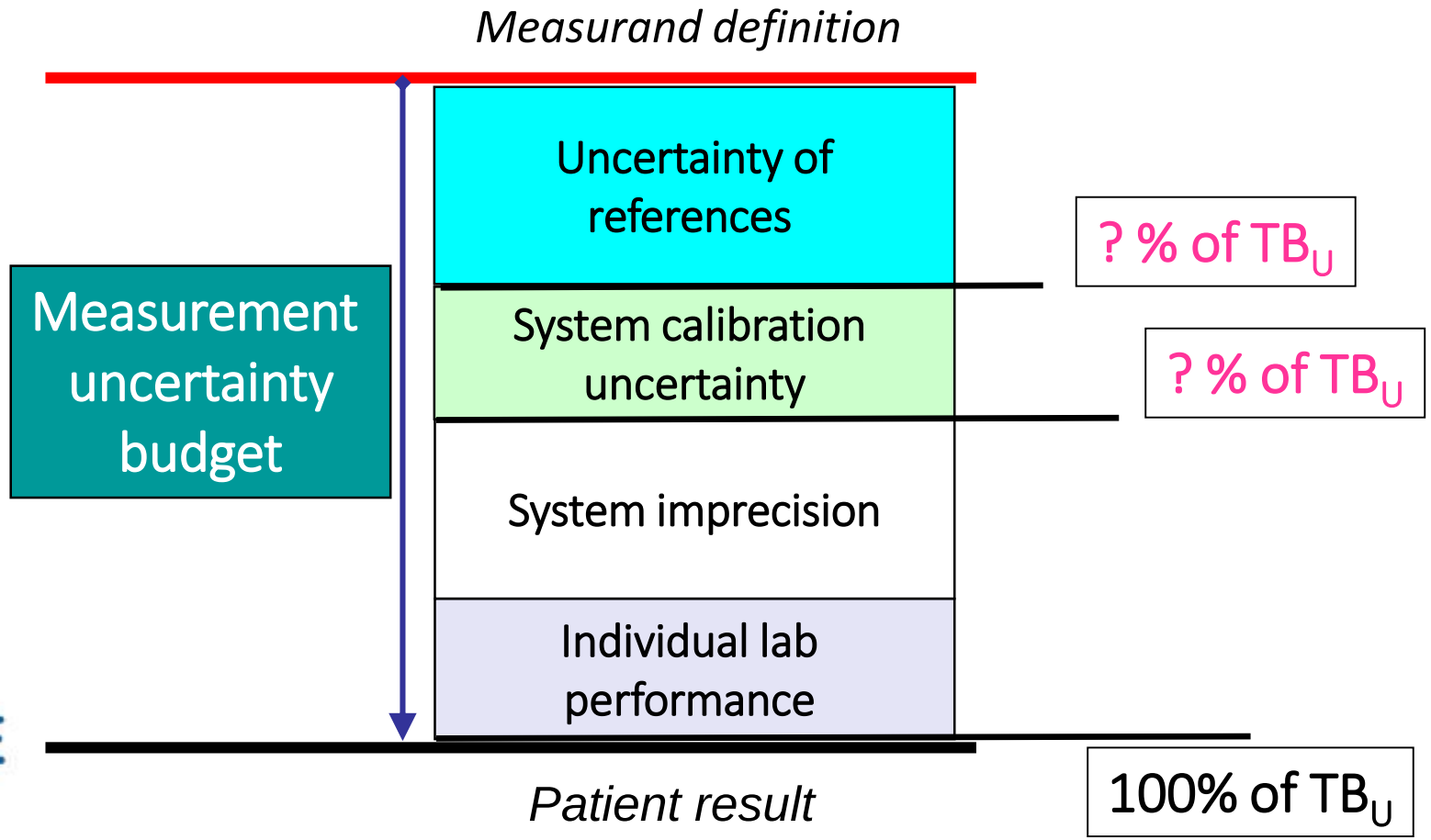
How much of the total MU budget [TB_U] should be used across the different steps of metrological traceability chain?



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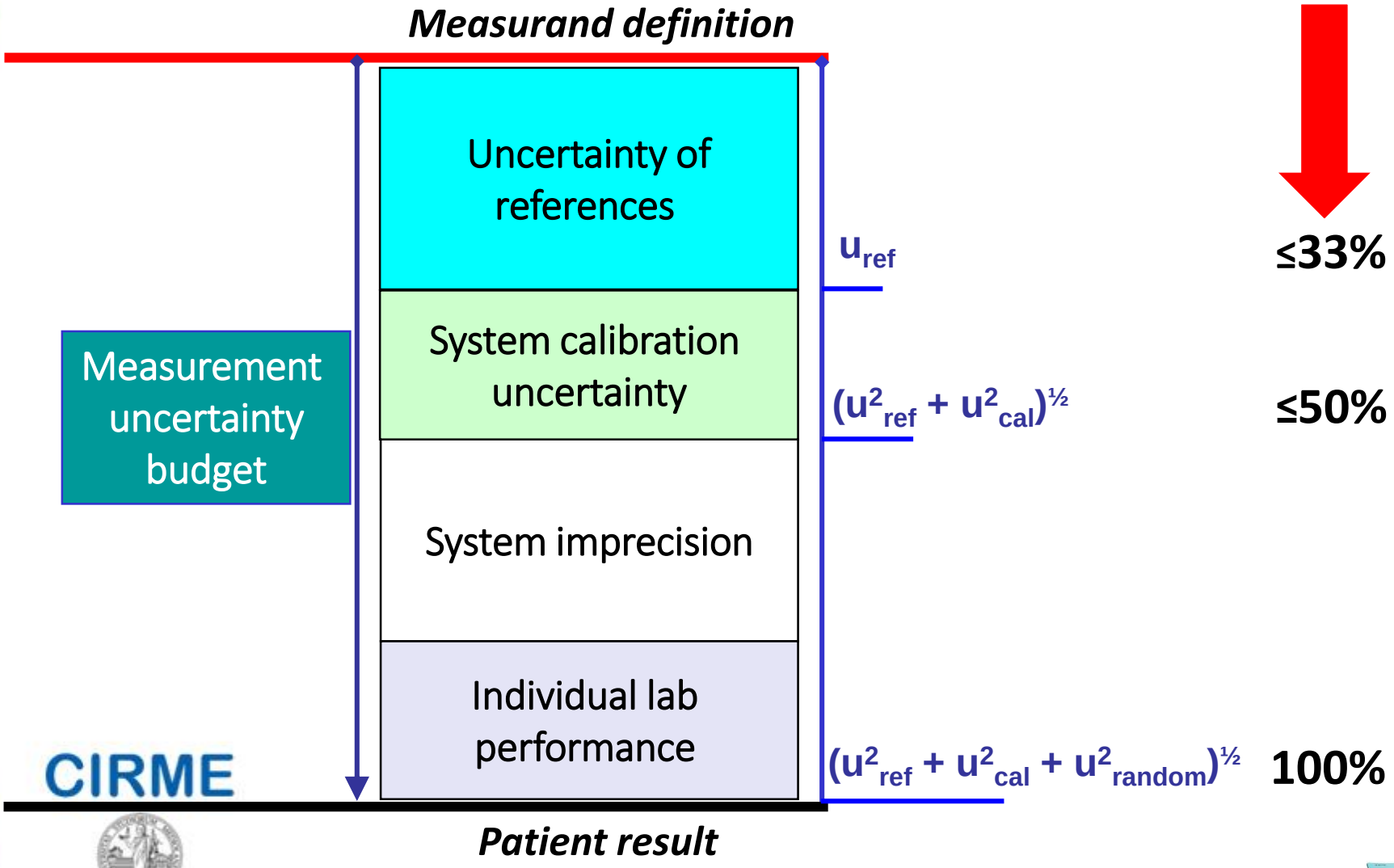
Recommended limits for combined MU budget (expressed as percentage of total budget goal)



