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Centre for Metrological Traceability in Laboratory Medicine (CIRME)

Director: Prof. Mauro Panteghini

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

1st EFLM Strategic Conference

Milan (IT)
24-25 November 2014

Defining analytical performance goals 15 years after the Stockholm Conference

8th CIRME International Scientific Meeting

EFLM
EUROPEAN FEDERATION OF CLINICAL CHEMISTRY AND LABORATORY MEDICINE

PERFORMANCE CRITERIA FOR COMBINED UNCERTAINTY BUDGET IN THE IMPLEMENTATION OF METROLOGICAL TRACEABILITY

Mauro Panteghini

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Centre for Metrological Traceability in Laboratory Medicine (CIRME)

Laboratory measurement paradigm:

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

Measurement results should be independent of:

- Time
- Location/laboratory
- Assay system

Laboratory results should be equivalent no matter where they are performed

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

EU 98/79/EC-IVD Directive

Objective of traceability implementation:

to enable the results obtained by the calibrated routine procedure to be expressed in terms of the values obtained at the highest available level of the calibration hierarchy.

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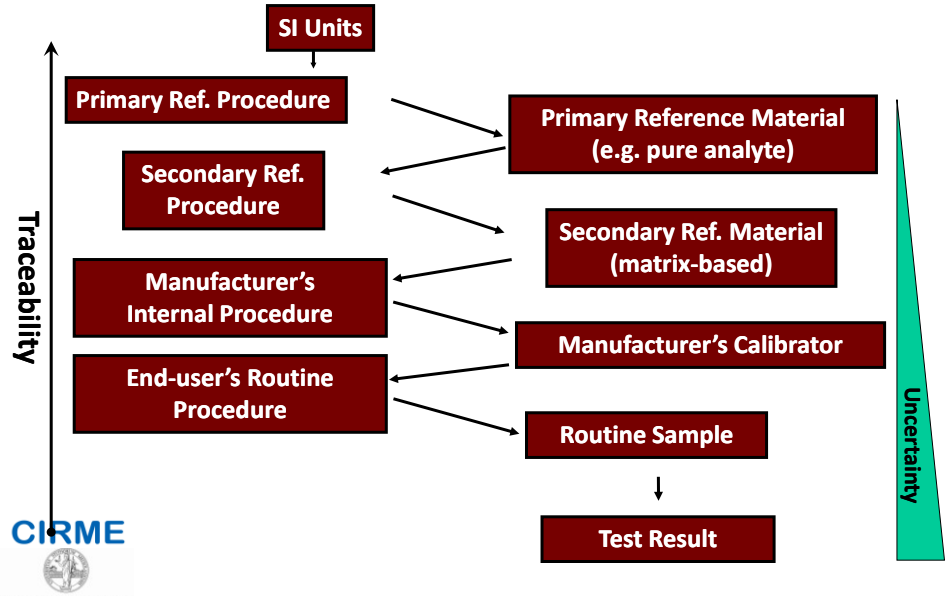
ISO/EN 17511 - Measurement of quantities in samples of biological origin - Metrological traceability of values assigned to calibrators and control materials.

Reference Measurement System



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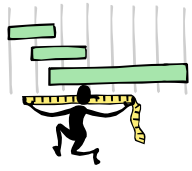
*Adapted from ISO 17511



Basic requirements to establish traceability

- Establishment of a calibration hierarchy
- Establishment of the metrological traceability for the measurement results (understand the measurements)
- Elimination of measurement bias
- Adequate estimation of measurement uncertainties

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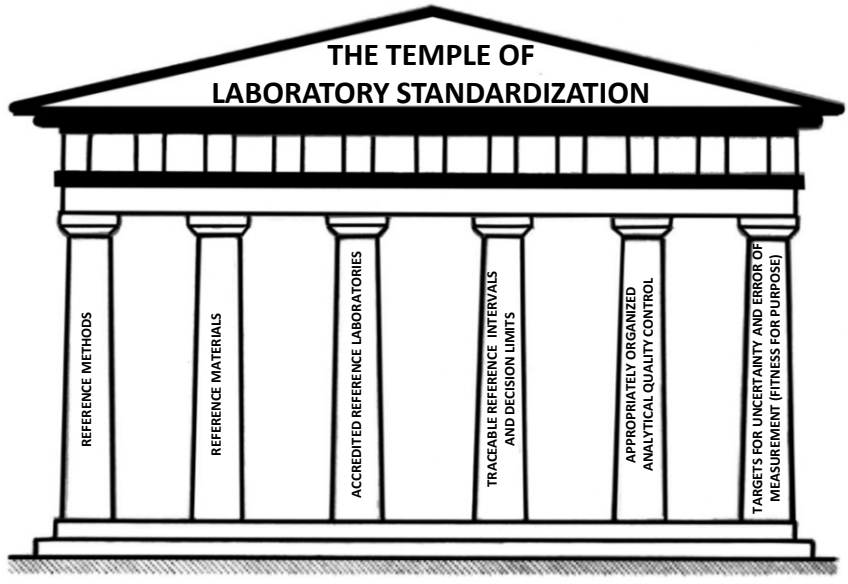

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Braga F & Panteghini M, Clin Chim Acta 2014;432:55

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).

