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Centre for Metrological Traceability in Laboratory Medicine (CIRME)

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

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

F. Braga

Centre for Metrological Traceability in Laboratory Medicine (CIRME)

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Laboratory measurement paradigm:

- **Measuring systems 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**
  - **Measuring system**

Laboratory results should be equivalent no matter where they are performed

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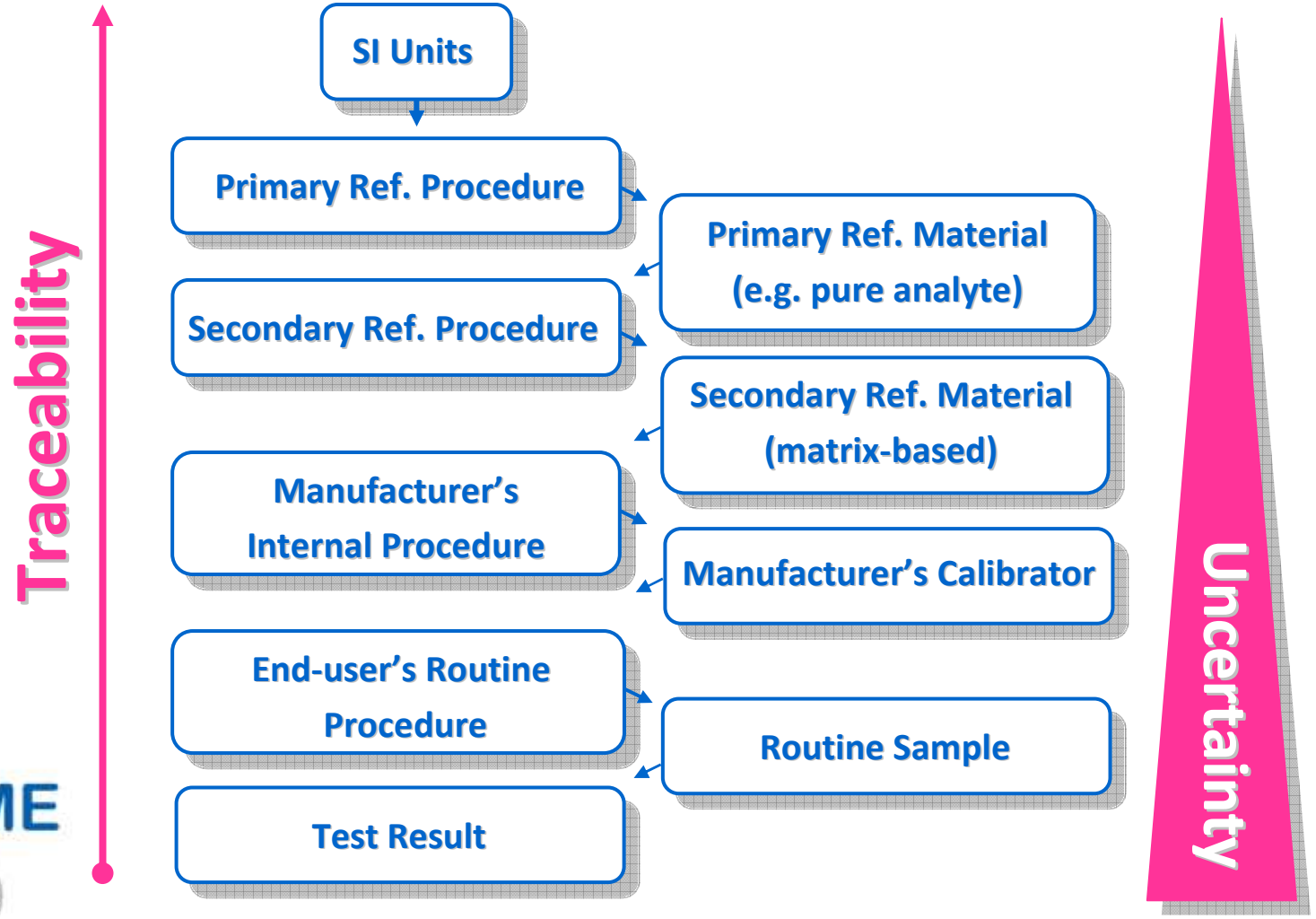
To become *equivalent for long term*, results must be traceable to higher-order references



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REGULATION (EU) 2017/746 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 April 2017 on *in vitro* diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU

Official Journal L 117
of the European Union

English edition — Legislation — Volume 60, 5 May 2017

Contents

I *Legislative acts*

REGULATIONS

* Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC (1) 1

* Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on *in vitro* diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU (1) 176

requires manufacturers to ensure traceability of their analytical systems to recognized higher order references

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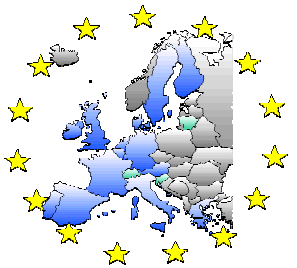

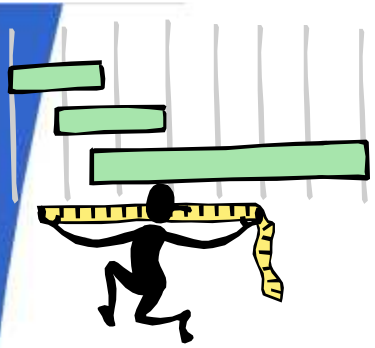

Basic requirements to establish traceability

1. Establishment of a calibration hierarchy starting from the unequivocal definition of the measurand
2. Elimination of measurement bias
3. Adequate estimation of measurement uncertainty

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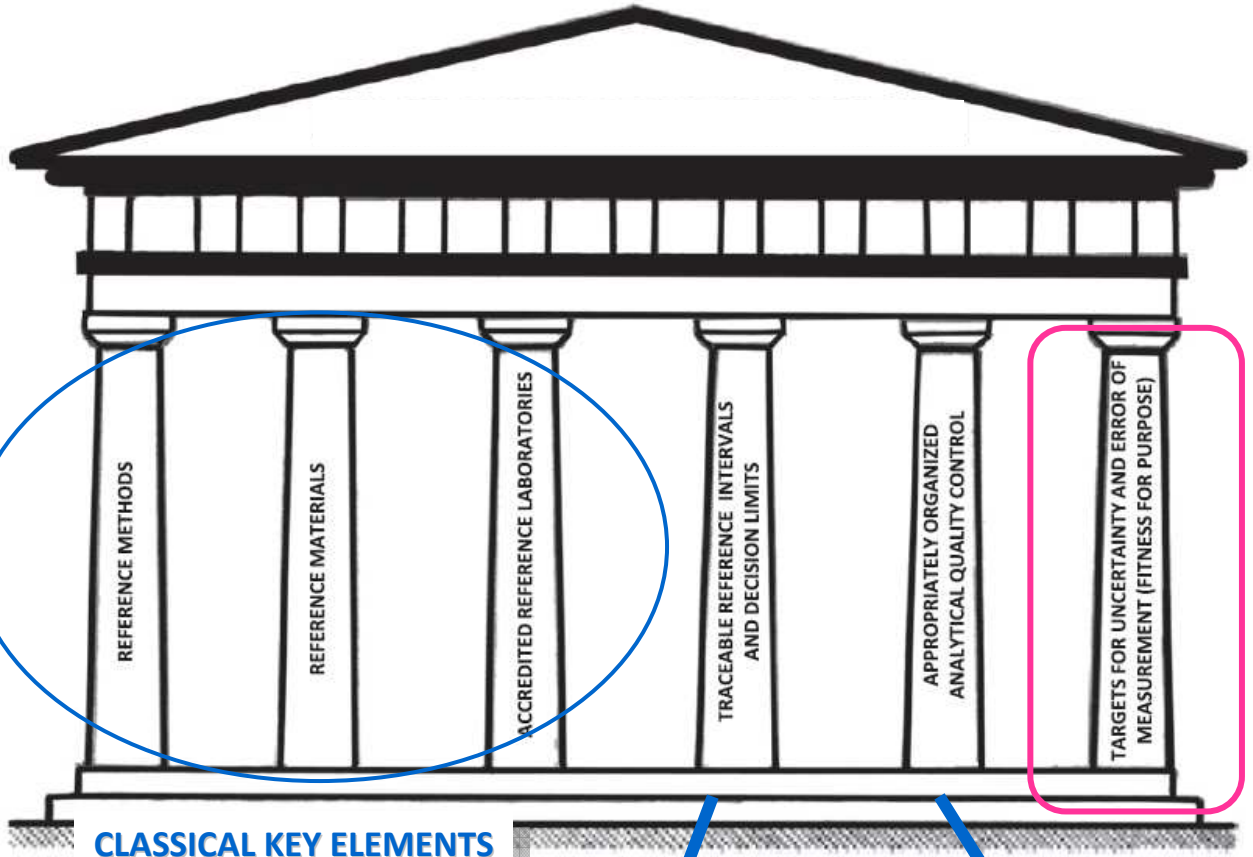
THE TEMPLE OF LABORATORY STANDARDIZATION