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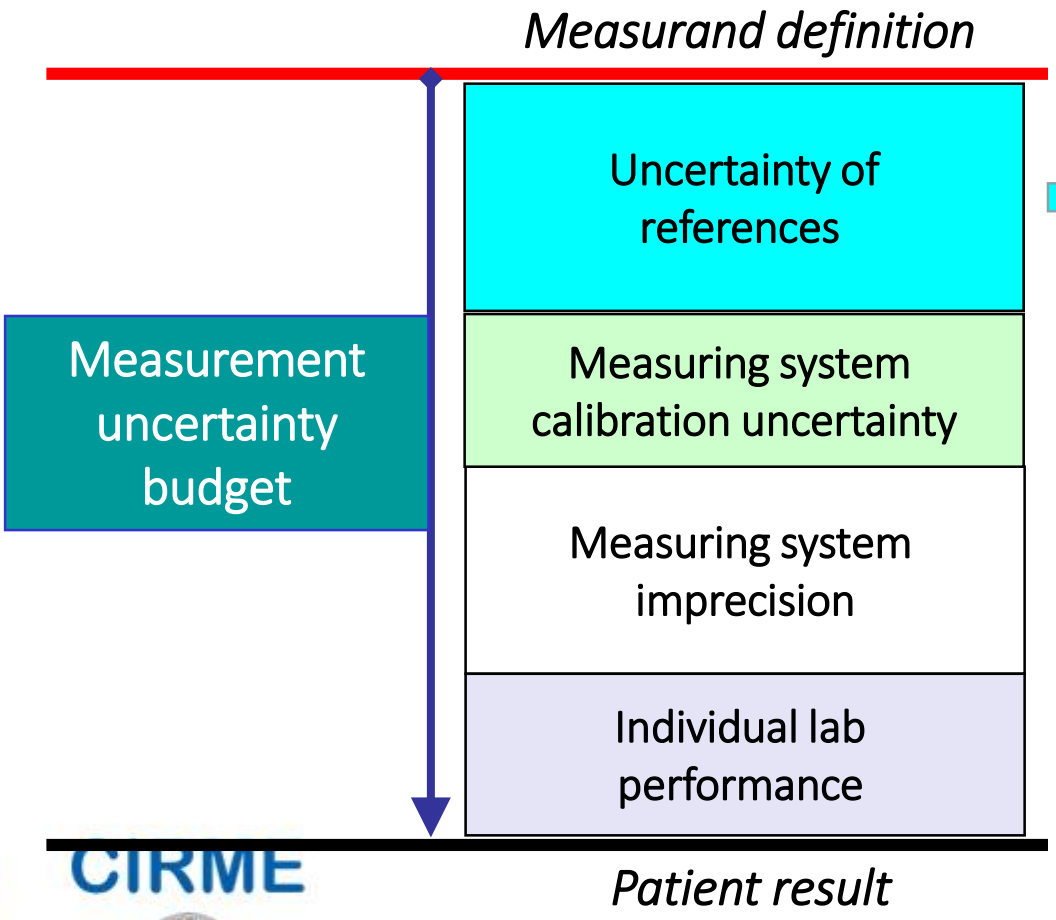
Braga F, Infusino I, Panteghini M. Clin Chem Lab Med 2015;53:905

Reference provider contribution to the MU budget



Reference provider

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

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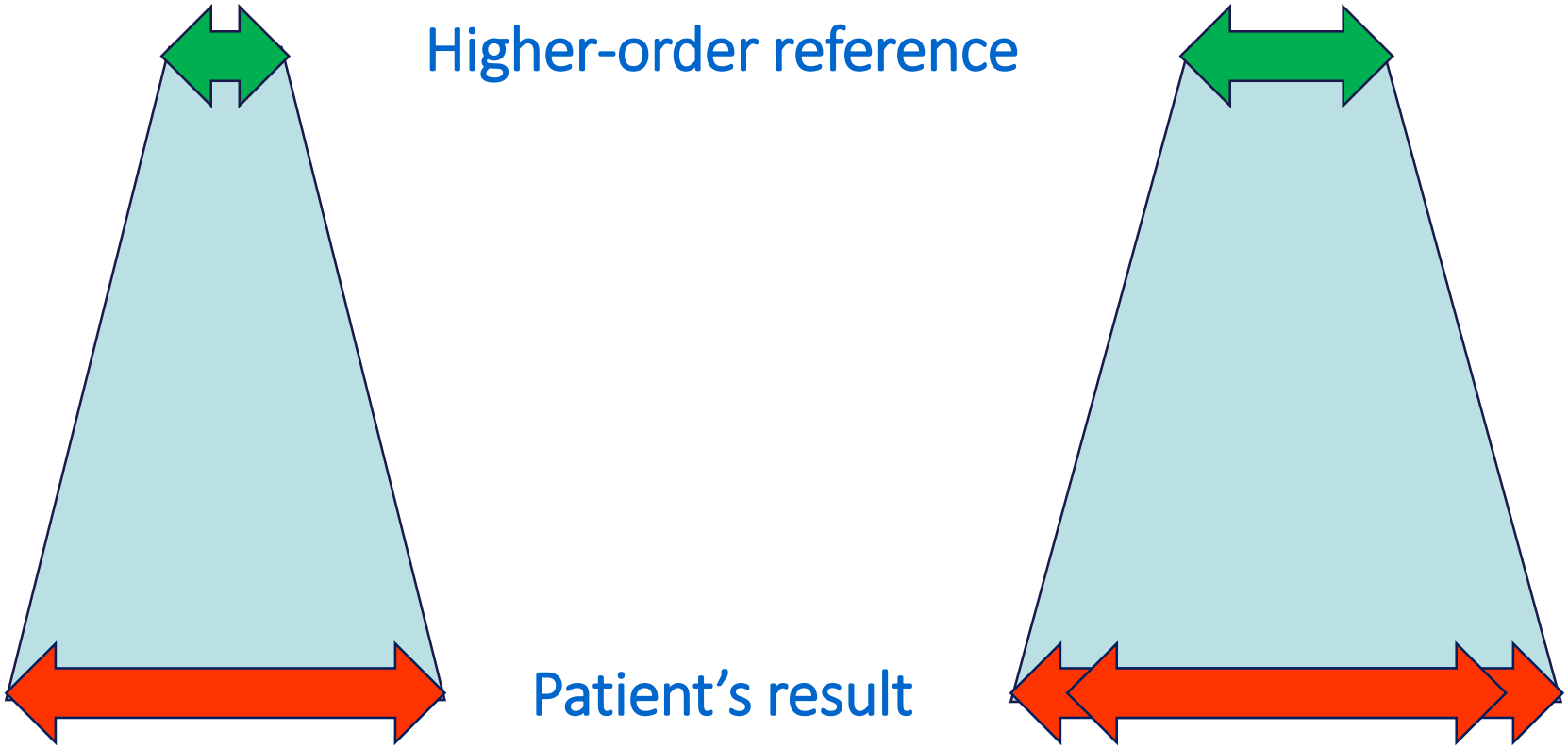
Uncertainty of references may strongly influence the uncertainty of patient's results



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Adapted from G. Jones, 5th CIRME International Scientific Meeting – Milan, IT – Nov 2011

