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Centre for Metrological Traceability in Laboratory Medicine (CIRME)

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

EuroMedLab Athens 2017
Exhibition, 12 - 14 JUNE

Roles and responsibilities in verification of traceability of in vitro medical diagnostics (IVD)

Federica Braga

University of Milan Medical School

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)

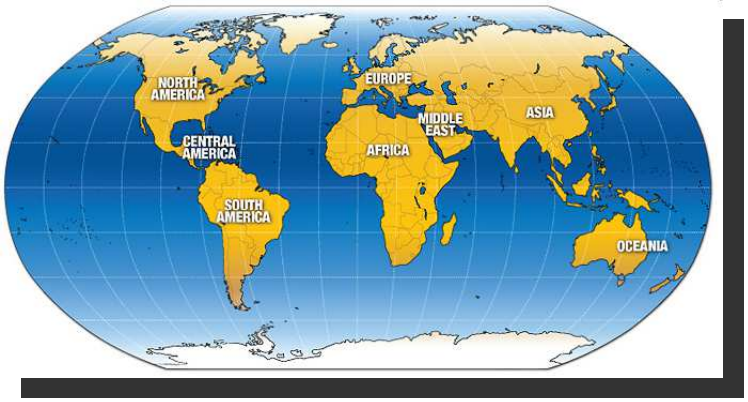
Measurement results should be independent of:

– Time

– Location/laboratory

– Assay system

Laboratory results should be equivalent no matter where they are performed



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EU 98/79/EC-IVD Directive

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

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.


INTERNATIONAL STANDARD ISO 17511

In vitro diagnostic medical devices — Measurement of quantities in biological samples — Metrological traceability of values assigned to calibrators and control materials

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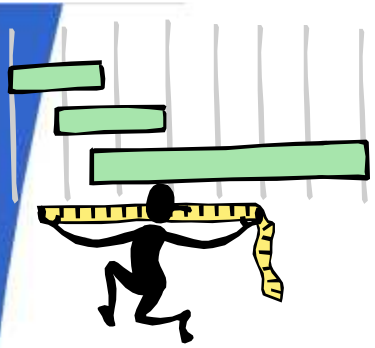
ISO/EN 17511 - Measurement of quantities in samples of biological origin - Metrological traceability of values assigned to calibrators and control materials.



Basic requirements to establish traceability

- Establishment of a calibration hierarchy starting from the unequivocal definition of the measurand
- Elimination of measurement bias
- Adequate estimation of measurement uncertainty

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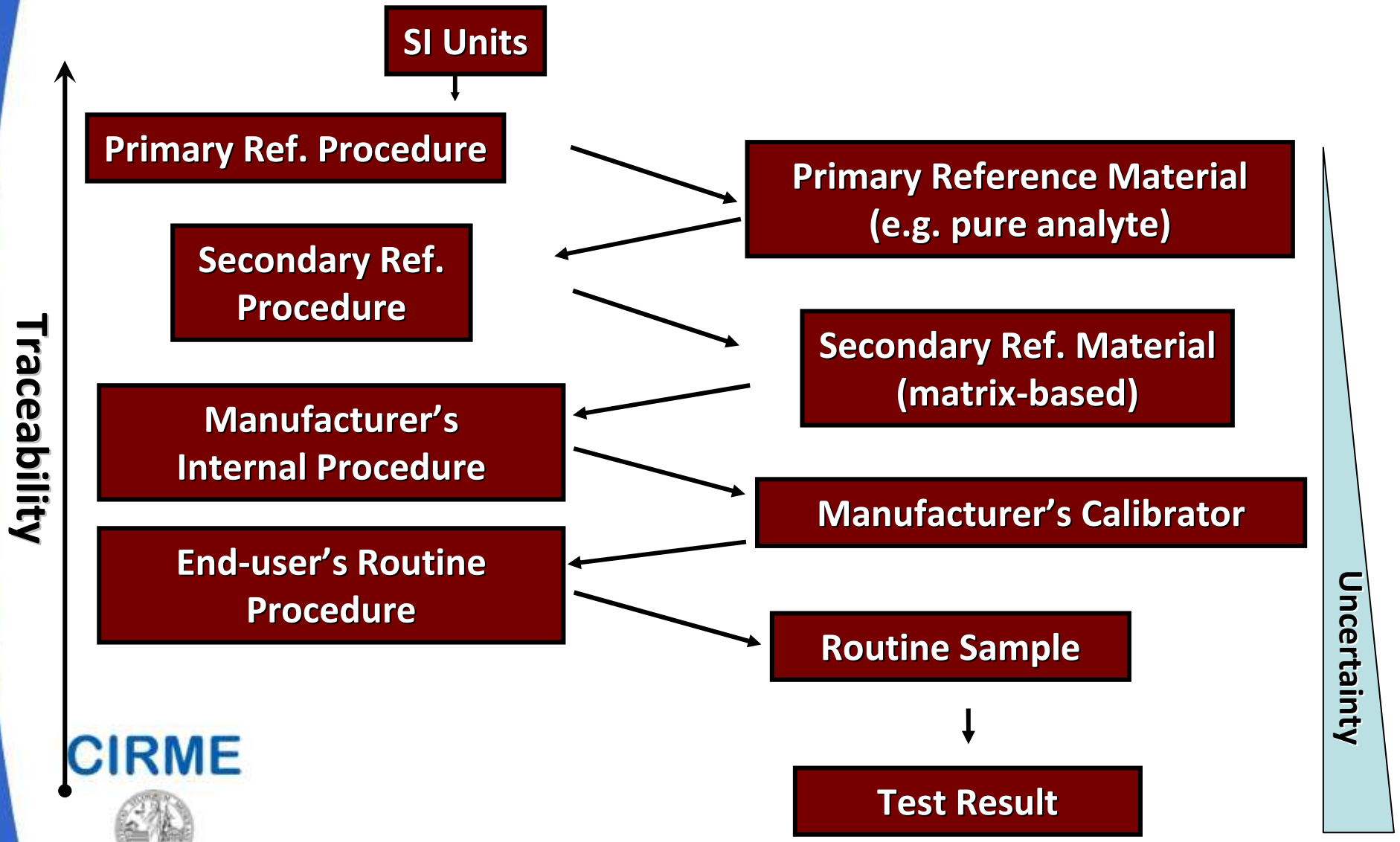
Reference Measurement System