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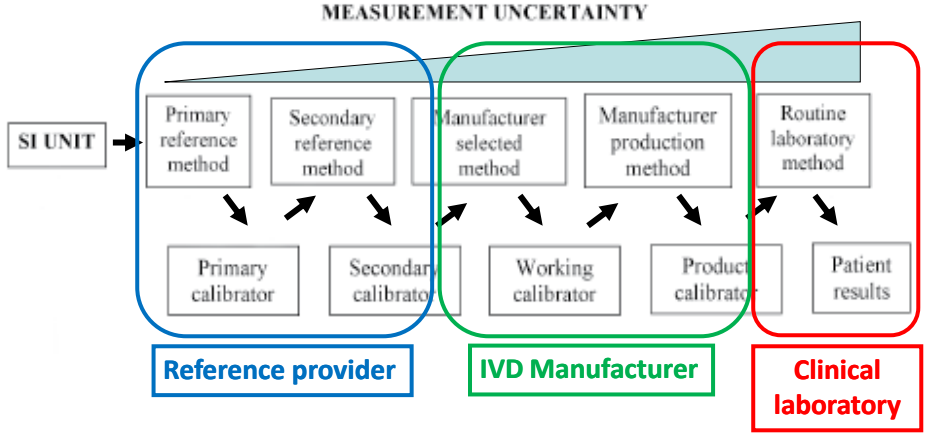
[Panteghini M, Clin Chem Lab Med 2012;50:1237]

Measurement uncertainty budget



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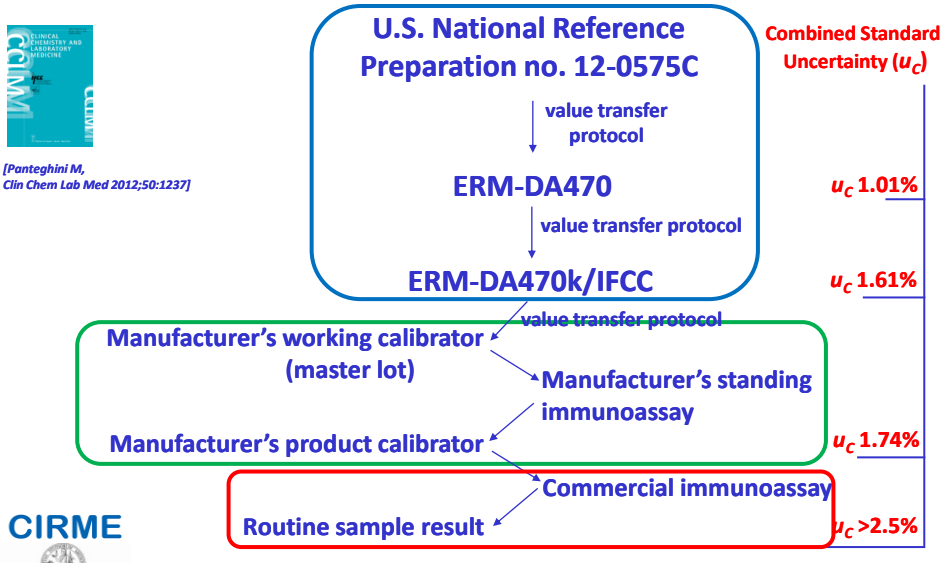
Serum albumin: Metrological traceability chain



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

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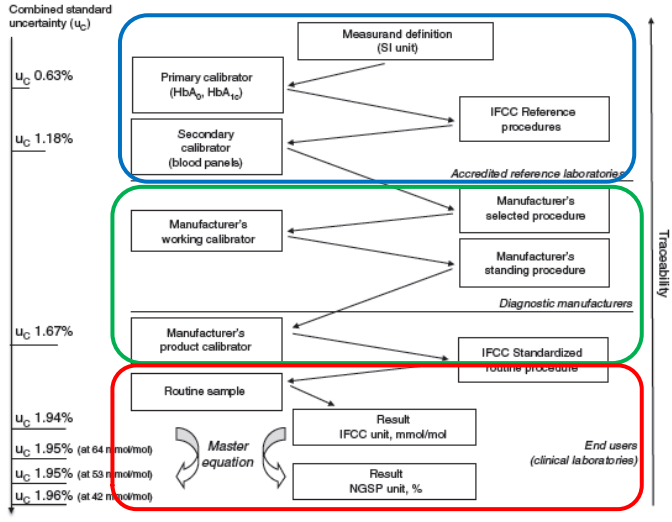
HbA_{1c}: Metrological traceability chain