Turning the problem upside down: focus first on the field assays

I. Infusino, M. Panteghini Clin Biochem 2018;57:3

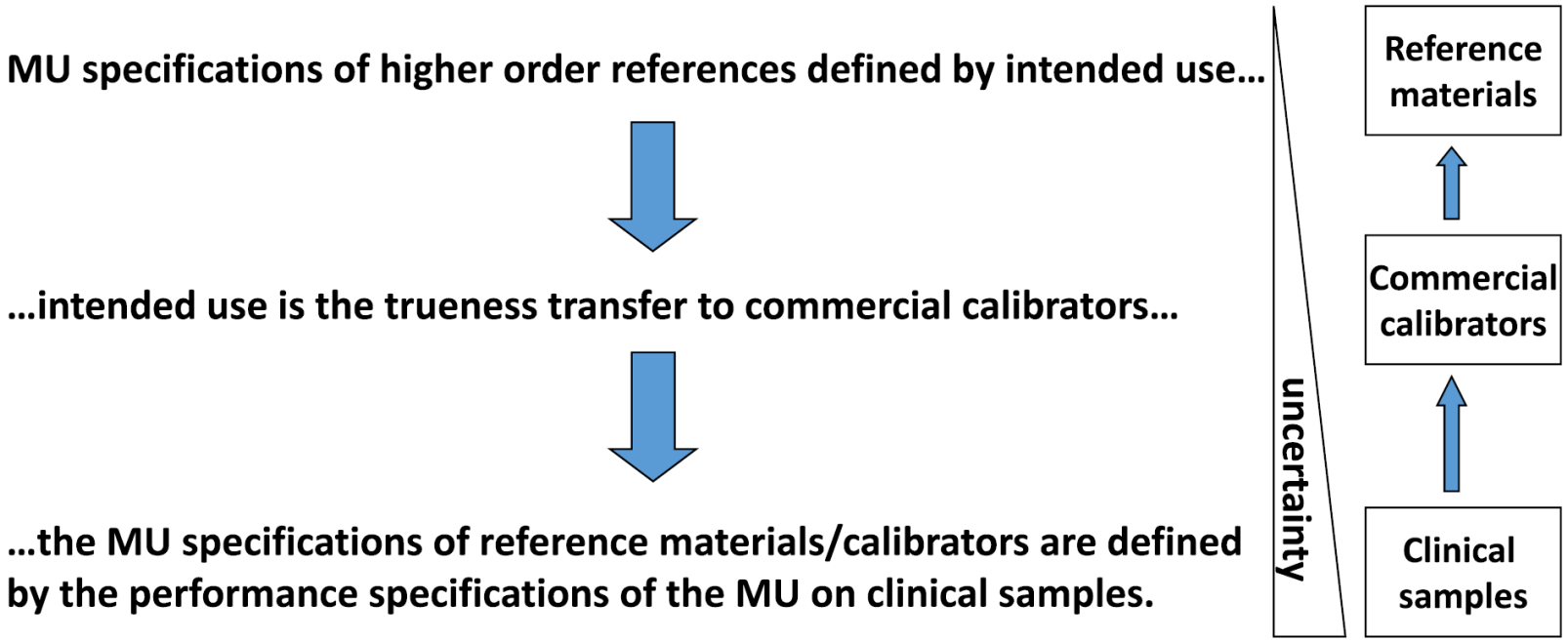
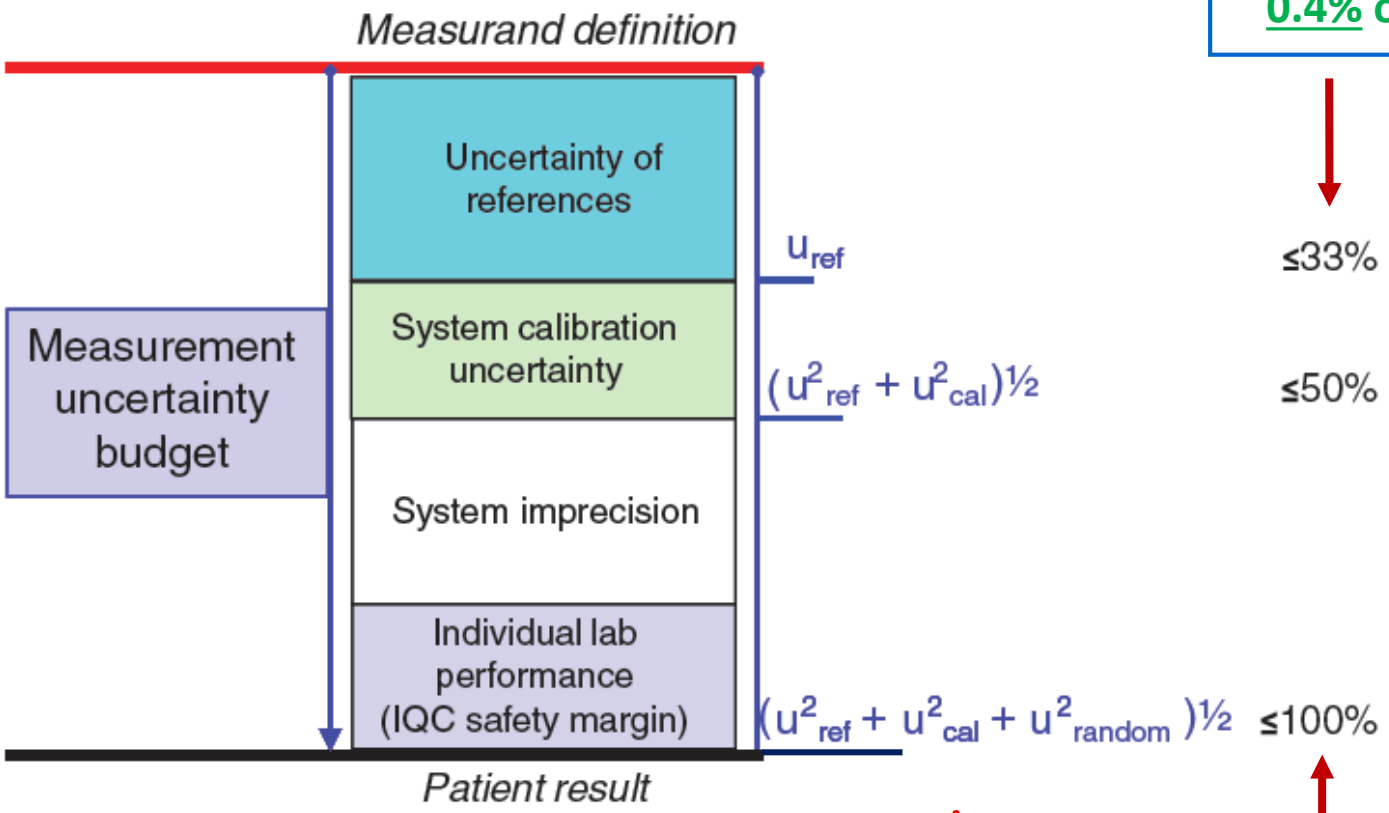


Fig. 3. Defining the suitability of the measurement uncertainty (MU) of higher order references by turning the approach upside down, focusing first on the established performance specifications for MU of clinical samples.