CLASSICAL KEY ELEMENTS

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

4th PILLAR
TRACEABLE REFERENCE INTERVALS AND DECISION LIMITS

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

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

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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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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

1. The measurand has a central role in diagnosis and monitoring of a specific disease ⇒ outcome model
2. The measurand has a high homeostatic control ⇒ biological variability model
3. Neither central diagnostic role nor sufficient homeostatic control ⇒ state-of-the-art model

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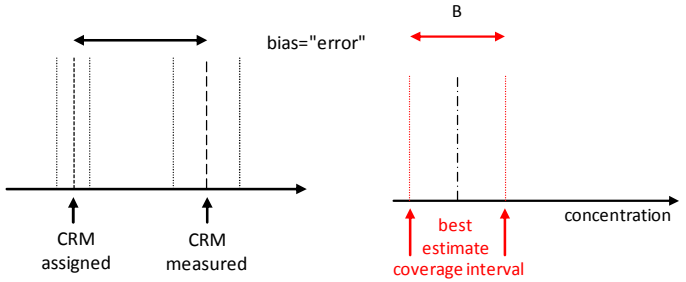
Assumption behind the *uncertainty concept*:

the bias should be appropriately eliminated



EXAMINATION PERFORMANCE SPECIFICATIONS

Minimum *Desirable* *Optimal*

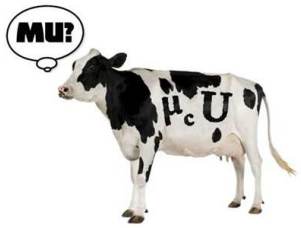
BIAS

Minimum *Desirable* *Optimal*

TOTAL ERROR

Minimum *Desirable* *Optimal*

IMPRECISION



UNCERTAINTY

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For uncertainty the relevant goal that should be considered is that classically related to the allowable analytical variability = IMPRECISION

Biological Variation approach

UNCERTAINTY

<0.75 x CV_I (Minimum)

<0.50 x CV_I (Desirable)

<0.25 x CV_I (Optimum)

$$U = u \times k$$

EXPANDED UNCERTAINTY

<(0.75 x CV_I) x 2 (Minimum)

<(0.50 x CV_I) x 2 (Desirable)

<(0.25 x CV_I) x 2 (Optimum)

G_U

Total budget of uncertainty

k=2 is recommended for a 95% confidence interval

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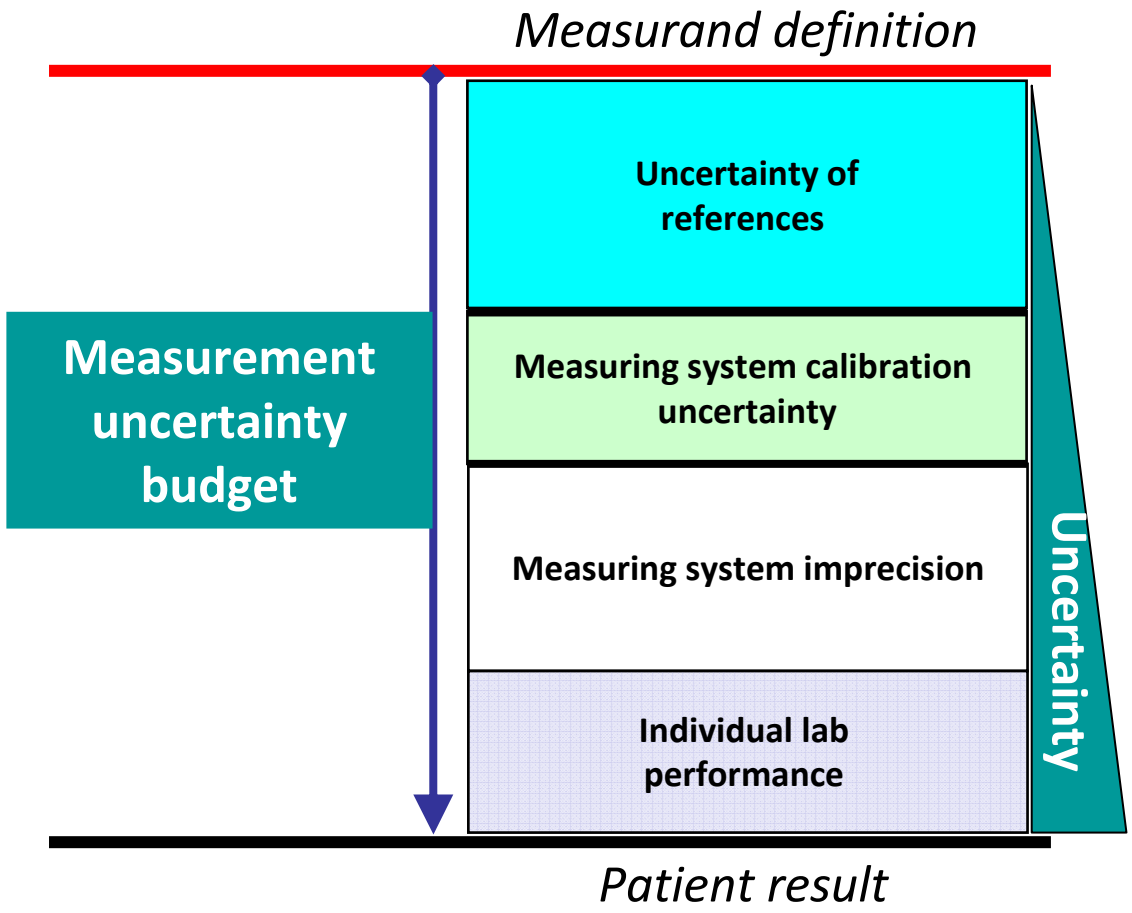
UNCERTAINTY BUDGET



G_U: budget that should be fulfilled when combining the uncertainty of the measuring system employed in the individual laboratory (random uncertainty) to that accumulated along all the steps of metrological traceability chain.

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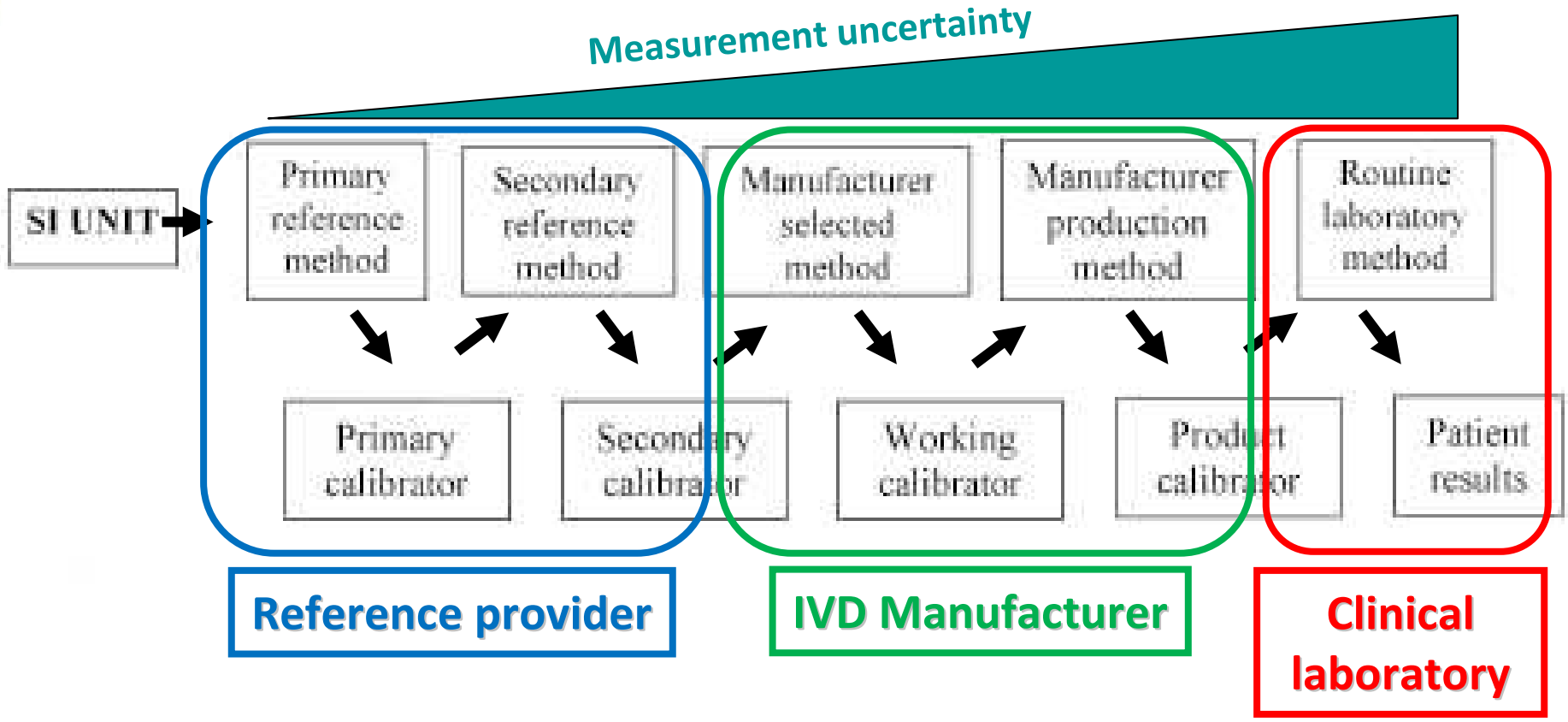
COMBINED UNCERTAINTY:

$$u_{result} = (u_{ref}^2 + u_{cal}^2 + u_{random}^2)^{½}$$

UNCERTAINTY BUDGET



Although independent in the tasks, their performances contribute together to the total measurement uncertainty budget

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How much of the G_U should be used across the different steps of metrological traceability chain?

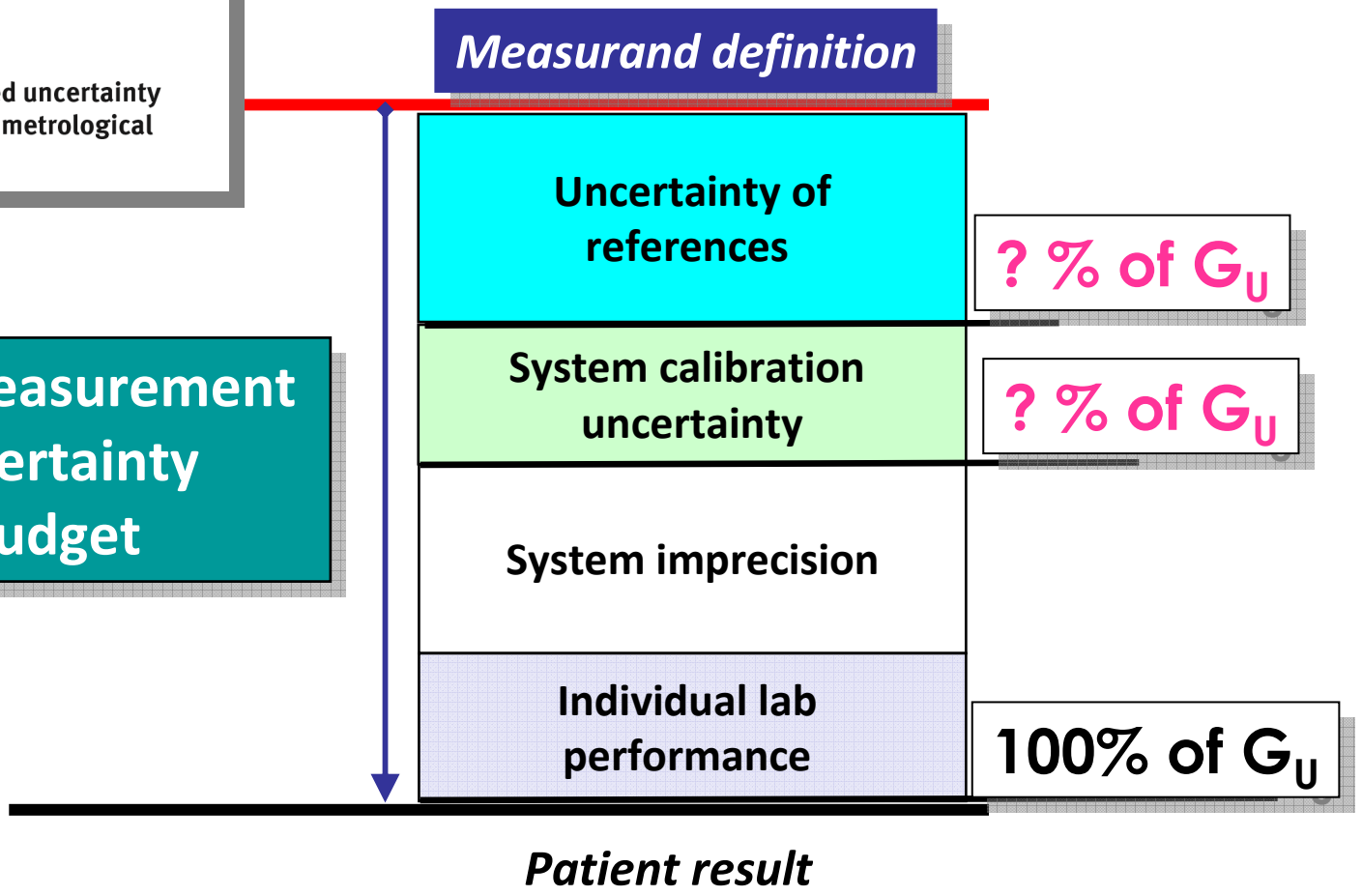
DE GRUYTER Clin Chem Lab Med 2015; 53(6): 905–912

Opinion Paper

Federica Braga*, Ilenia Infusino and Mauro Panteghini

Performance criteria for combined uncertainty budget in the implementation of metrological traceability

Total measurement uncertainty budget



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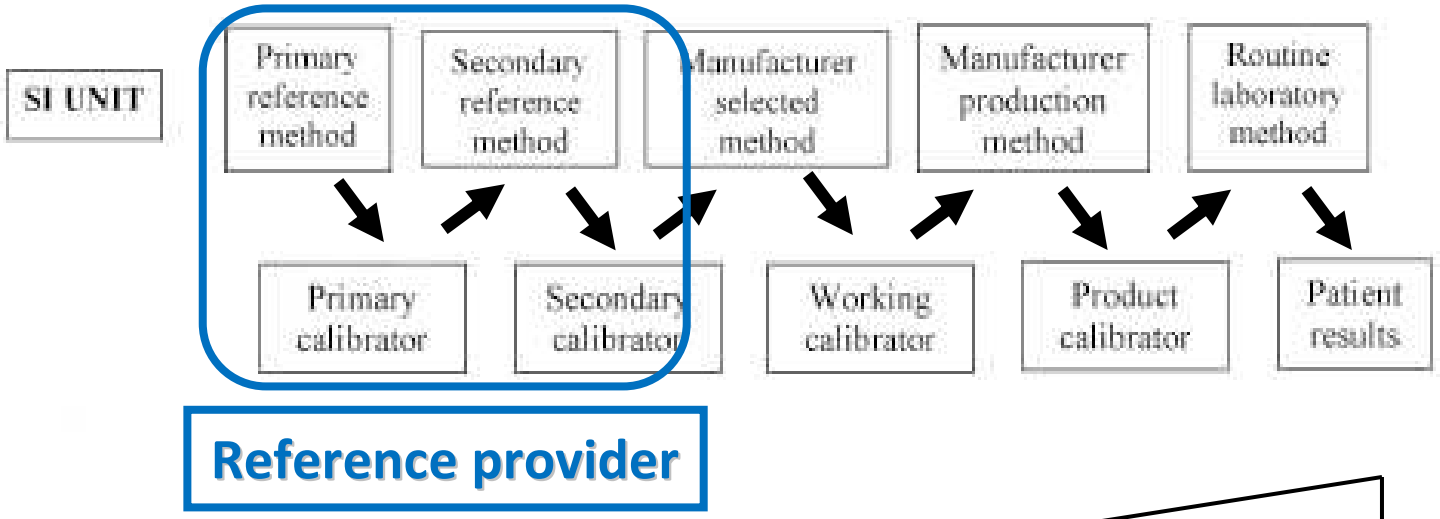
UNCERTAINTY LIMITS FOR HIGHER ORDER REFERENCES