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Braga F & Panteghini M. Clin Chem Lab Med 2013;51:1719

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

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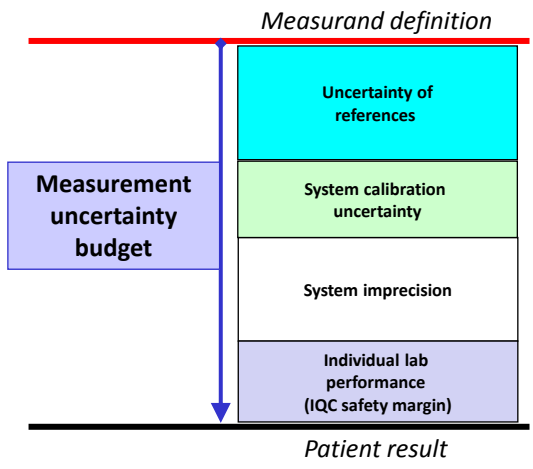
[Panteghini M, Clin Chem Lab Med 2012;50:1237]



The value assigned to the measurement standard(s) at each level in the calibration hierarchy shall have an uncertainty of measurement that includes the uncertainty contributions from each higher calibration step in the hierarchy.

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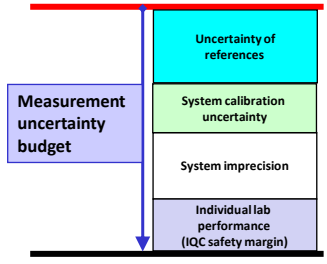
Estimate the combined uncertainty!

[The square root of the sum of the squares of the components of the uncertainty gives the combined uncertainty]



$$\mu_{result} = (\mu^2_{ref} + \mu^2_{cal} + \mu^2_{random})^{1/2}$$

and then expand uncertainty:

a coverage factor

***k* = 2**

is recommended for a confidence level of ~95% for a normal distribution.

$$U = u \times k$$

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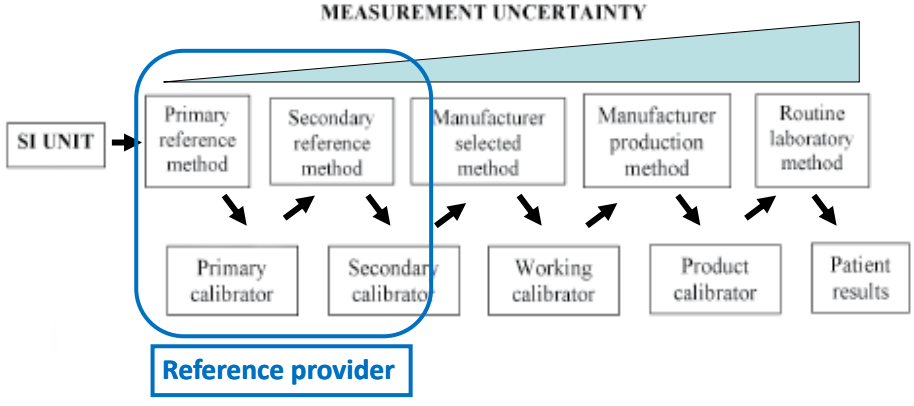
Measurement uncertainty budget



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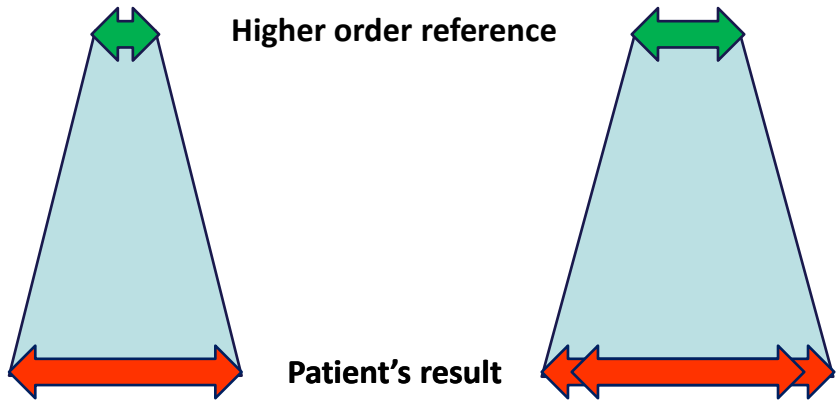
Uncertainty of references may affect the uncertainty of patient's results