EXAMPLE

Allowable limit for the standard MU of creatinine reference materials @ 33% of the goal

1.1% minimum
0.75% desirable
0.4% optimum



Creatinine uncertainty

3.3% minimum
2.2% desirable
1.1% optimum

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Synopsis of higher-order references for creatinine in the JCTLM database and of their potential to fulfill goals for suitable uncertainty

Secondary CRM or RMP	Combined standard uncertainty
JRC BCR-573	1.02 (fulfill minimum specification)
JRC BCR-574	0.62 (fulfill desirable specification)
JRC BCR-575	0.88 (fulfill minimum specification)
LGC ERM-DA250a	5.87 (do not fulfill specifications)
LGC ERM-DA251a	5.58 (do not fulfill specifications)
LGC ERM-DA252a	15.6 (do not fulfill specifications)
LGC ERM-DA253a	3.56 (do not fulfill specifications)
LNE CRM Bio 101a Level 1	1.09 (fulfill minimum specification)
LNE CRM Bio 101a Level 2	0.56 (fulfill desirable specification)
CENAM DMR 263	2.18 (do not fulfill specifications)
ID-GC-MS	0.49 to 0.50 (fulfill desirable specification)
ID-LC-MS	0.40 to 0.82 (fulfill desirable/min specs)
ID-SERS	1.23 to 2.24 (do not fulfill specifications)

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

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

Identify and describe available reference measurement systems and metrological traceability chains **in their entirety**, based on the information available on JCTLM database

Illustrate the evolution of **measurement uncertainty** through the entire metrological traceability chains

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Task Force on Reference Measurement System Implementation

Identify those measurands for which **further advancements** to existing reference systems are needed or some components of the reference system are lacking

Review the JCTLM guidance document on reporting metrological traceability and propose modifications, in a consistent way with the revised ISO 17511 standard

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Roles and responsibilities of IVD manufacturers

To fulfill the EU IVD Directive and
REGULATION (EU) 2017/746 Requirements

CE

- Identification of higher-order metrological REFERENCES
- Definition of a CALIBRATION HIERARCHY to assign traceable values to their system calibrators
- Estimation of combined MU of calibrators
- Fulfil MU GOALS, which represent a proportion of the uncertainty budget allowed for clinical laboratory results

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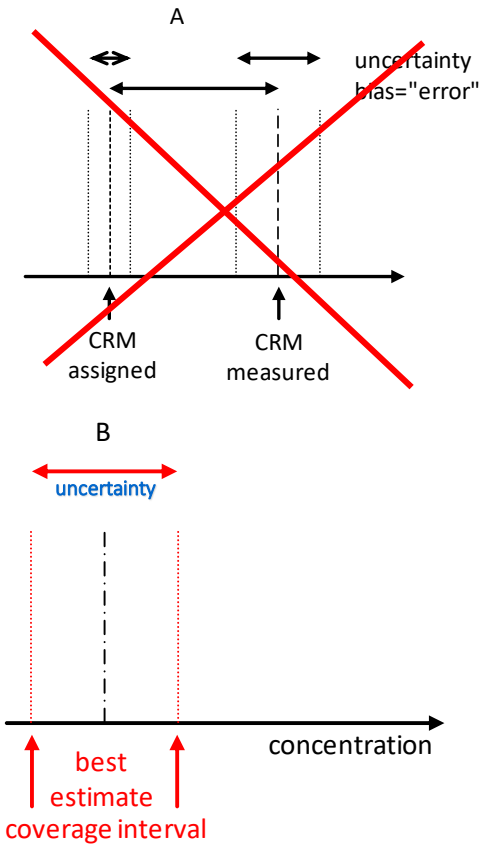
[Braga F & Panteghini M, Clin Chim Acta 2014;432:55]

Role of IVD manufacturers



1) Elimination of measurement bias relative to the higher-order reference selected

CRM = certified reference material

2) Estimation of combined MU @ the calibrator level

Clinical laboratories have to rely on the manufacturers who must ensure traceability of their analytical systems to the highest available level. Therefore, estimation of a bias by the end-user laboratory should be rarely required.

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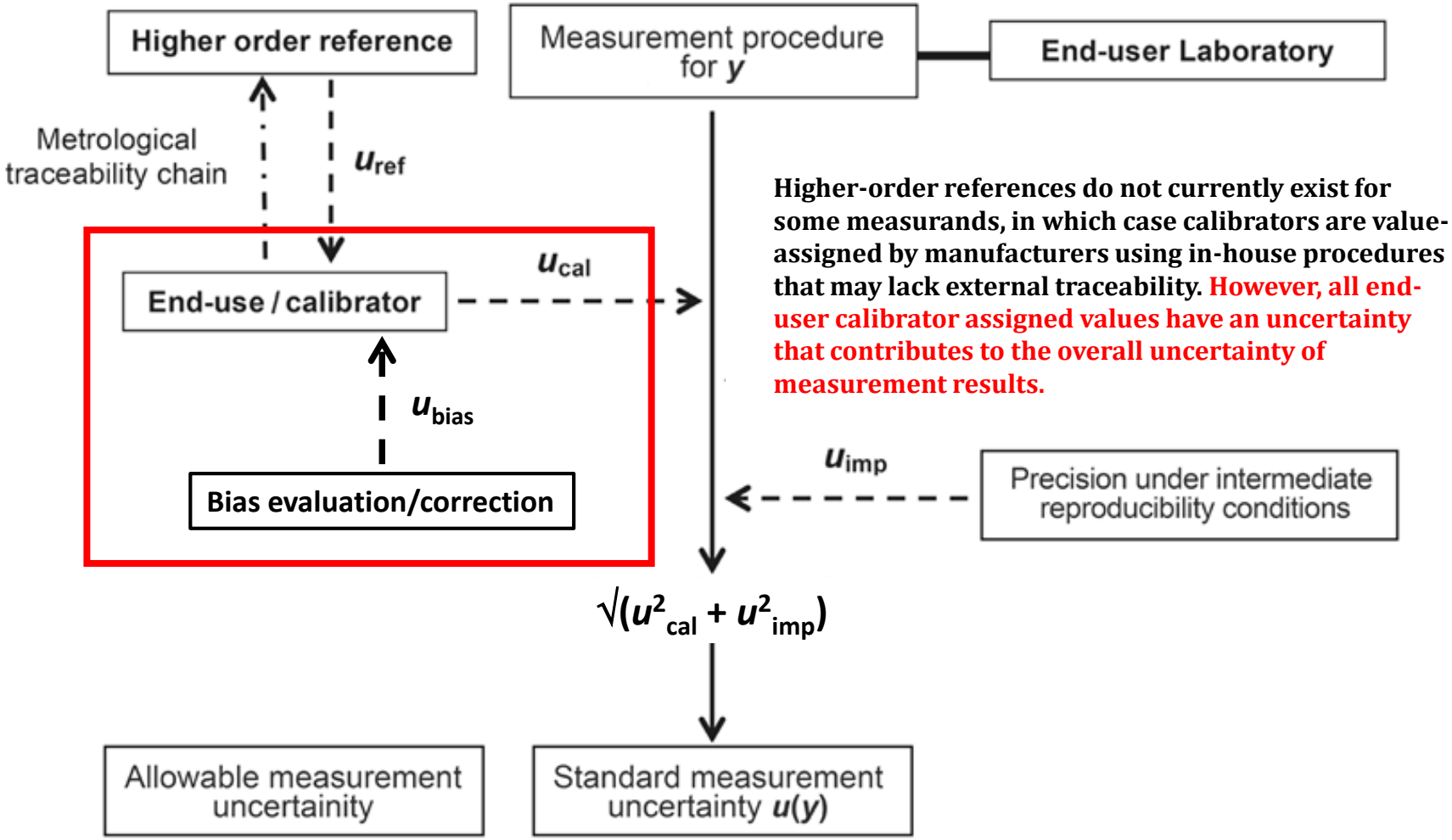
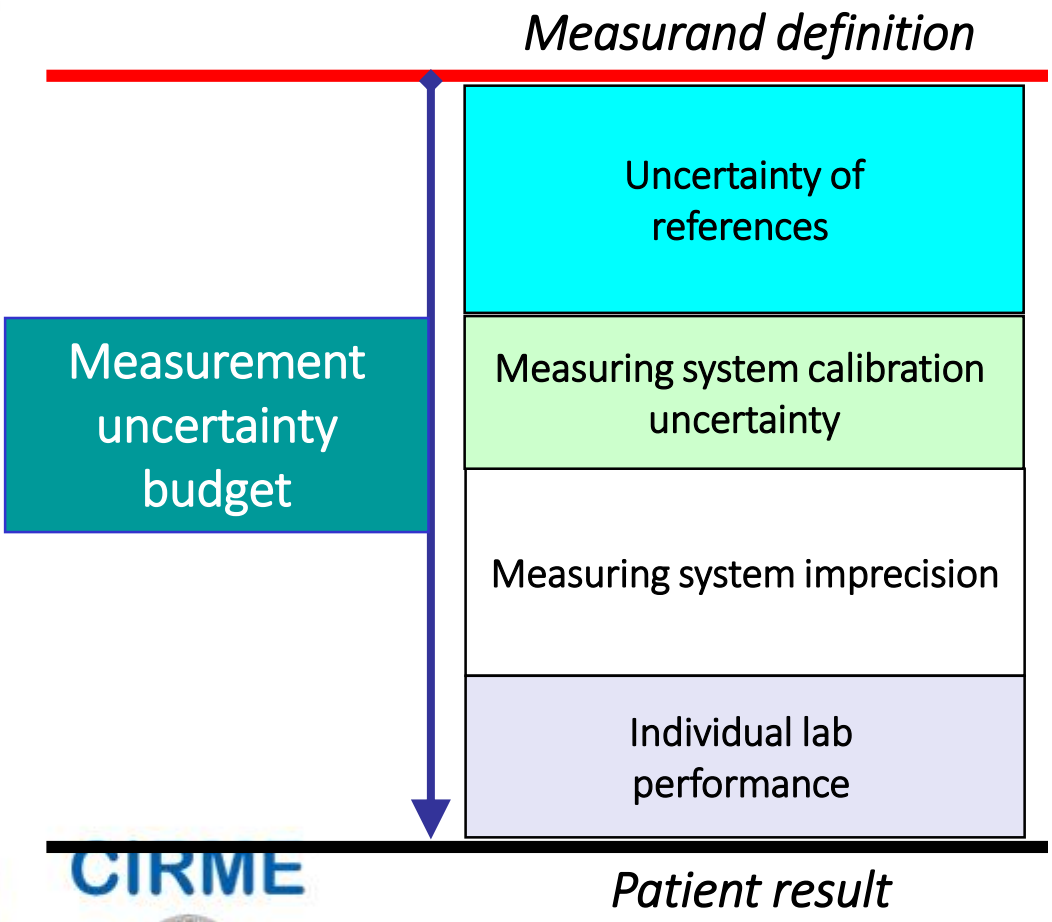