Activities

Characterization of certified reference materials



33%

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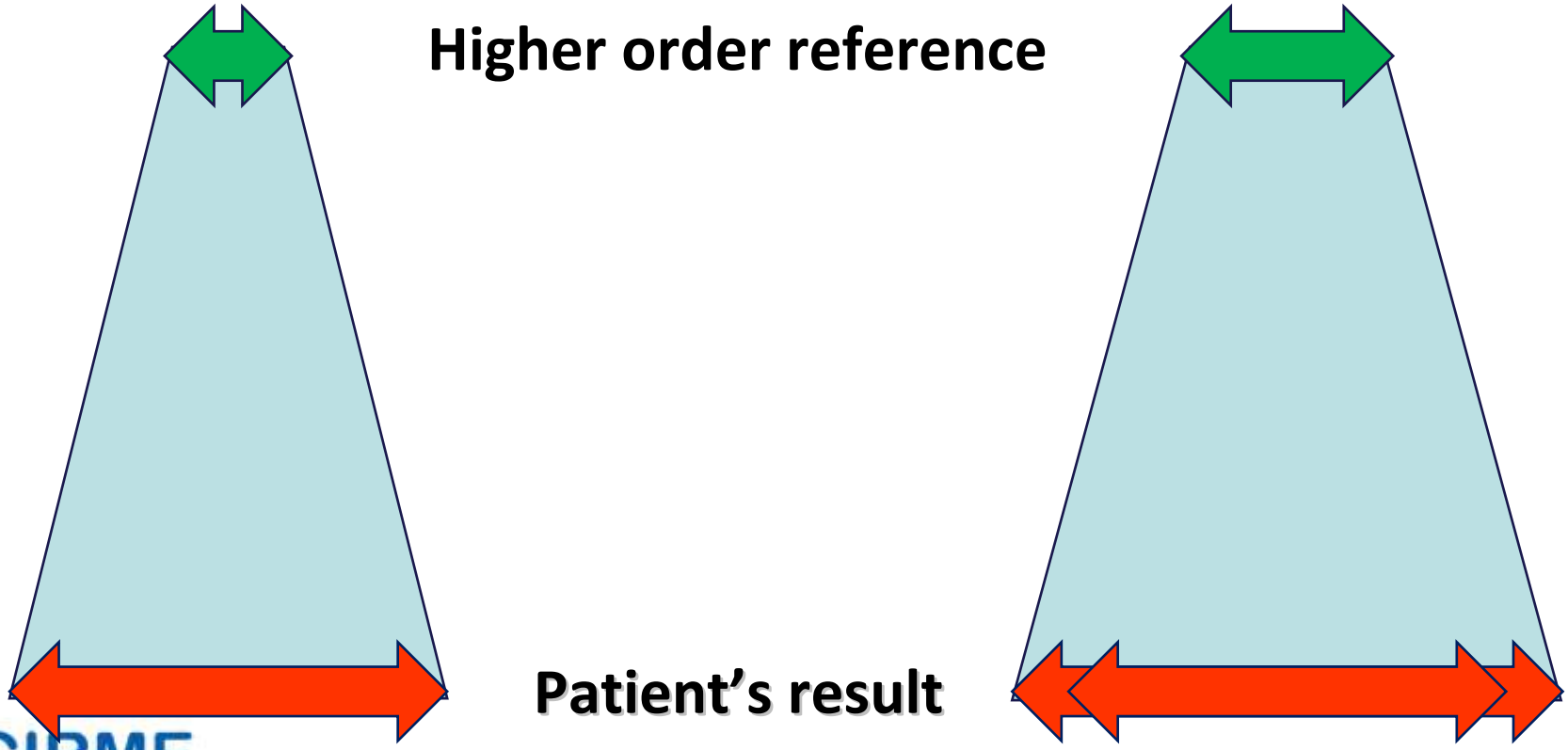
Uncertainty of references may affect the uncertainty of patient's results



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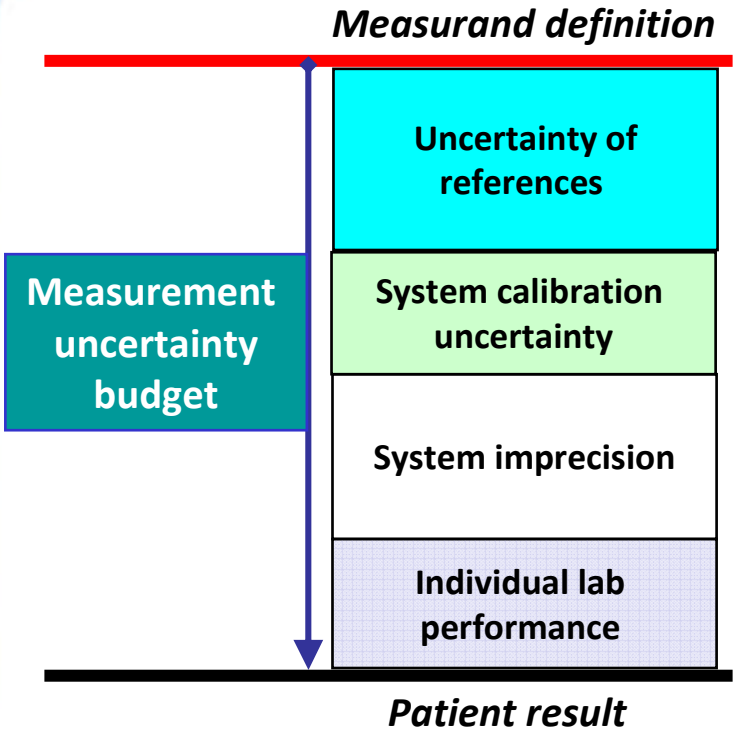
Adapted from G. Jones, 5th CIRME International Scientific Meeting – Milan, IT – Nov 2011

IFCC WG-TNI Technical Discussion

Value assignment of NIST SRM 2922 and measurement uncertainty



≤33% of uncertainty budget due to SRM uncertainty (~4.5%).

According to the outcome-based study of misclassification rates, the maximum allowable goal for 100% total uncertainty budget of cTnI assays is 13% (minimum quality goal) for the clinical result and which allows for <2% result misclassification.

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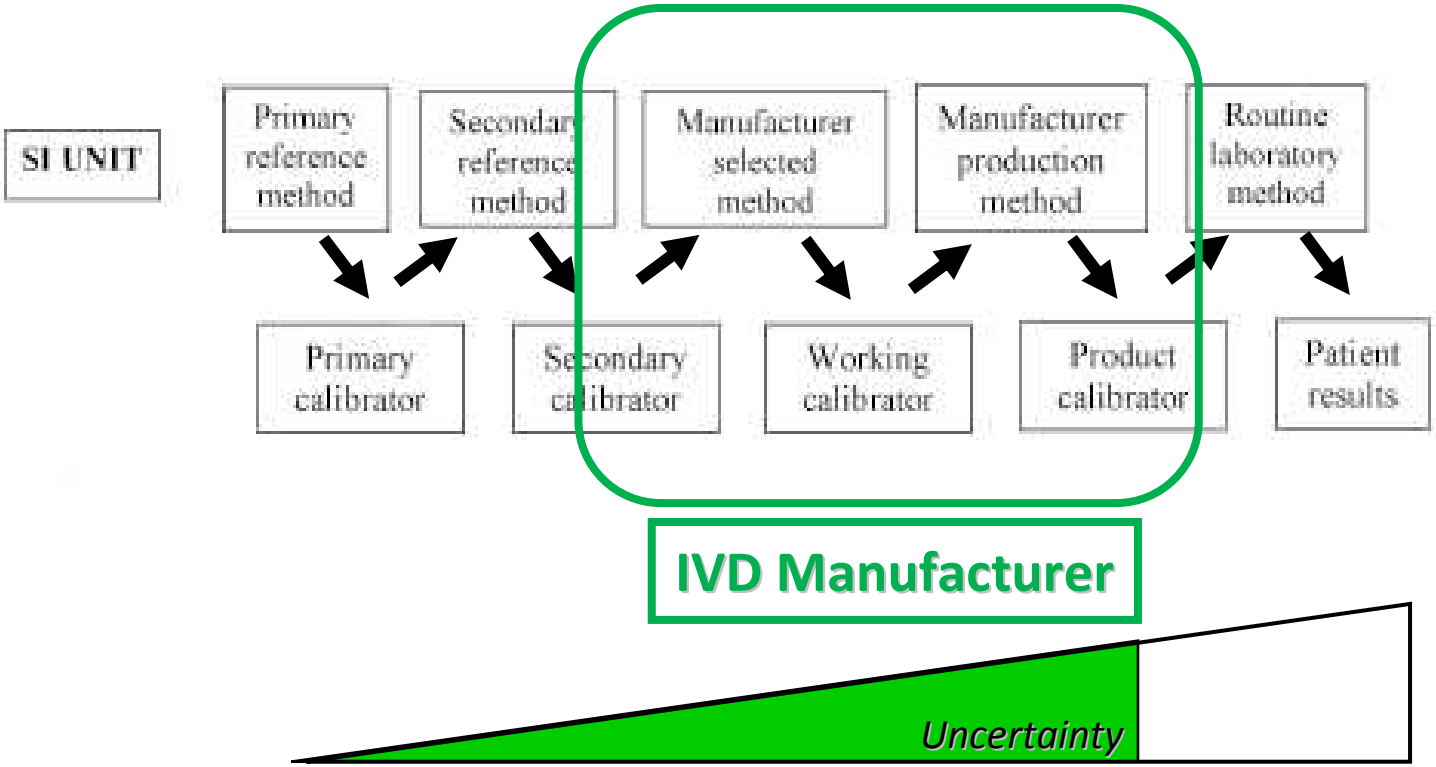
UNCERTAINTY LIMITS FOR COMMERCIAL SYSTEM CALIBRATION