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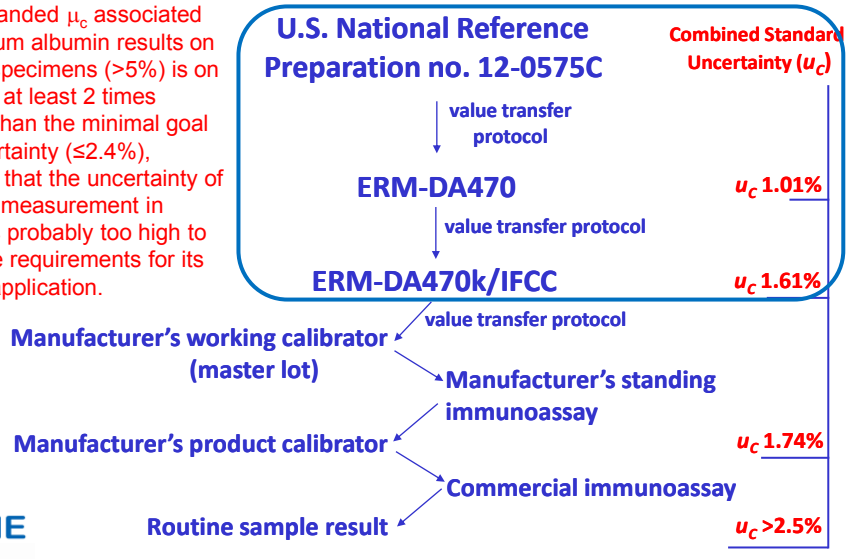
Adapted from G. Jones, 5th CIRME International Scientific Meeting – Milan, IT – Nov 2011

Serum albumin: An example

The expanded μ_c associated with serum albumin results on patient specimens (>5%) is on average at least 2 times 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.



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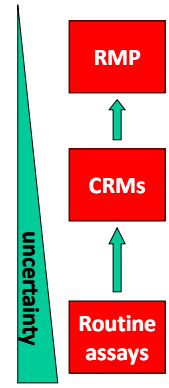
Panteghini M, Clin Chem Lab Med 2012;50:1237
Infusino I & Panteghini M, Chim Clin Acta 2013;419:15
Braga F & Panteghini M, Clin Chim Acta 2014;432:55

To assure that the expanded combined uncertainty associated with patient results fulfill the total budget goal, the higher order references should display uncertainty at most equal to 1/3 of the total budget goal.

Specifications of reference measurement procedure defined by intended use…

…intended use is the certification of reference materials…

…the specifications of certified reference materials are defined by the performance needs of the clinical assays.



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5th CIRME International Scientific Meeting
Milano - 30 November 2011

MATERIAL MEASUREMENT LABORATORY

Synopsis of proposed analytical performance goals for cardiac troponin I measurement

[Panteghini M, AACB Troponin Monograph 2012]

Quality level	Imprecision goal (as CV)			Bias goal
	Outcome-based	Biological variability	Expert opinion	Biological variability
Minimum	<13%[a]	<7.3%	<20%	±21.6 %
Desirable	<10%[b]	<4.9%	<10%	±14.4 %
Optimum	<6%[c]	<2.4%	-	±7.2 %

Assuming a diagnostic misclassification of [a]1.8%, [b]1.0% and [c]0.5%.
[Sheehan P et al., Ann Clin Biochem 2002;39:213]

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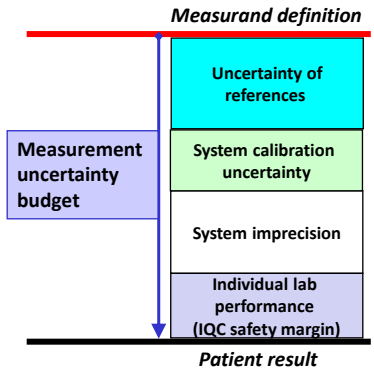
IFCC WG-TNI Technical Discussion
Value Assignment of NIST SRM 2922 and measurement uncertainty



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

Anticipate 50% of uncertainty budget (6.5%) at manufacturer's calibration and value transfer level.

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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Fulfillment of the Requirements of the EU IVD Directive by Manufacturers

EU 98/79/EC-IVD Directive

- Preparation of the necessary technical documentation
- All data that characterize the product
- Testing protocols
- Labels and instruction for use
- Assigned values and metrological traceability
  - Traceability chain and calibration hierarchy
  - Transfer protocols
  - Commutability testing
  - Determination of uncertainty (fitness for purpose)
- Stability testing

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Role of IVD manufacturers: "do"

IVD manufacturers should define a calibration hierarchy to assign traceable values to their system calibrators and to fulfil during this process uncertainty limits, which represent a proportion of the uncertainty budget allowed for clinical laboratory results.