Higher-order references do not currently exist for some measurands, in which case calibrators are value-assigned by manufacturers using in-house procedures that may lack external traceability. However, all end-user calibrator assigned values have an uncertainty that contributes to the overall uncertainty of measurement results.

Commercial calibrator contribution to the MU budget



IVD Manufacturer

Manufacturers should estimate the combined uncertainty!

$$u_{cal} = (u^2_{ref} + u^2_{value\ ass})^{½}$$

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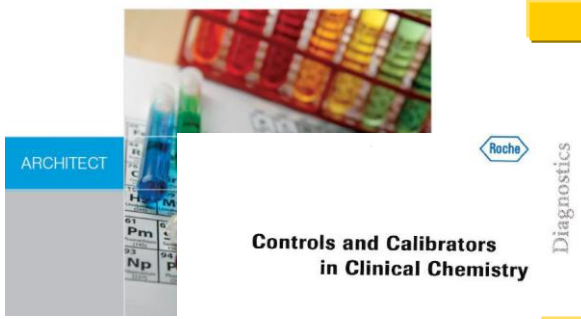
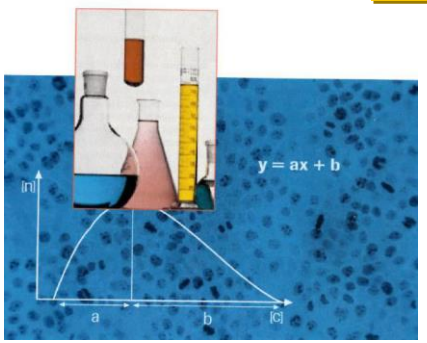
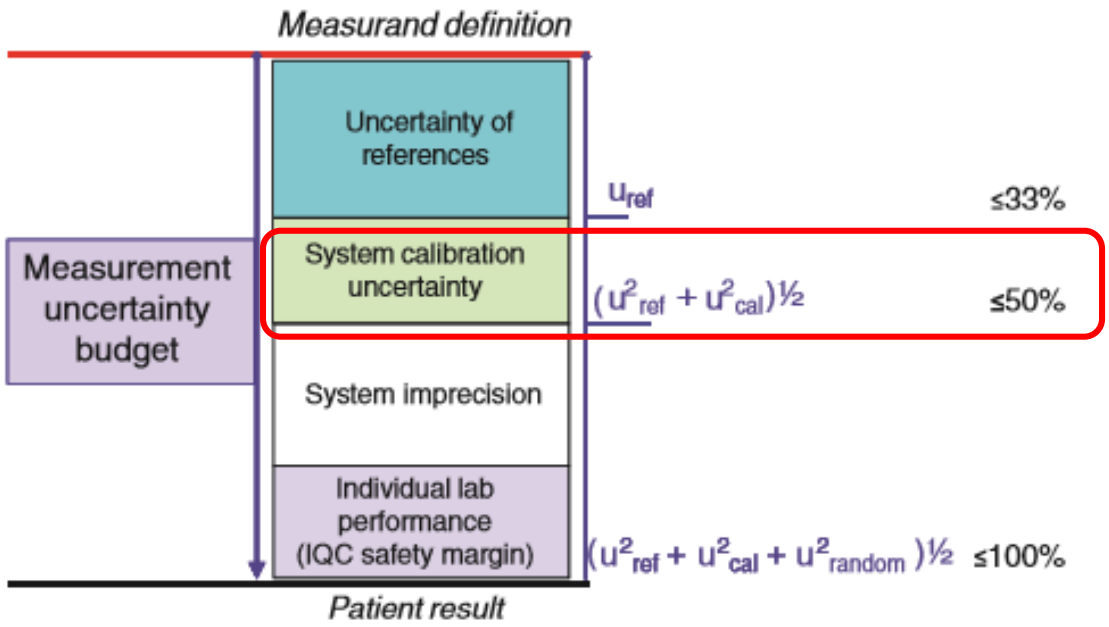
And fulfil MU goals, which represent a proportion of the uncertainty budget allowed for clinical laboratory results

TRACEABILITY AND UNCERTAINTY OF MEASUREMENT







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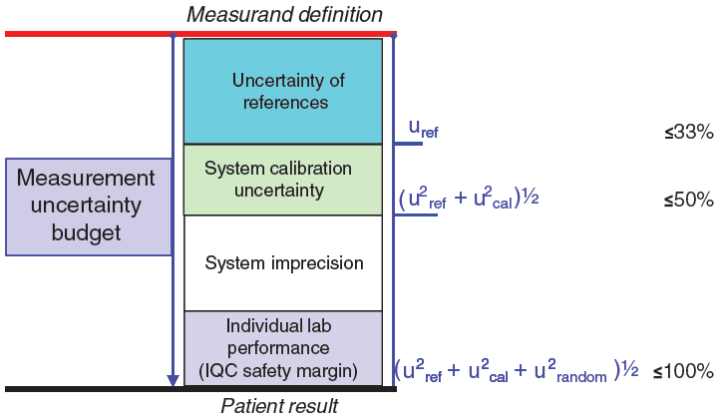
EXAMPLE

Metrological traceability chain and MU of the calibrator of Architect enzymatic creatinine assay