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*Adapted from ISO 17511

Profession (e.g., IFCC, JCTLM): 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 component I: testing system controls to confirm and verify manufacturer's declared performance (CE marked – virtually unbiased)
- EQA: true value in commutable materials for defining measurement error of laboratory

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

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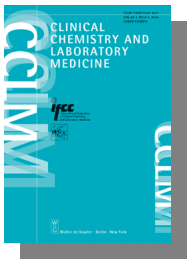

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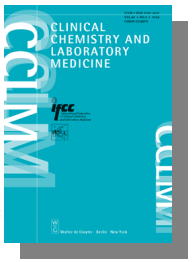

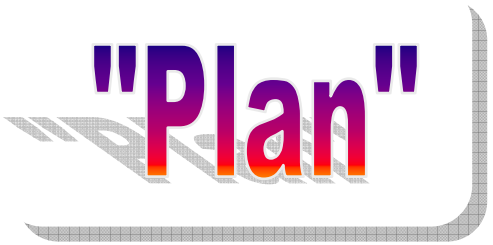

Role of Professional Organization:

- Unequivocal definition of the *measurand* as the quantity subject to measurement
- Definition of the *reference measurement system*
- Definition of *analytical performance specifications*

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Measurand

TYPE A MEASURANDS

- Well defined compounds;
- Traceable to SI units;
- Results are not method-dependent;
- Approx. 65 analytes (metabolites, electrolytes, steroid hormones);

TYPE B MEASURANDS

- Not well defined (often heterogeneous mixtures);
- Analytes can be bound or in free state;
- Not traceable to SI units, but to arbitrary units (e.g. WHO International Units);
- Immunochemical procedures show inherent variability (different epitopes);
- 400-600 analytes (tumour markers, viral antigens, clotting factors);

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Reference measurement system

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

Analytical performance specifications

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

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.

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L Thienpont et al., Clin Chem Lab Med 2004;42:842
Braga F & Panteghini M, Clin Chim Acta 2014;432:55

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)

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

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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Outcome approach

a. Done by direct outcome studies – investigating the impact of analytical performance of the test on clinical outcome.

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 outcome, e.g., by simulation analysis.

Biological Variation approach

Intra-individual BV: CV_I%

Inter-individual BV: CV_G%

IMPRECISION: $\leq 0.25\ CV_I$ (O)
$\leq 0.5\ CV_I$ (D)
$\leq 0.75\ CV_I$ (M)

BIAS: $< 0.125\ (CV_I^2 + CV_G^2)^{1/2}$ (O)
$< 0.25\ (CV_I^2 + CV_G^2)^{1/2}$ (D)
$< 0.375\ (CV_I^2 + CV_G^2)^{1/2}$ (M)

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Biological Variation approach

UNCERTAINTY

[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]

<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)

Total uncertainty 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.