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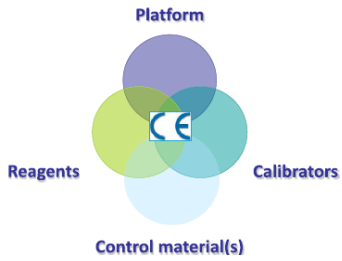
Braga F & Panteghini M, Clin Chim Acta 2014;432:55

Paradigm shift in the thinking

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



- **If the manufacturer should assume 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 analytical 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 analytical 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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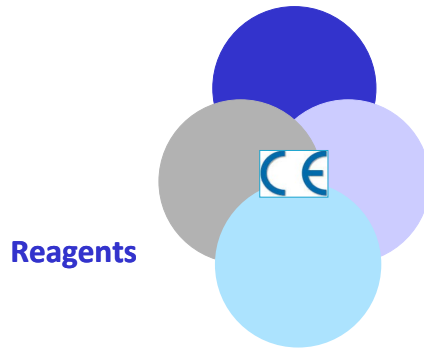
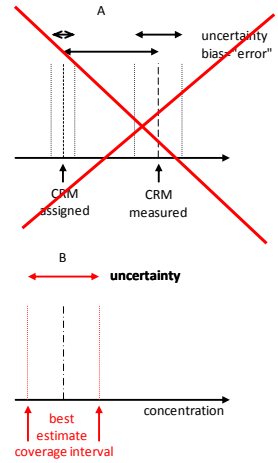
Thus, clinical laboratories need to rely on the manufacturers who must ensure traceability of their analytical system to the highest available level



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



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

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In theory… IVD manufacturers:

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

In practice… IVD manufacturers:

- **Need to select <u>suitable</u> ref. materials and/or identify <u>who is performing</u> ref. procedures**
- **Need to establish the <u>acceptability</u> for the calibrator uncertainty**

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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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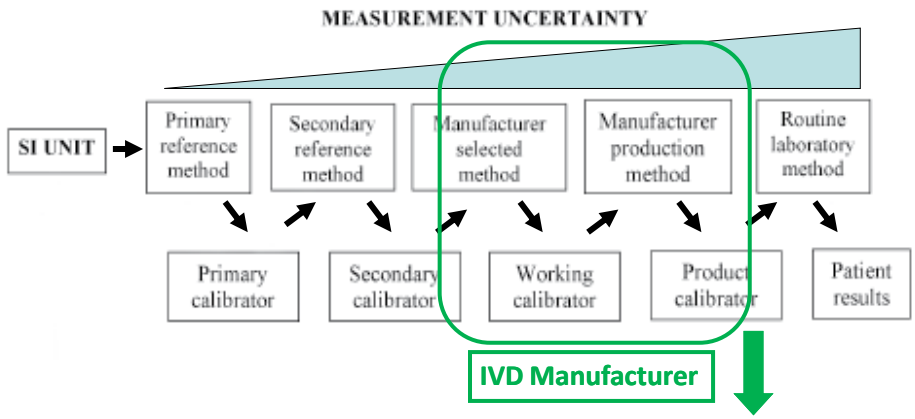
Panteghini M. Clin Biochem 2009;42:236

Measurement uncertainty budget



The manufacturer must indicate the combined uncertainty (expanded) associated with calibrators when used in conjunction with other components of the analytical system (platform and reagents). Such uncertainty estimates provided by the manufacturer should include the uncertainty associated with higher levels of the metrological traceability chain.

INVITED CRITICAL REVIEW

Table 1

Metrological traceability and uncertainty information derived from calibrator package inserts of commercial systems measuring blood glucose marketed by four IVD companies.

Company	Platform	Principle of commercial method	Calibrator	Declared standard uncertainty[a]	Higher-order reference employed		Type of traceability chain used[b]	Combined standard uncertainty associated with the used chain[c]
					Method	Material		
Abbott	Architect	ND	Multiconstituent calibrator	2.70%	IDMS	NIST SRM 965	A	1.22-1.45%[d]
Beckman	AU	Hexokinase	System calibrator	ND	ND	NIST SRM 965	A	1.22-1.45%[d]
	Synchron	Hexokinase	Synchron multicalibrator	ND	ND	NIST SRM 917a	D	1.60-3.00%[e]
Roche	Cobas c	Hexokinase	C.f.a.s.	0.84%	IDMS	ND	B	1.70%
	Integra	Hexokinase	C.f.a.s.	0.62%	IDMS	ND	B	1.70%
	Modular	Hexokinase	C.f.a.s.	0.84%	IDMS	ND	B	1.70%
		GOD		0.84%	IDMS	ND	B	1.70%
Siemens	Advia	Hexokinase	Chemistry calibrator	1.30%	Hexokinase	NIST SRM 917a	C	1.88-3.26%[f]
		GOD		0.80%	Hexokinase	NIST SRM 917a	C	1.88-3.26%[f]

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

"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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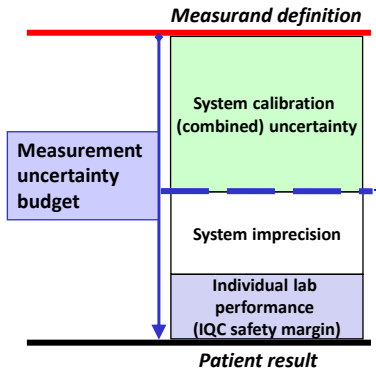
Need to define criteria for manufacturers that can be achieved for their calibrators leaving enough uncertainty budget for the laboratories to produce clinically acceptable results.