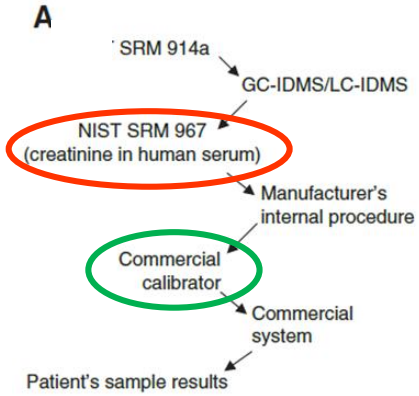
Abbott

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



≤33% **1.06%**

≤50% **1.29%**



From MILAN APS MODEL 2

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Creatinine uncertainty

3.3% minimum

2.2% desirable

1.1% optimum

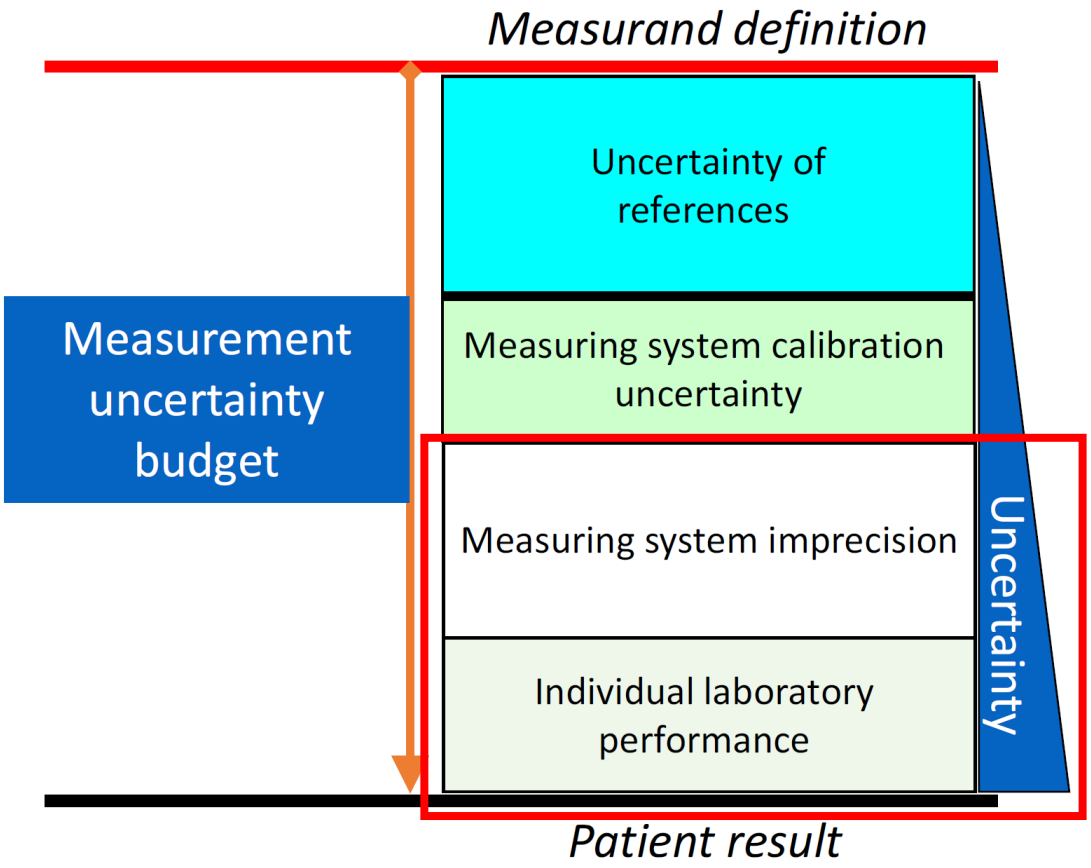
Allowable limit for the standard MU of creatinine calibrator @ 50% of the goal →

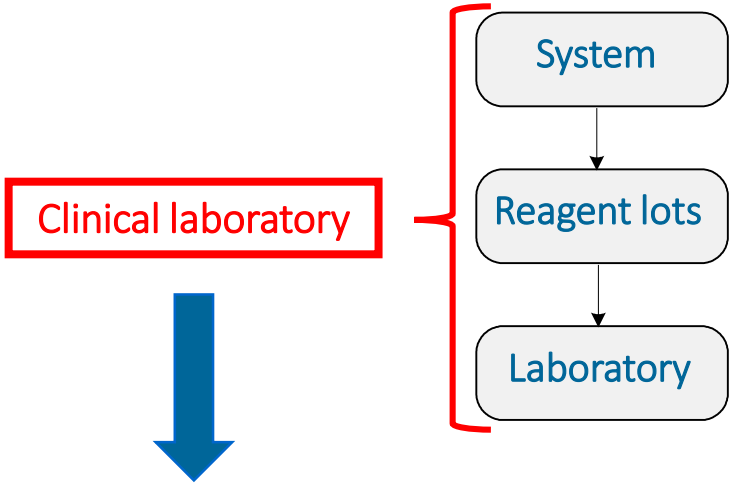
1.65% minimum

1.10% desirable

0.55% optimum

Uncertainty margins for clinical laboratories





The individual laboratory should monitor the variability of the measuring system used locally through the Internal Quality Control

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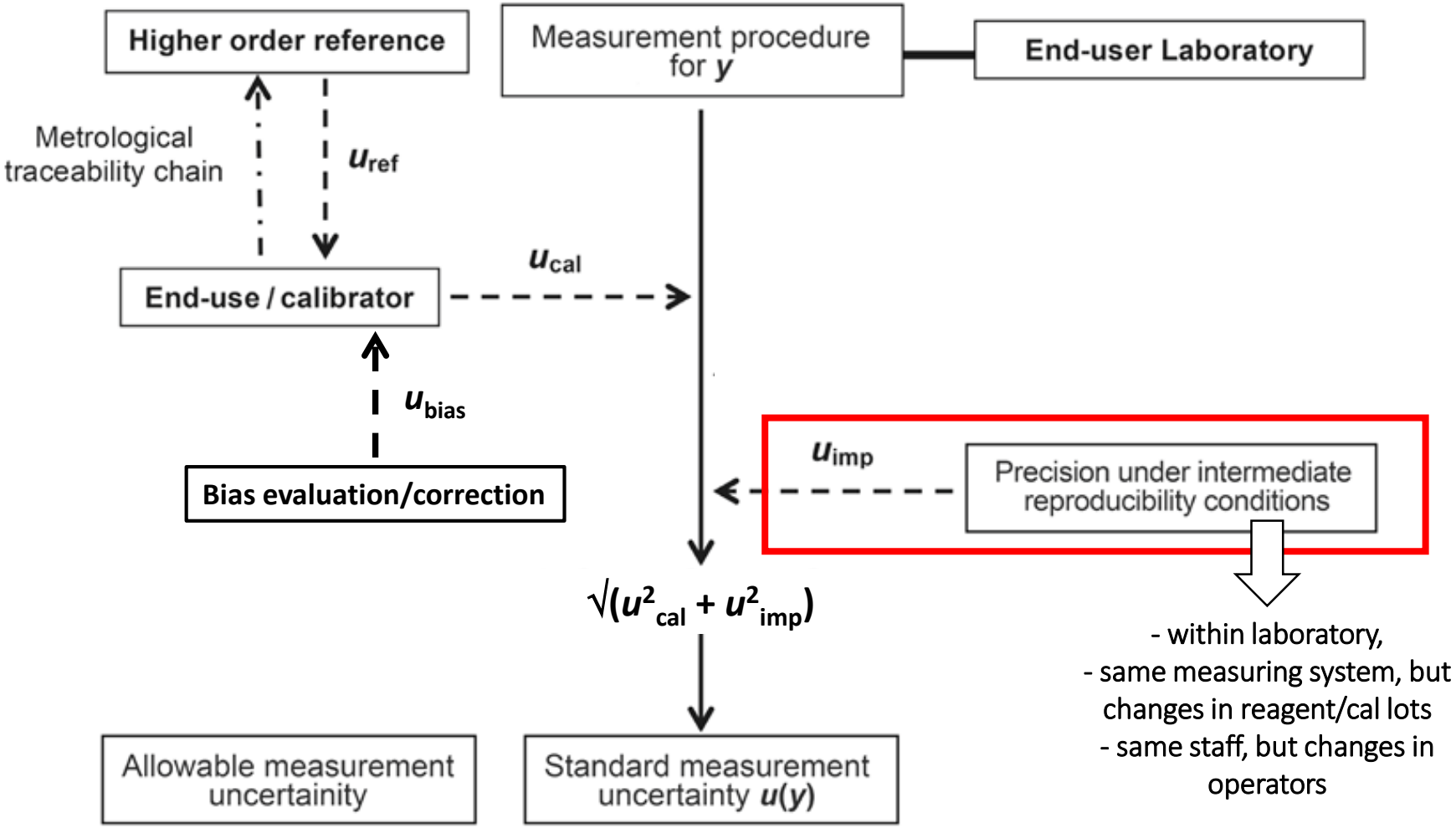