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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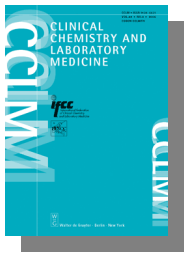
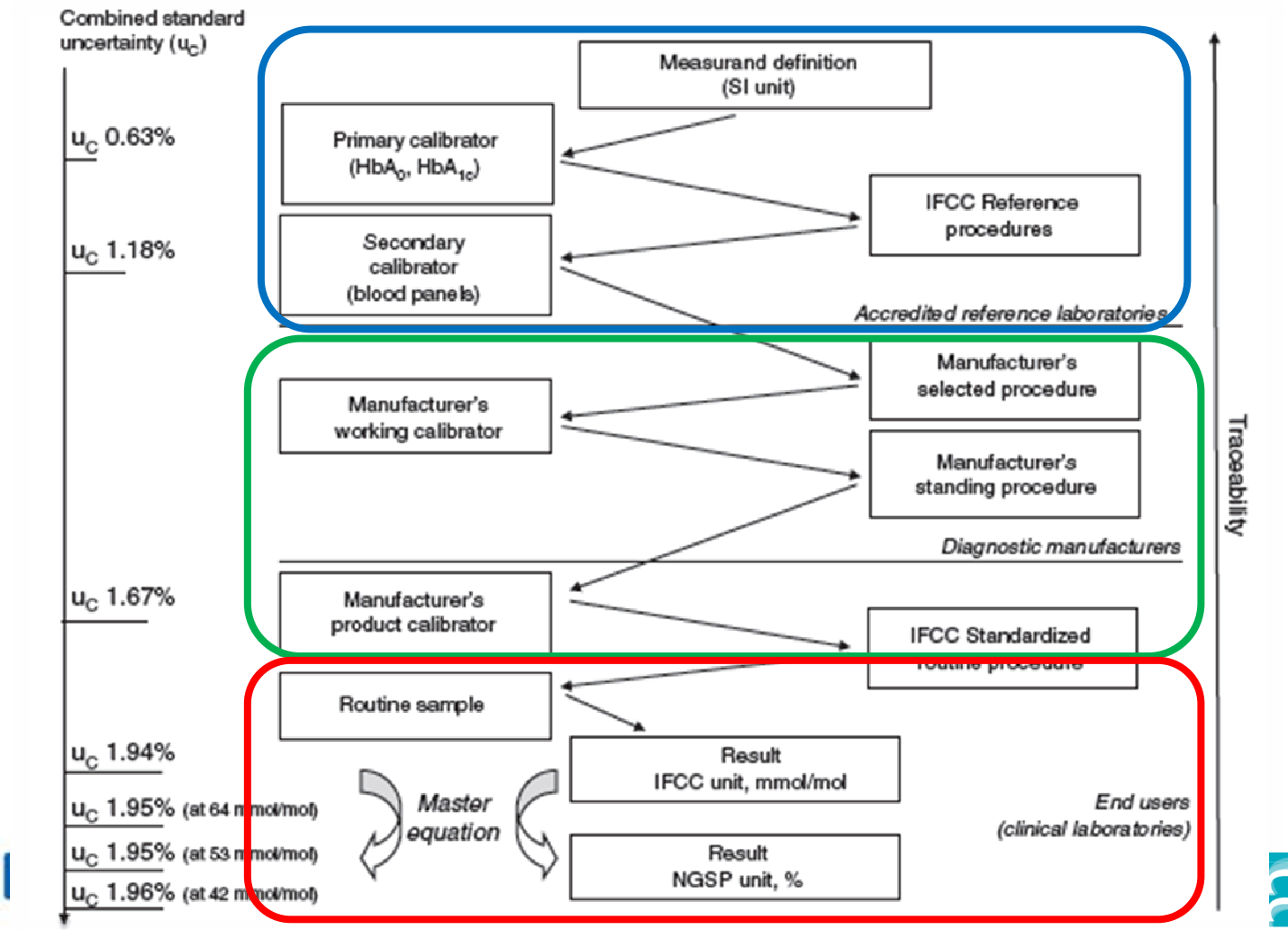


[Panteghini M, Clin Chem Lab Med 2012;50:1237]