Activities

- **Identification of the higher order materials or methods**
- **Definition of the metrological traceability chain to assign values (and uncertainty) to assay calibrators**



50%

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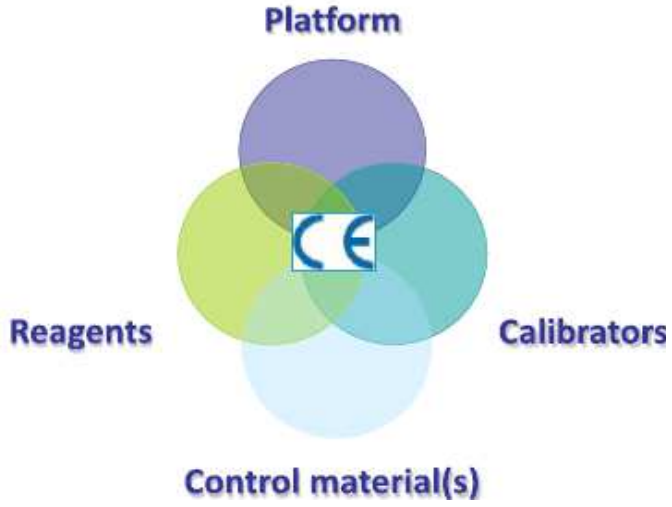
Paradigm shift in the thinking

F. Braga, M. Panteghini / Clinica Chimica Acta 432 (2014)



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

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Role of IVD manufacturers

To 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 total uncertainty budget allowed for clinical laboratory results.

In practice they have to…

1. select suitable *reference materials* and/or identify a *reference laboratory* performing the *reference procedure*
2. define a *calibration hierarchy* to assign traceable value to their system calibrator
3. calculate the *[expanded] combined uncertainty* associated to the commercial calibrator and verify that it fulfils the uncertainty limit
4. make the *full information* about the traceability and uncertainty of commercial calibrator *available to end users* (ideally in the assay or calibrator package inserts)

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JCTLM

Accurate results for patient care

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)

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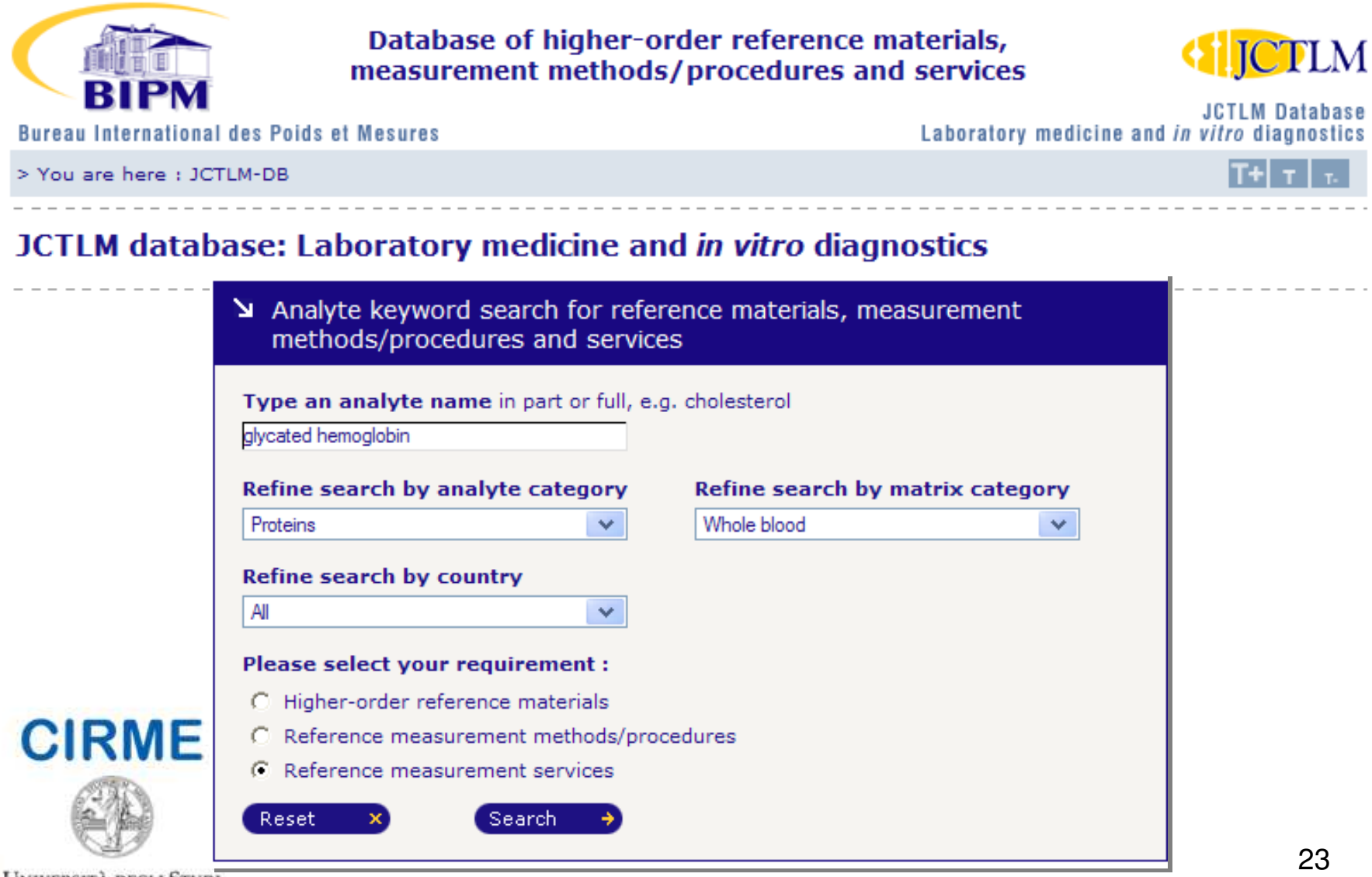
Panteghini M. Clin Biochem 2009;42:236