→ **Allowable limit for the expanded (combined) uncertainty of manufacturer's commercial calibrators @ 50% of the goals**

[note that these are goals for random variability, as at the calibrator level the systematic error (bias), in agreement with the metrological traceability theory, must be corrected if present in a non negligible amount]

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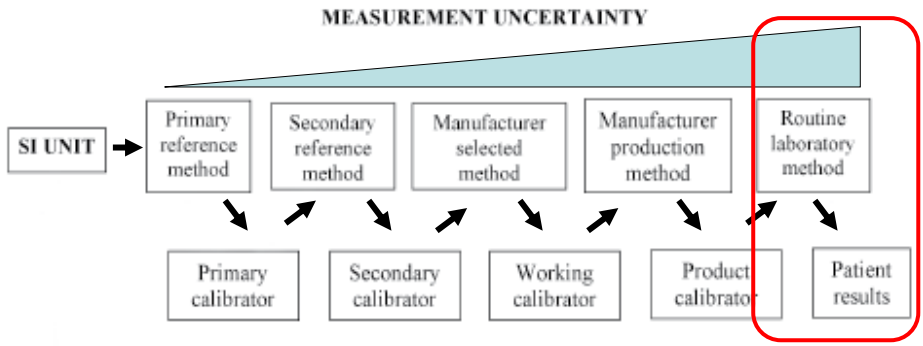
Opinion Paper Clin Chem Lab Med 2013; 51:973

Renze Bais*, Dave Armbruster, Rob T. P. Jansen, George Klee, Mauro Panteghini, Joseph Passarelli and Ken A. Sikaris on behalf of the IFCC Working Group on Allowable Error for Traceable Results (WG-AETR)

Defining acceptable limits for the metrological traceability of specific measurands

Measurement uncertainty budget



Clinical laboratory

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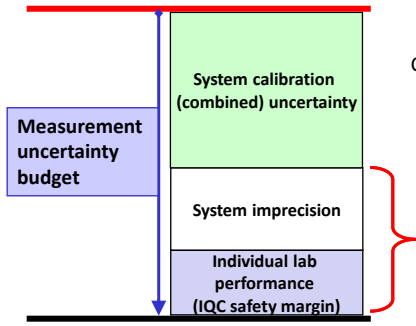
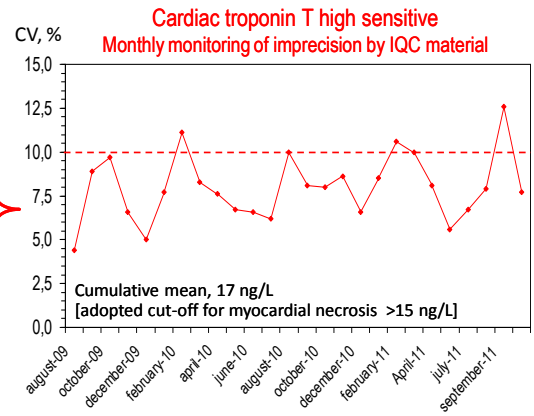
Monitoring the reliability of the analytical system through Internal Quality Control: Evaluate the system + individual lab imprecision





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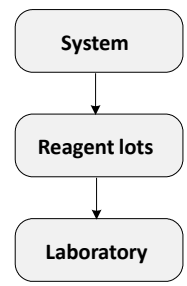
Internal Quality Control (Component II)

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

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



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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 system control material used for checking alignment
Specimens closely resembling authentic patient 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

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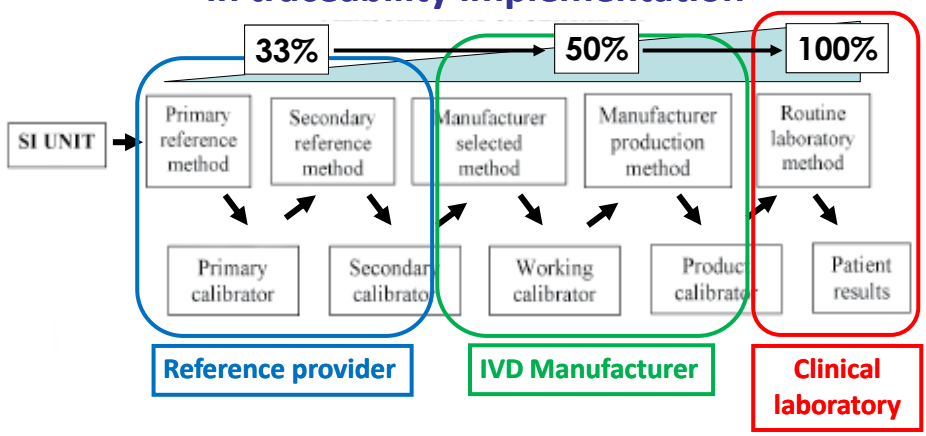
Limits for combined uncertainty budget (expressed as percentage of total budget goal) in traceability implementation