Higher order reference
Measurement procedure for y
End-user Laboratory
Metrological traceability chain
u_{ref}
End-use / calibrator
u_{cal}
u_{bias}
Bias evaluation/correction
u_{imp}
Precision under intermediate reproducibility conditions
$\sqrt{(u^2_{cal} + u^2_{imp})}$
- within laboratory,
- same measuring system, but changes in reagent/cal lots
- same staff, but changes in operators
Allowable measurement uncertainity
Standard measurement uncertainty $u(y)$

Testing MU due to the random effects [u_{imp}]

The intermediate reproducibility should be estimated from consecutive 6-month data in order to capture systematic sources of uncertainty, such as those caused by different lots of reagents, different calibrations, different environmental conditions such as room temperature and humidity.

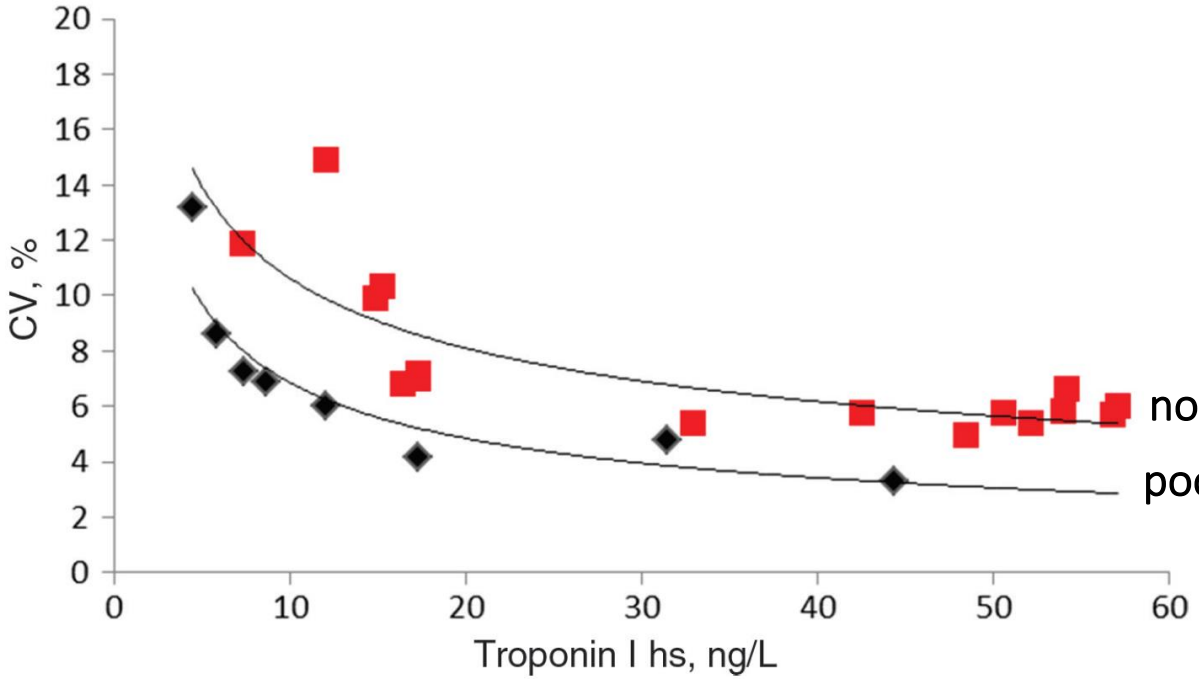
Table 1: Main characteristics for a control material to be used in the internal quality control component II program in order to derive the uncertainty of the analytical system due to the random effects.

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

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

ISO/TS 20914:2019
MEDICAL LABORATORIES -- PRACTICAL GUIDANCE FOR THE ESTIMATION OF MEASUREMENT UNCERTAINTY

It is generally assumed that for a given measurement procedure the magnitude of imprecision for both IQC and typical human samples is similar, so that a standard uncertainty calculated for an IQC material is considered applicable to human samples with similar measurand values. This assumption should be validated by a performing a precision study of representative human samples and relevant IQC material(s) and their variances compared



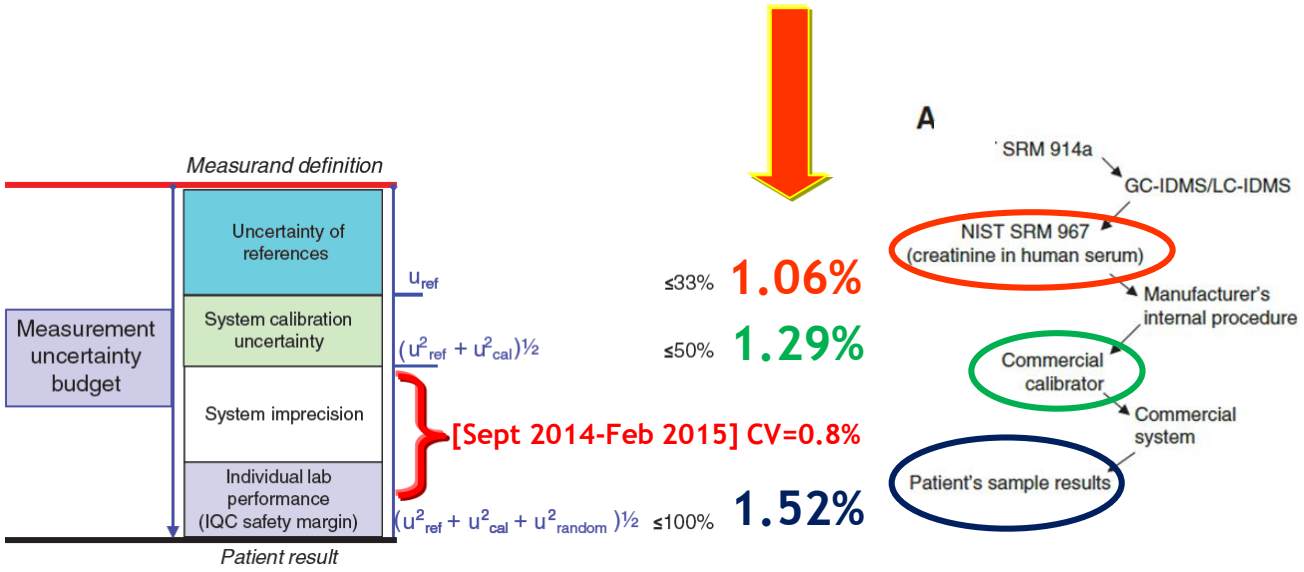
Hage-Sleiman et al. Clin Chem Lab Med 2019;57:e49

EXAMPLE

Performance in terms of MU of the Abbott Architect enzymatic creatinine assay

Abbott

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



From MILAN APS MODEL 2

Creatinine uncertainty

3.3% minimum

2.2% desirable

1.1% optimum

Allowable limits for the standard MU of serum creatinine measured on clinical samples

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Defining permissible limits for the combined uncertainty budget in the implementation of metrological traceability

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CHALLENGE STARTS NOW!