http://www.bipm.org/jctlm/



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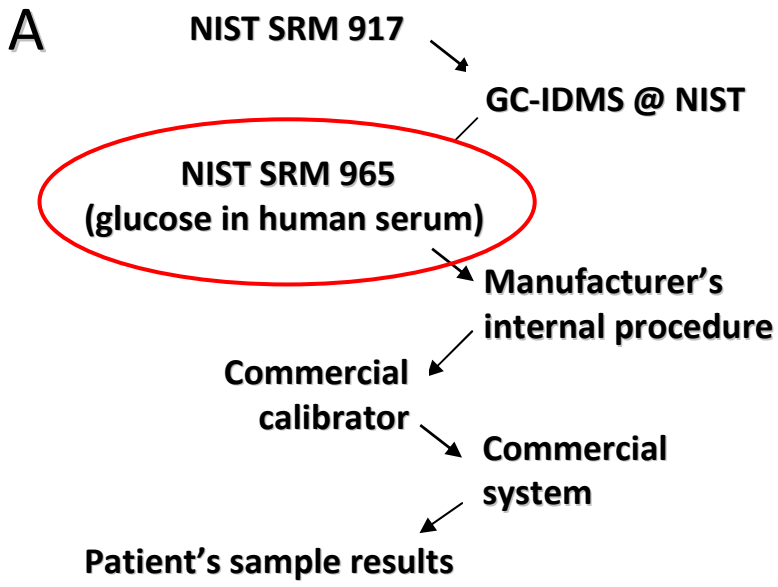
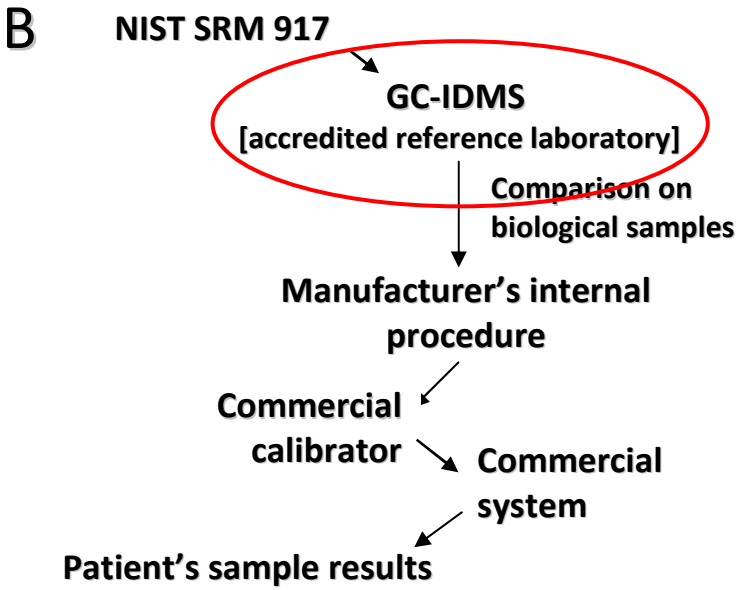
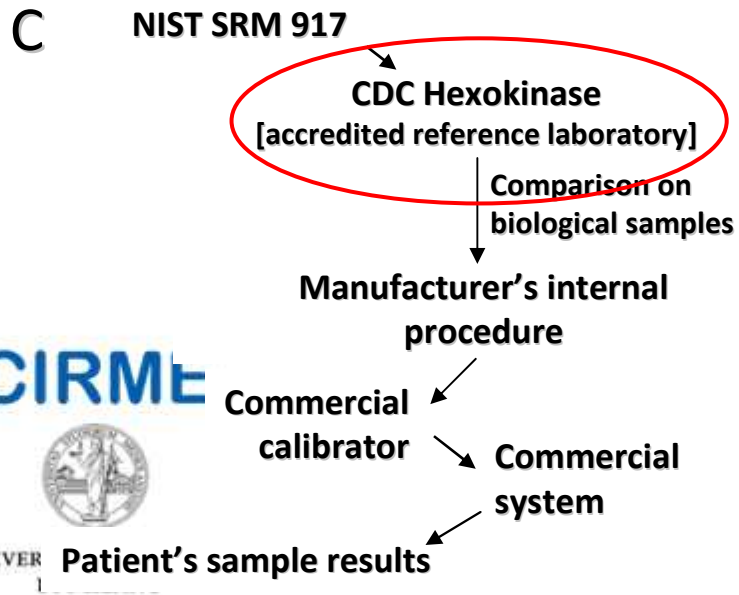
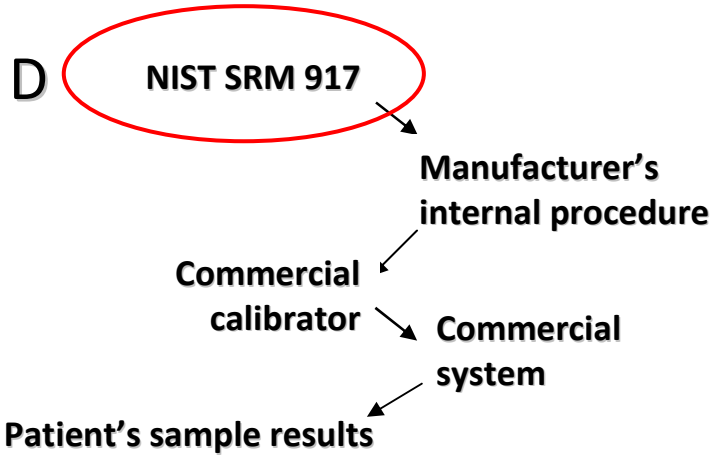
Types of metrological chains that can be used to implement the traceability of blood glucose results*







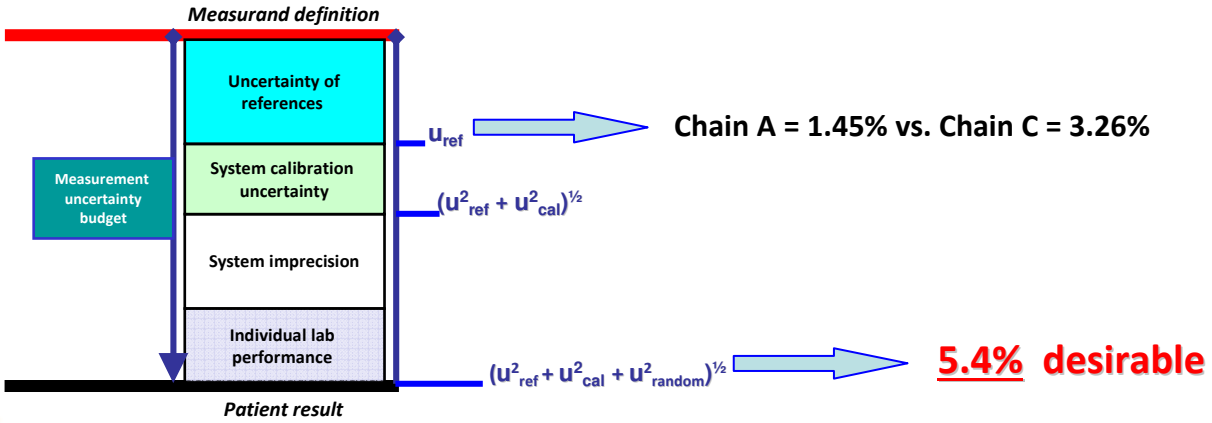


*all JCTLM recognized

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

Are the measuring systems commercially available for glucose determination able to achieve the desirable limit for combined uncertainty in a clinical setting?

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 = 1.45% vs. Chain C = 3.26%

5.4% desirable

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Braga F & Panteghini M, Clin Chim Acta 2014;432:55
Pasqualetti S, Braga F, Panteghini M, Clin Biochem 2017;50:587-94

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"A recommendation about the type of uncertainty that must be provided by manufacturers at the calibrator level, in addition to the need to standardize the approach employed by manufacturers to estimate it, is therefore urgent."

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

ISO/TC 212 Working Group 2
Reference systems
New revision of ISO 17511
in prep

IVD medical devices — Requirements for establishing metrological traceability of values assigned to calibrators, trueness control materials and human samples

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In principle, laboratory users should be able to access the following:

a) an indication of higher order references (materials and/or procedures) used to assign traceable values to calibrators,

b) which internal calibration hierarchy has been applied by the manufacturer, and

c) a detailed description of each step,

d) the expanded combined uncertainty value of commercial calibrators, and

e) which, if any, acceptable limits for uncertainty of calibrators were applied in the validation of the analytical system.