HbA_{1c}: Metrological traceability chain



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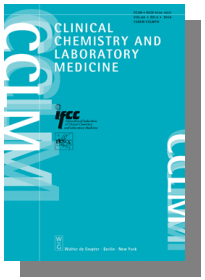
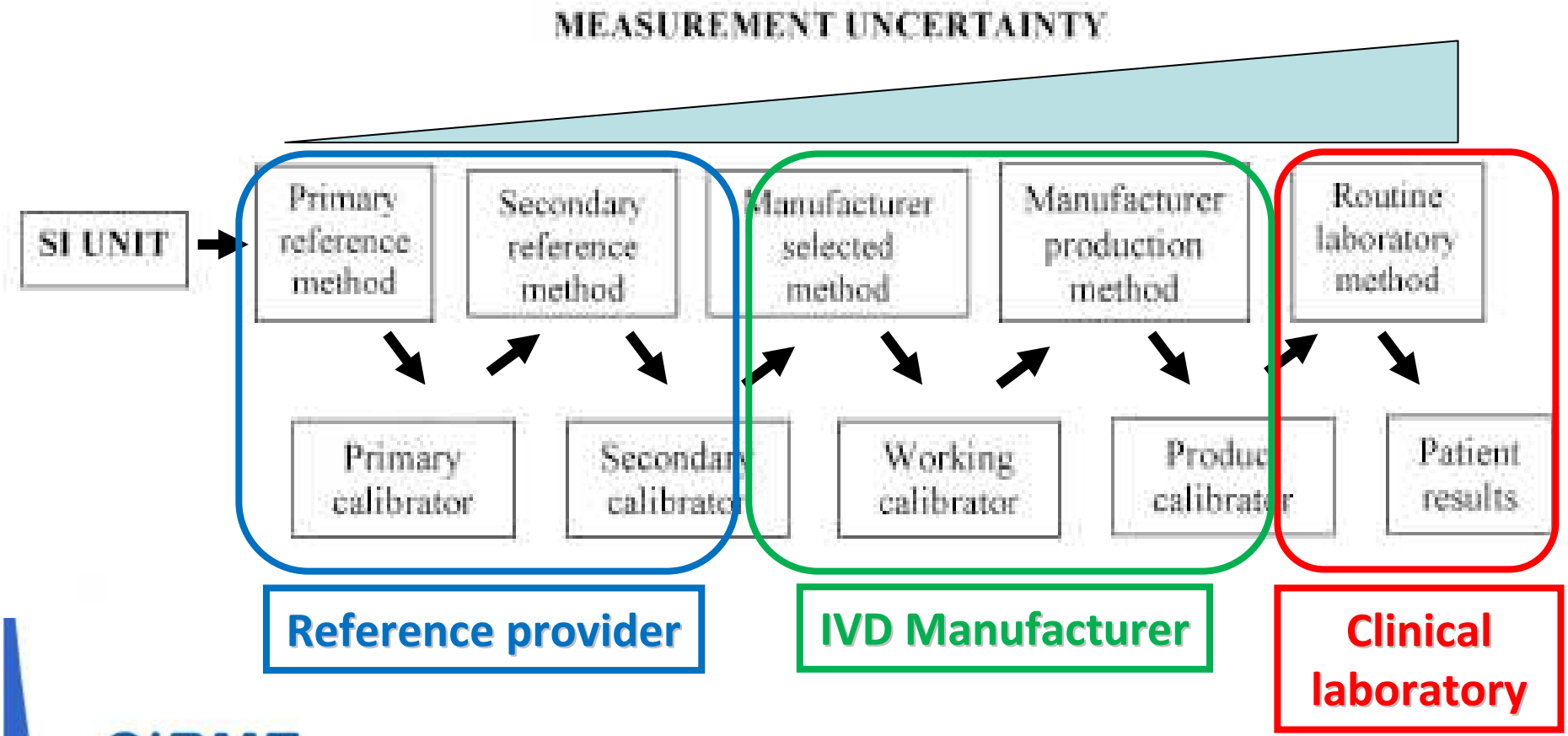
Braga F & Panteghini M. Clin Chem Lab Med 2013;51:1719



Uncertainty budget



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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

Measurand definition

Total measurement uncertainty budget

Uncertainty of references — **33%**

System calibration uncertainty — **50%**

System imprecision

Individual lab performance (IQC safety margin) — **100%**

Patient result

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

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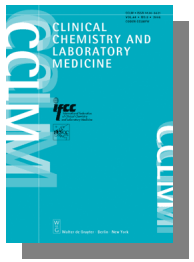
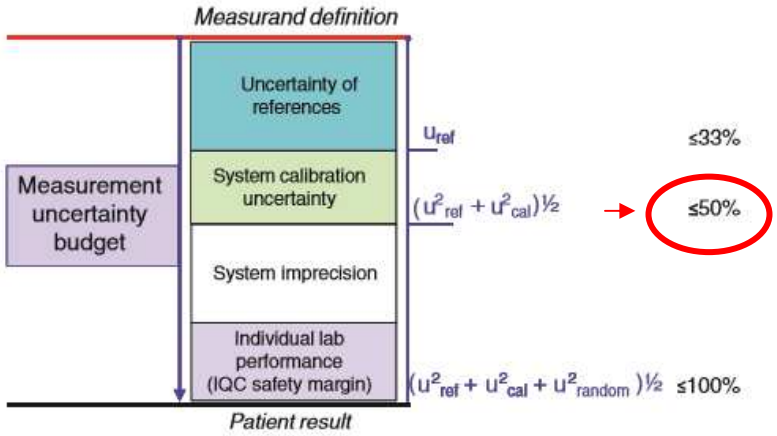


"Do"