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$$(\mu^2_{ref} + \mu^2_{cal} + \mu^2_{random})^{1/2}$$

Limitations of CE mark

[stating compliance with legislation, mainly by means of European standards]

- Does ***not*** mean that manufacturer has transferred trueness successfully
- Does ***not*** mean that uncertainty of calibrator meets clinical needs
- Does ***not*** mean that comparators (e.g., similar assays) are also traceable

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Adapted from G. Jones, JCTLM & IVD Industry Meeting – Los Angeles, USA 2012

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

- **Selection of different types of traceability chains**
- **Uncertainty (including imprecision) of the analytical system may be too large**
- **Commercial assay may not be specific for the measurand → Interfering substances may influence the result**

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

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[redacted]

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

INVITED CRITICAL REVIEW

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Beckman	AU	Hexokinase	System calibrator	ND	ND	NIST SRM 965	A	1.22-1.45%[d]
	Synchron	Hexokinase	Synchron multicalibrator	ND	ND	NIST SRM 917a	D	1.60-3.00%[e]
Roche	Cobas c	Hexokinase	C.f.a.s.	0.84%	IDMS	ND	B	1.70%
	Integra	Hexokinase	C.f.a.s.	0.62%	IDMS	ND	B	1.70%
	Modular	Hexokinase	C.f.a.s.	0.84%	IDMS	ND	B	1.70%
		GOD		0.84%	IDMS	ND	B	1.70%
Siemens	Advia	Hexokinase	Chemistry calibrator	1.30%	Hexokinase	NIST SRM 917a	C	1.88-3.26%[f]
		GOD		0.80%	Hexokinase	NIST SRM 917a	C	1.88-3.26%[f]

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

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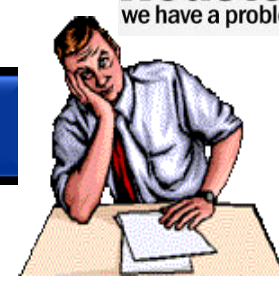
Braga F & Panteghini M, Clin Chim Acta 2014;432:55

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

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

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

c) a detailed description of each step,

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

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

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

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

- **Selection of different types of traceability chains**
- **Uncertainty (including imprecision) of the analytical system may be too large**
- **Commercial assay may not be specific for the measurand → Interfering substances may influence the result**

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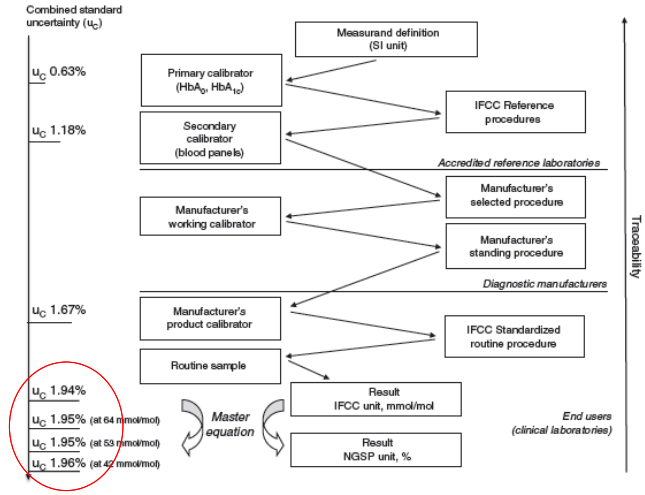
Federica Braga* and Mauro Panteghini

Standardization and analytical goals for glycated hemoglobin measurement

Clin Chem Lab Med 2013;51:1719–26

HbA_{1c} reference system and associated combined standard uncertainty



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Standardization and analytical goals for glycated hemoglobin measurement

Clin Chem Lab Med 2013;51:1719–26

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

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

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

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Clin Chem Lab Med 2008;46(4):567–572 © 2008 by Walter de Gruyter • Berlin • New York. DOI 10.1515/CCLM.2008.113

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

International Federation of Clinical Chemistry and Laboratory Medicine (IFCC)[3)]
IFCC Scientific Division
Mauro Panteghini* on behalf of the IFCC Scientific Division

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

- The alkaline picrate method is unable to measure solely creatinine
- Endogenous and exogenous substances may significantly interfere
- Interfering substances in serum, particularly proteins, can lead to significant overstimation with various alkaline picrate methods
- Interference from glucose and ketones particularly important in diabetics who are at high-risk for CKD

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

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Metrological traceability and uncertainty information derived from calibrator package inserts of commercial systems measuring serum creatinine marketed by four IVD companies