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(ideally all this information should be available in the assay or calibrator package inserts)

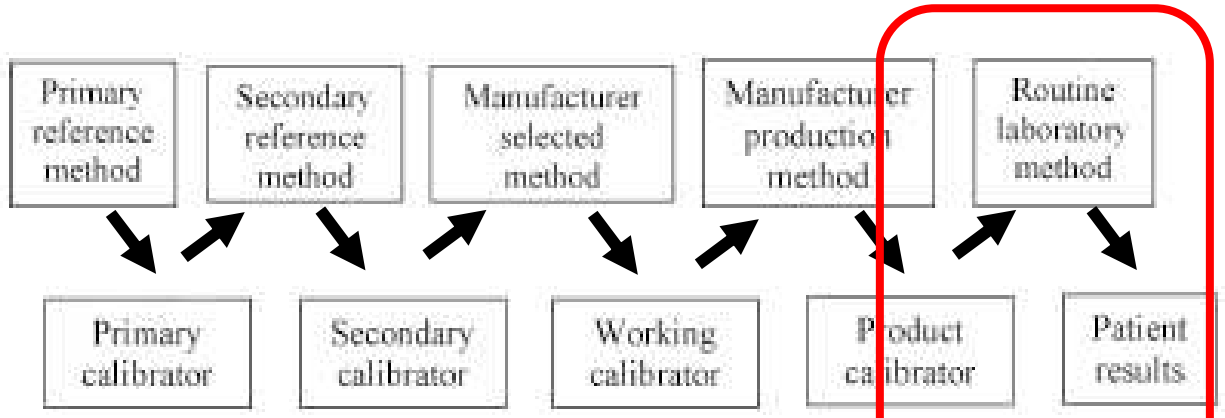
Braga F & Panteghini M, Clin Chim Acta 2014;432:55

UNCERTAINTY MARGINS FOR CLINICAL LABORATORIES

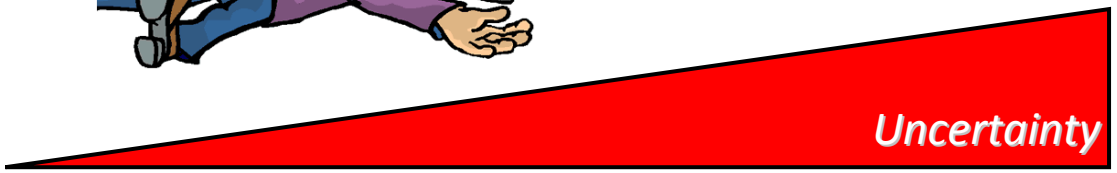
Activities

Measuring clinical samples and estimating their performance (e.g., the lot-to-lot reagent variation)

SI UNIT



Clinical laboratory



G_U

Total budget of uncertainty

100%

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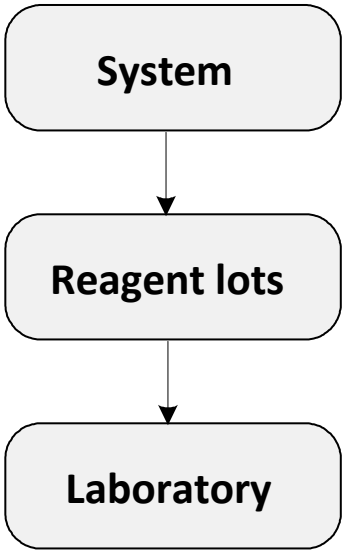
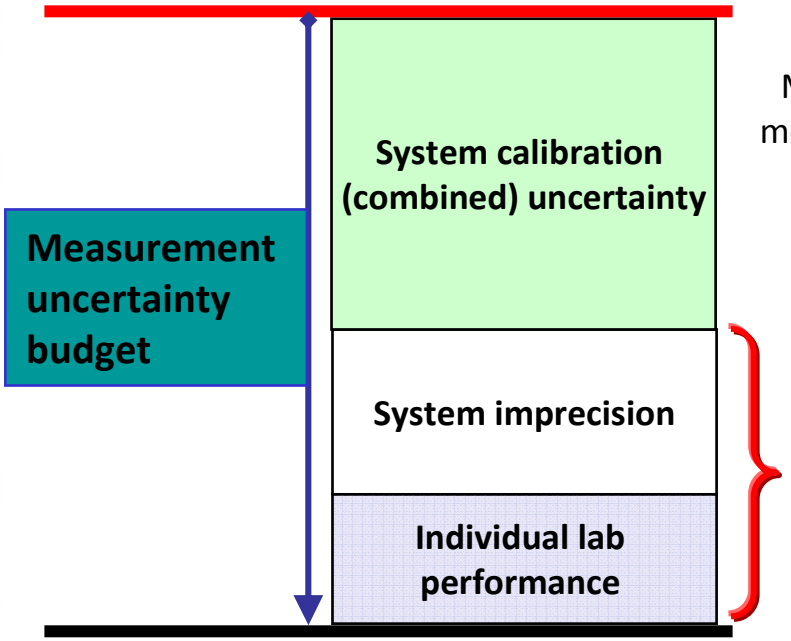
Internal Quality Control (Component II)

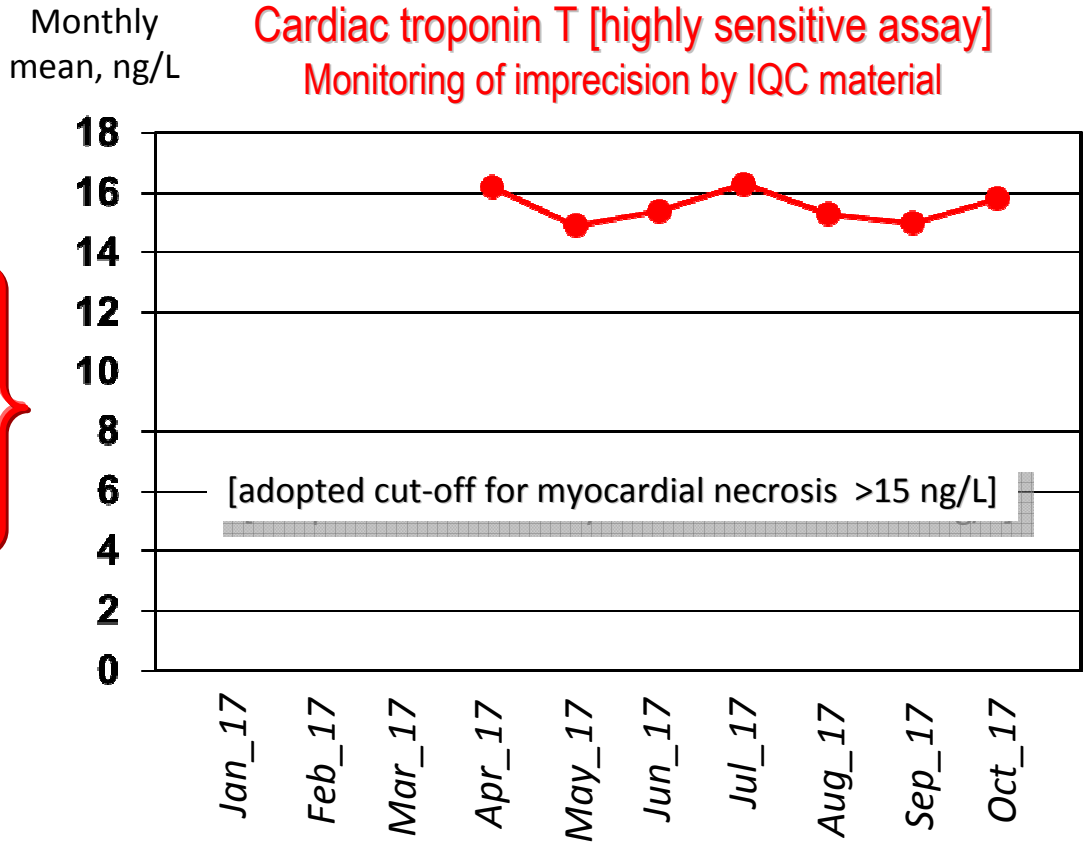
System stability at medium/long term → ***Testing the uncertainty due to the random effects***

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



Monitoring the reliability of the measuring system through Internal Quality Control: Evaluate the system + individual lab imprecision