Role of IVD manufacturers

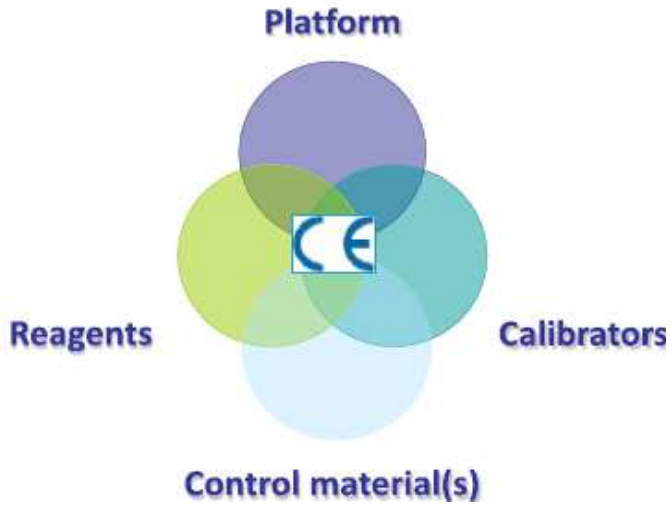
IVD manufacturers should define a calibration hierarchy to assign traceable values to their system calibrators and to fulfil during this process uncertainty limits,

which represent a proportion of the uncertainty budget allowed for clinical laboratory results.



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

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

Post-marketing surveillance of IVD metrological traceability

End users (clinical laboratories):

Survey assay and laboratory performance through:
- IQC component I: testing system controls to confirm and verify manufacturer's declared performance (CE marked – virtually unbiased)
- EQA: true value in commutable materials for defining measurement error of laboratory

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

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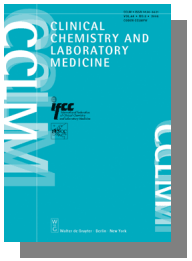

"Check"

Post-marketing surveillance

The role of the end-users

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

2. Daily surveillance of IVD system traceability

3. Estimating the measurement uncertainty due to the random effects

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

"Check"

Post-marketing surveillance

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

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

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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Some organisations are frequently mentioned (often without explanation): used as a “trusted brand”

- NIST, IRMM, IFCC, CLSI (protocols)

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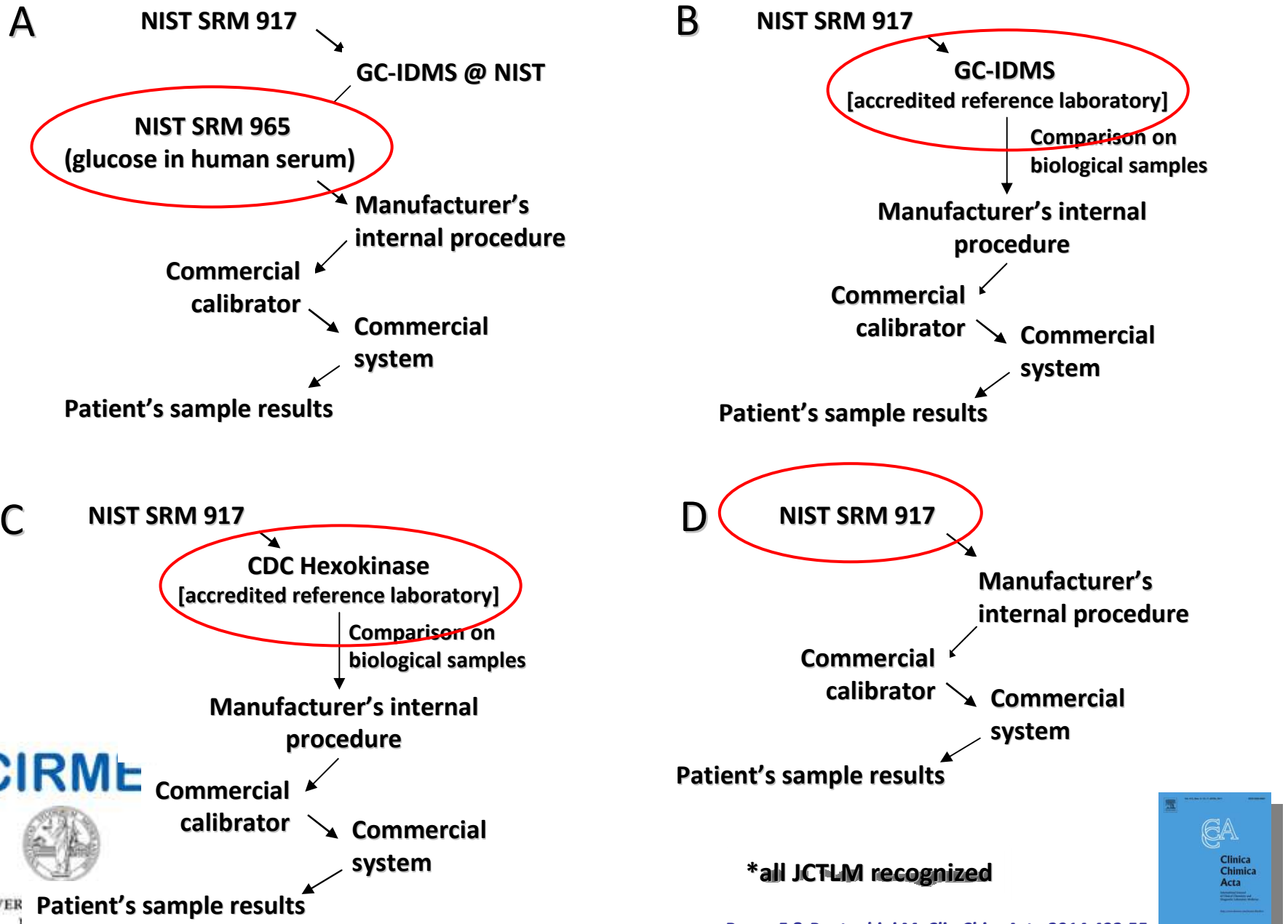
Types of metrological chains that can be used to implement the traceability of blood glucose results*