Company	Platform	Principle of commercial method	Calibrator	Declared standard uncertainty	Higher-order reference employed		Type of traceability chain used	Combined standard uncertainty associated with the used chain
					Method	Material		
Abbott	Architect	Enzymatic	Multigent Clin Chem calibrator	1.48%	IDMS	NIST SRM 967	A	2.12-2.79%
		ND	Multiconstituent calibrator	2.7%	IDMS	NIST SRM 967	A	2.12-2.79%
Beckman	AU	Enzymatic	System calibrator	ND	ND	NIST SRM 967	A	2.12-2.79%
		Alkaline picrate	System calibrator	ND	IDMS	NIST SRM 967	A	2.12-2.79%
		Uncompensated alk. 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%
Roche	Cobas c	Enzymatic	C.f.a.s.	0.91%	IDMS	ND	D	1.5%
		Alkaline picrate compensated	C.f.a.s.	1.62%	IDMS	ND	D	1.5%
		Alkaline picrate rate-blanked and compensated	C.f.a.s.	1.42%	IDMS	ND	D	1.5%
	Integra/Cobasc111	Enzymatic	C.f.a.s	1.06%	IDMS	ND	D	1.5%
	Integra400/Cobasc111	Alkaline picrate compensated	C.f.a.s	0.30%	IDMS	ND	D	1.5%
	Integra800	Alkaline picrate compensated	C.f.a.s	0.72%	IDMS	ND	D	1.5%
	Modular	Enzymatic	C.f.a.s	0.91%	IDMS	ND	D	1.5%
		Alkaline picrate compensated	C.f.a.s	1.38%	IDMS	ND	D	1.5%
		Alkaline picrate rate-blanked and compensated	C.f.a.s	0.79%	IDMS	ND	D	1.5%
Siemens	Dimension Vista	Enzymatic	ECREA calibrator A	5.08%	ND	NIST SRM 914a	C	NA
			ECREA calibrator B	3.16%	ND	NIST SRM 914a	C	NA
		Alkaline picrate	Chemistry calibrator	1.6%	GC-IDMS	NIST SRM 914a	D	1.5%
	Advia	Enzymatic	Chemistry calibrator	0.45%	IDMS	NIST SRM 914a NIST SRM967	A	2.12-2.79%
		Alkaline picrate rate-blanked and compensated	Chemistry calibrator	1.6%	IDMS	NIST SRM 967	A	2.12-2.79%

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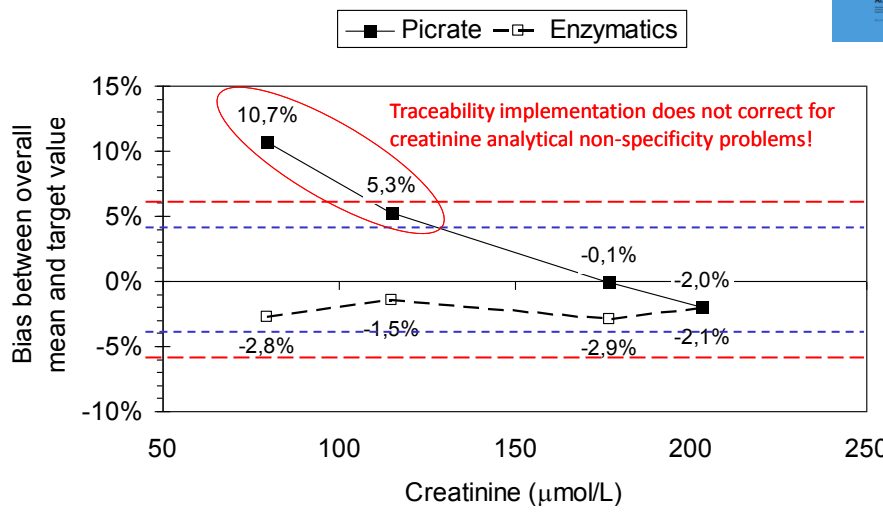
Note: For serum creatinine measurements on patient samples, the acceptable limits for expanded uncertainty derived from its CV_I are 3.0% (desiderable) and 4.5% (minimum quality level), respectively.

Carobene A et al., Clin Chim Acta 2014;427:100



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

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"THE TRACEABILITY REVOLUTION MANIFESTO"

- **Definition and approval by JCTLM of reference measurement systems, possibly in their entirety;**
- **Implementation by IVD industry of traceability to such reference systems in a scientifically sound and transparent way;**
- **Definition by the profession of the clinically acceptable measurement error for each of the analytes used in the clinical field;**
- **Adoption by EQAS providers of commutable materials and use of an evaluation approach exclusively based on trueness;**
- **Monitoring of the analytical performance of individual laboratories by the participation in EQAS meeting metrological criteria and application of clinically acceptable limits;**
- **Abandonment by users (and consequently by industry) of nonspecific methods and/or of assays with demonstrated insufficient quality.**

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