Time to move to practice

Now that the theory has been consolidated, it is necessary to widespread apply it in the laboratory medicine practice. Particularly, it becomes mandatory to verify for each analyte measured in the clinical laboratory if the status of the uncertainty budget of its measurement associated with the proposed metrological traceability chain is suitable for clinical application of the test.

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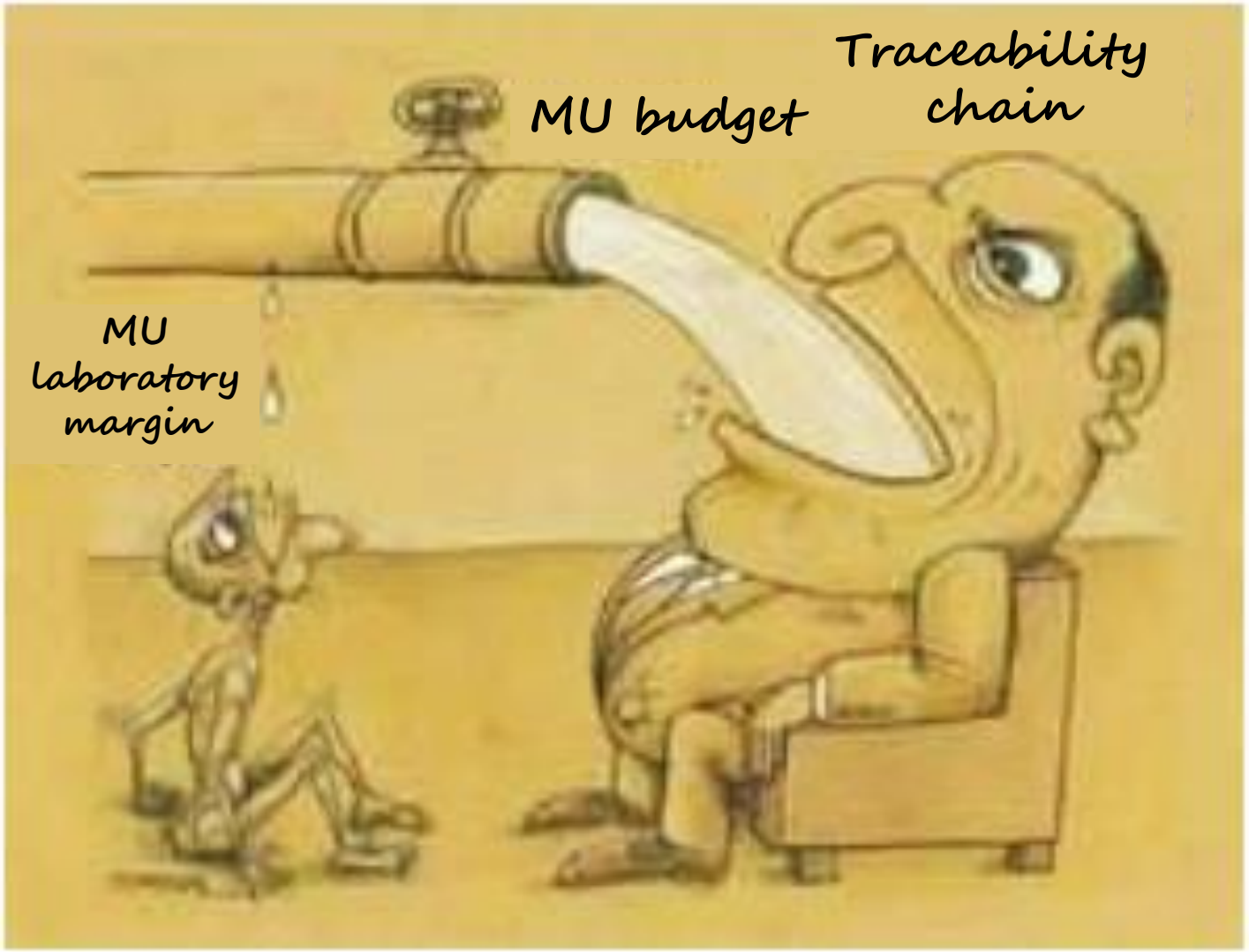

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Adapted from M. Thelen, 10th CIRME International Scientific Meeting – Milan, IT – Nov 2016

Example 1: Glucose (Plasma)

		Desirable MU limit
Reference material	(NIST SRM 965b) **0.61-0.73%** (depends on the concentration level)	0.9% — 33% TB_U
XY manufacturer's calibrator	C1: 120 ± 2.4 mg/dL C2: 497 ± 10.0 mg/dL **≤1.25%**	1.35% — 50% TB_U
Clinical samples	***The end user has a margin until a CV of 2.4%***	 2.7% — TB_U

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The uncertainty of this measuring system has a *high probability* to fulfil the desirable performance specifications for the total uncertainty budget (TB_u)

Example 2: Creatinine (Serum)

		Desirable MU limit
Reference material	(NIST SRM 967a) L1: 0.847 ± 0.018 mg/dL L2: 3.877 ± 0.082 mg/dL **1.06%**	0.75% — 33% TB_U
XY manufacturer's calibrator	4.0 ± 0.12 mg/dL **1.50%**	1.1% — 50% TB_U
Clinical samples	***The end user has a margin until a CV of 2.0%***	 2.2% — TB_U

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The uncertainty of this measuring system has a *medium probability* to fulfil the desirable performance specifications for the total uncertainty budget (TB_u)

Example 3: Sodium (Serum)

		Desirable MU limit	
Reference material	(NIST SRM 956d) 120 ± 0.7 mg/dL **0.29%**	0.17%	33% TB_U
XY manufacturer's calibrator	C1: 120 ± 1.5 mmol/L **0.63%** C2: 160 ± 1.5 mmol/L **0.47%**	0.25%	50% TB_U
Clinical samples	***The end user has no margin to fulfil specifications***	0.50%	TB_U

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The uncertainty of this measuring system has *no possibility* to fulfil the desirable performance specifications for the total uncertainty budget (TB_u)

The importance of grading different quality levels for analytical performance specifications

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

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

Example 3: Sodium (Serum)

		Minimum MU limit	
Reference material	(NIST SRM 956d) 120 ± 0.7 mg/dL **0.29%**	0.25%	33% TB_U
XY manufacturer's calibrator	C1: 120 ± 1.5 mmol/L **0.63%** C2: 160 ± 1.5 mmol/L **0.47%**	0.38%	50% TB_U
Clinical samples	***The end user has a margin until a CV of 0.6%***	0.75%	TB_U

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The uncertainty of this measuring system has a *realistic possibility* to fulfil the minimum performance specifications for the total uncertainty budget (Tb_u)

To estimate MU is not enough!

- MU is not a finding to be calculated only to fulfil accreditation parameters and then immediately forgotten
- Together with the MU, the laboratory must define the performance specifications (PS) to validate it
- All attempts must be made to improve on the MU value if PS are not achieved, including, as last option, the replacement of the measuring system
- MU must become a Key Quality Indicator in clinical laboratories because it can be used to describe both the performance of an IVD measuring system and the laboratory itself.

Infusino I, Panteghini M. Clin Biochem 2018;57:3

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.

CII

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