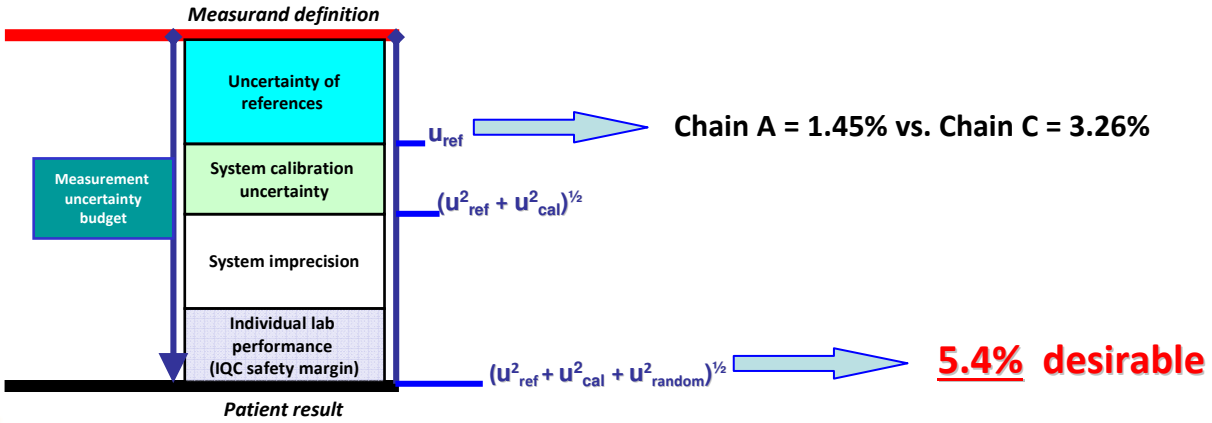


*all JCTLM recognized

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 Mar 11. pii: S0009-9120(17)30116-9

The importance of the post-marketing surveillance

Schumann G, et al.
Clin Chem Lab Med 2011;49:1439-46

Letter to the Editor

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

Federica Braga*, Erika Frusciante, Ilenia Infusino, Elena Aloisio, Elena Guerra, Ferruccio Ceriotti and Mauro Panteghini

Evaluation of the trueness of serum alkaline phosphatase measurement in a group of Italian laboratories

EQA experiment
(performed 5 years later *the availability of the IFCC RMP*) to evaluate the level of ALP standardization

L 59,9 U/L | M 186.9 U/L | H 401.5 U/L

- *ALP target values assigned with IFCC RMP*
- *Measured in triplicate in 3 consecutive days by participating laboratories*

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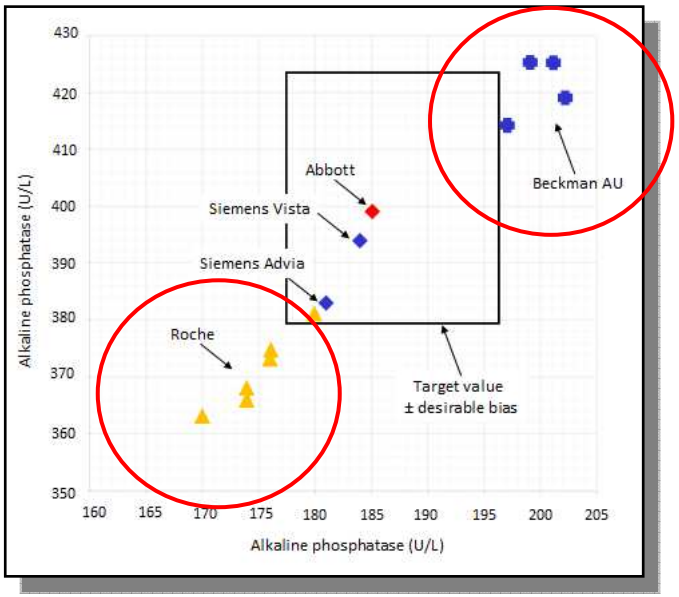