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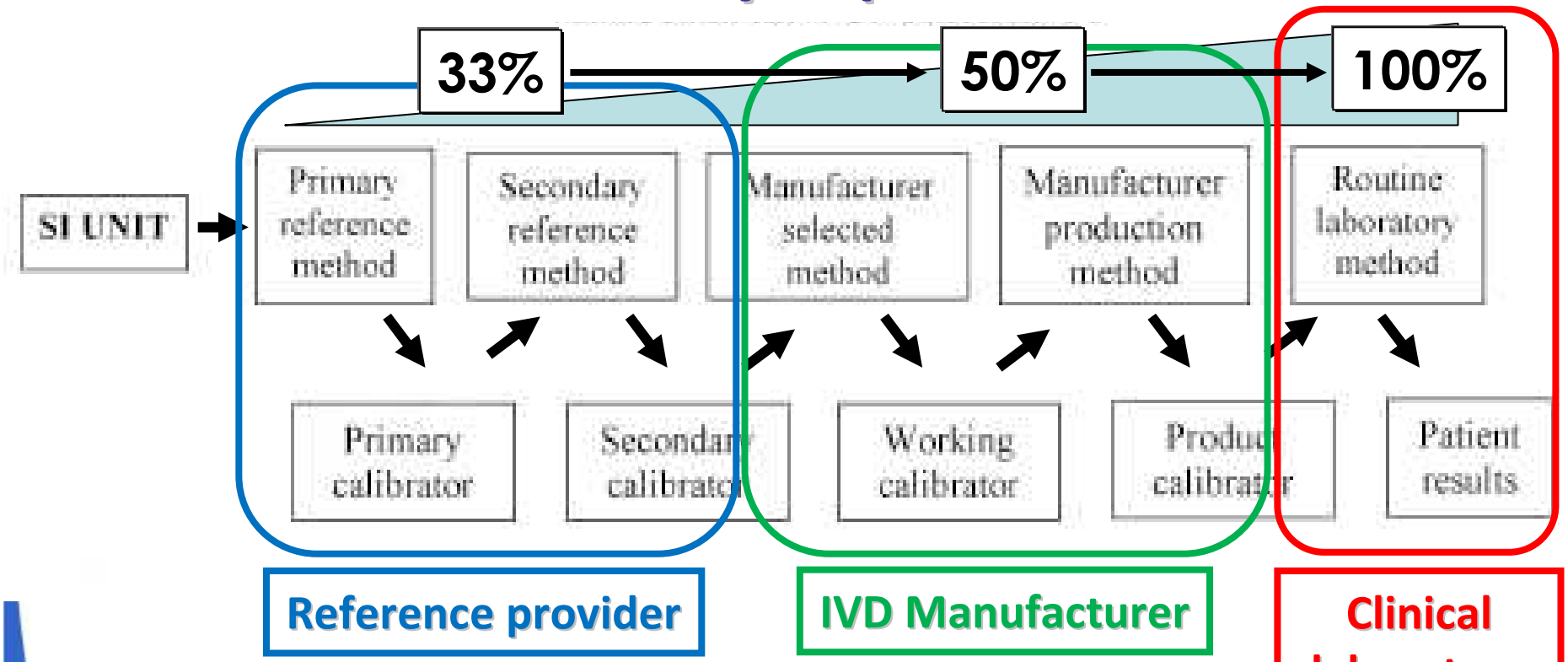
Requirements for IQC material (Component II)

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

Limits for combined uncertainty budget (expressed as percentage of total budget goal) in traceability implementation



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$$(U_{ref}^2 + U_{cal}^2 + U_{random}^2)^{1/2}$$

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

It would be interesting to verify, for each analyte measured in the clinical laboratory, 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.

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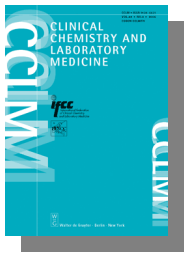
[Panteghini M, Clin Chem Lab Med 2012;50:1237]



Example 1
Glucose (Plasma)

Desirable U limit

Reference Materials

(NIST SRM 917c)
99.7±0.3% pure

(NIST SRM 965b)
1.22-1.45%
(depends on the concentration level)

1.8% — 1/3 G_U

XY Manufacturer's calibrator

C1: 120 ± 2.4 mg/dL
C2: 497 ± 10.0 mg/dL
≤2.47%

2.7% — 50% G_U

Clinical Samples

The end user has a margin until a CV of 2.4%

5.4% — G_U

DESIRABLE GOAL FROM BIOLOGICAL VARIATION

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The uncertainty of this measuring system has a high probability to fulfil the desirable specifications for the total uncertainty budget

Example 2
Creatinine (Serum)

Desirable U limit

Reference Materials

(NIST SRM 914a)
99.7±0.3% pure

(NIST SRM 967a)
L1: 0.847 ± 0.018 mg/dL
L2: 3.877 ± 0.082 mg/dL

2.1%

2.0% — 1/3 G_U

XY Manufacturer's calibrator

4.0 ± 0.12 mg/dL

3.18%

3.0% — 50% G_U

Clinical Samples

The end user has a margin until a CV of 2.55%

6.0% — G_U

DESIRABLE GOAL FROM BIOLOGICAL VARIATION

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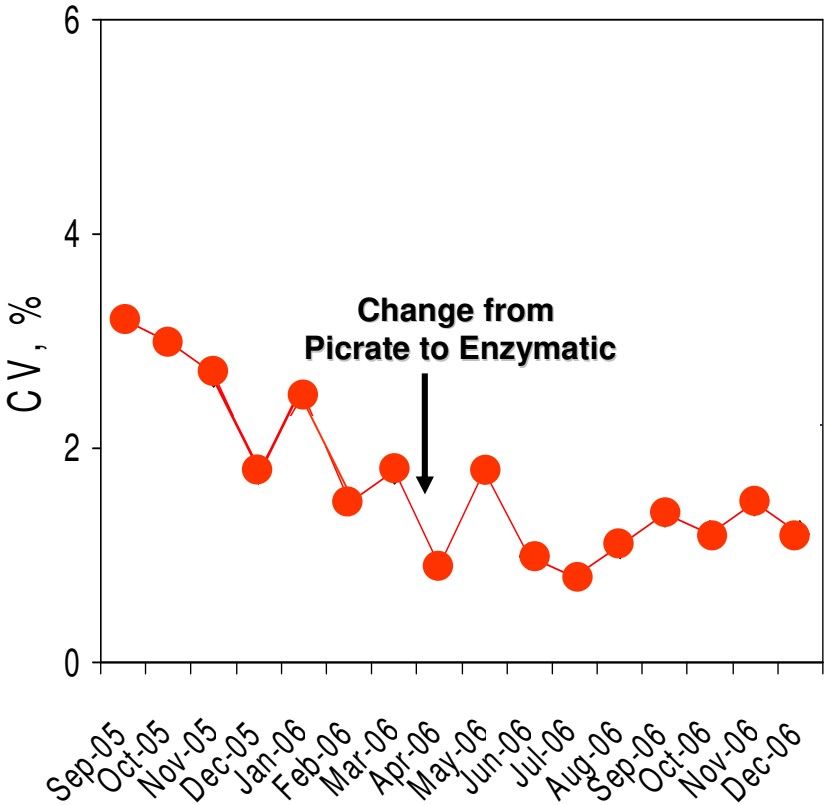
The uncertainty of this measuring system has a medium probability to fulfil the desirable specifications for the total uncertainty budget

Overall improvement in precision of serum creatinine measurements using an enzymatic assay



Infusino I et al., Clin Chem Lab Med 2007

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Example 3
Sodium (Serum)

Desirable U limit

Reference Materials

(NIST SRM 919b)
99.835±0.020% pure

(NIST SRM 956d)
120 ± 0.7 mg/dL

0.58%

0.33% 1/3 G_U

XY Manufacturer's calibrator

C1: 120 ± 1.5 mmol/L

1.25%

C2: 160 ± 1.5 mmol/L

0.93%

0.5% 50% G_U

Clinical Samples

The end user has no margin to fulfil specifications

1.0% G_U

DESIRABLE GOAL FROM BIOLOGICAL VARIATION

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The uncertainty of this measuring system has no possibility to fulfil the desirable specifications for the total uncertainty budget

Grading different quality levels

The utility to elaborate specifications at different levels of quality to move, in case, from desirable to minimum quality goals and, in the meantime, ask 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

Example 3
Sodium (Serum)

Minimum U limit

Reference Materials

(NIST SRM 919b)
99.835±0.020% pure

(NIST SRM 956d)
120 ± 0.7 mg/dL

0.58%

0.50% 1/3 G_U

XY Manufacturer's calibrator

C1: 120 ± 1.5 mmol/L

1.25%

C2: 160 ± 1.5 mmol/L

0.93%

0.75% 50% G_U

Clinical Samples

The end user has a margin until a CV of 0.6%

1.50% G_U

MINIMUM GOAL FROM BIOLOGICAL VARIATION

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The uncertainty of this measuring system has a realistic possibility to fulfil the minimum specifications for the total uncertainty budget

Final remarks

✓ In addition to the correct implementation of calibration traceability, the *definition and the fulfillment of* G_U is essential in assuring that laboratory measurements are clinically usable.

✓ To understand if it is possible to achieve this specification, *combined uncertainty budget limits across the entire metrological traceability chain* must be defined.

✓ This is very helpful to *identify those analytes for which further technological advancements are probably needed* in order to *reduce uncertainty associated with higher-order metrological references* and/or to *increase the precision of commercial measuring systems.*

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