ID Lab	Measuring system	Bias			Regression parameters	
		Pool L	Pool M	Pool H	Slope	Intercepts
1	Roche Cobas 6000	-7.2%	-9.0%	-9.6%	0.8998 (P=0.0005)	1.8 (P=0.065)
2	Roche Cobas 6000	-5.4%	-5.9%	-7.0%	0.9271 (P=0.0029)	1.7 (P=0.37)
3	Beckman AU5800	5.9%	6.6%	5.8%	1.0573 (P=0.0029)	0.7 (P=0.69)
4	Roche Cobas 8000	-5.2%	-6.8%	-8.6%	0.9074 (P=0.0047)	3.3 (P=0.31)
5	Roche Cobas 6000/8000	-3.0%	-4.0%	-5.1%	0.9452 (P=0.0028)	2.0 (P=0.32)
6	Beckman AU680	4.4%	5.6%	3.1%	1.0263 (P=0.0086)	2.8 (P=0.57)
7	Beckman AU6800	8.6%	8.3%	4.3%	1.0320 (P=0.012)	5.7 (P=0.46)
8	Beckman AU5800	6.3%	7.4%	5.9%	1.0566 (P=0.0055)	1.5 (P=0.63)
9	Siemens Advia	-2.3%	-2.9%	-4.5%	0.9500 (P=0.0049)	2.5 (P=0.41)
10	Roche Cobas 8000	-5.0%	-5.6%	-6.8%	0.9275 (P=0.0037)	2.0 (P=0.38)
11	Roche Cobas 8000	-5.8%	-6.8%	-8.6%	0.9075 (P=0.0056)	3.0 (P=0.38)
12	Siemens Vista	-6.1%	-1.4%	-2.0%	0.9868 (P=0.0054)	1.9 (P=0.54)
13	Abbott Architect c16000	2.3%	-1.0%	-0,6%	0.9895 (P=0.0039)	1.3 (P=0.57)

Desirable and minimum APS for bias: 8.3% and 5.5%

The ability to meet or not the desirable APS for bias is clearly dependent on the measuring system used.

The importance of the post-marketing surveillance

Letter to the Editor

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

Federica Braga*, Erika Frusciante, Ilenia Infusino, Elena Aloisio, Elena Guerra, Ferruccio Ceriotti and Mauro Panteghini

Evaluation of the trueness of serum alkaline phosphatase measurement in a group of Italian laboratories

Company	Platform	Principle of commercial method	Calibrator	Declared standard uncertainty	Higher-order reference employed
Abbott	Architect	p-NPP/AMP	Calibration factor	NA	IFCC reference method (2011)
		p-NPP/AMP	Calibration factor	NA	Molar extinction coefficient
Beckman	AU	IFCC (1983)	System calibrator	6.00%	Beckman Coulter Master Calibrator
		p-NPP/DEA	System calibrator	NA	Beckman Coulter Master Calibrator
	Synchron	p-NPP/AMP	Enzyme Validator level 1	6.22%	IFCC reference method (2011)
			Enzyme Validator level 2	1.86%	IFCC reference method (2011)
		p-NPP/AMP	Enzyme Validator level 1	3.64%	DGKC standard method
			Enzyme Validator level 2	1.27%	DGKC standard method
Roche	Cobas c	IFCC gen. 2	C.f.a.s.	0.59%	IFCC reference method (1983)
	Integra	IFCC gen. 2	C.f.a.s	1.22%	IFCC reference method (1983)
	Modular	IFCC liquid	C.f.a.s	1.65%	IFCC reference method (1983)
Siemens	Dimension Vista	p-NPP/AMP	ALPI calibrator	4.51%[c]	IFCC reference method (2011)
	Advia	p-NPP/AMP	Chemistry calibrator control 1	3.70%	IFCC reference method (2011)
			Chemistry calibrator control 2	1.00%	IFCC reference method (2011)
		p-NPP/DEA	Chemistry calibrator control 1	1.40%[c]	Molar extinction coefficient
			Chemistry calibrator control 2	1.30%[c]	Molar extinction coefficient

The importance of the post-marketing surveillance

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Evaluatio
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		p-NPP/DEA	Chemistry calibrator control 1	1.40%[c]	Molar extinction coefficient
			Chemistry calibrator control 2	1.30%[c]	Molar extinction coefficient

Conclusions

- The availability of an internationally agreed reference measurement system does not automatically mean that the traceability to it is implemented!
- ***If a post-marketing surveillance is lacking alternatives that do not comply with the EU Directive can remain undisturbed on the market.***
- Some manufacturers continue to offer assays based on different experimental conditions (e.g. use of diethanolamine instead of 2-amino-2-methyl-1-propanol as reaction buffer for ALP) that may significantly influence the measurement selectivity and, ultimately, the measurand definition, one of the indispensable prerequisites in the field of enzyme standardization.

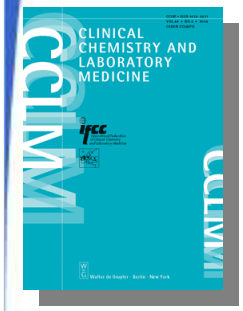
Clin Chem Lab Med 2008;46(4):567–572 © 2008 by Walter de Gruyter • Berlin • New York. DOI 10.1515/CCLM.2008.113

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 issue of analytical non-selectivity: 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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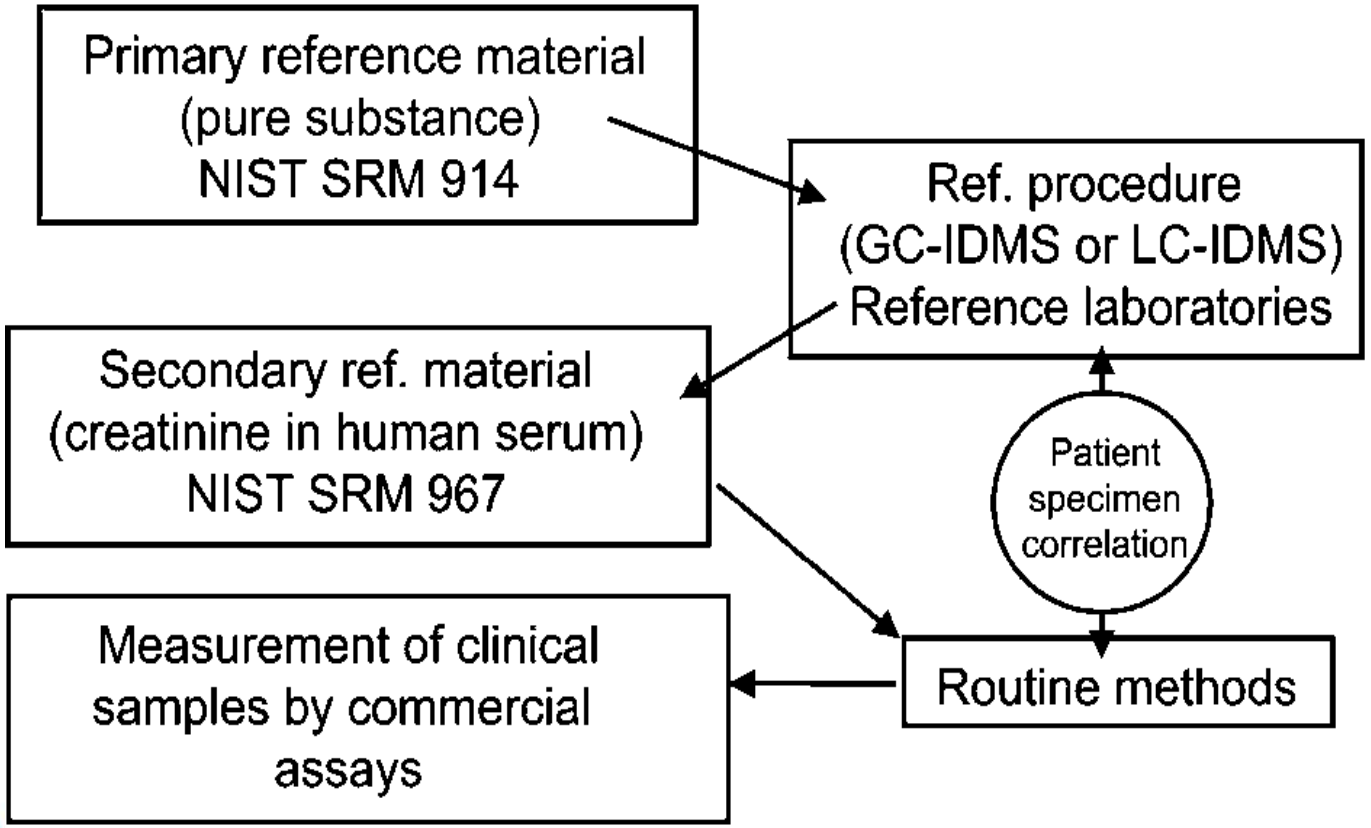
Reference System for Creatinine



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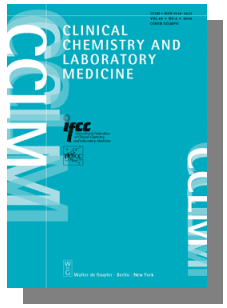
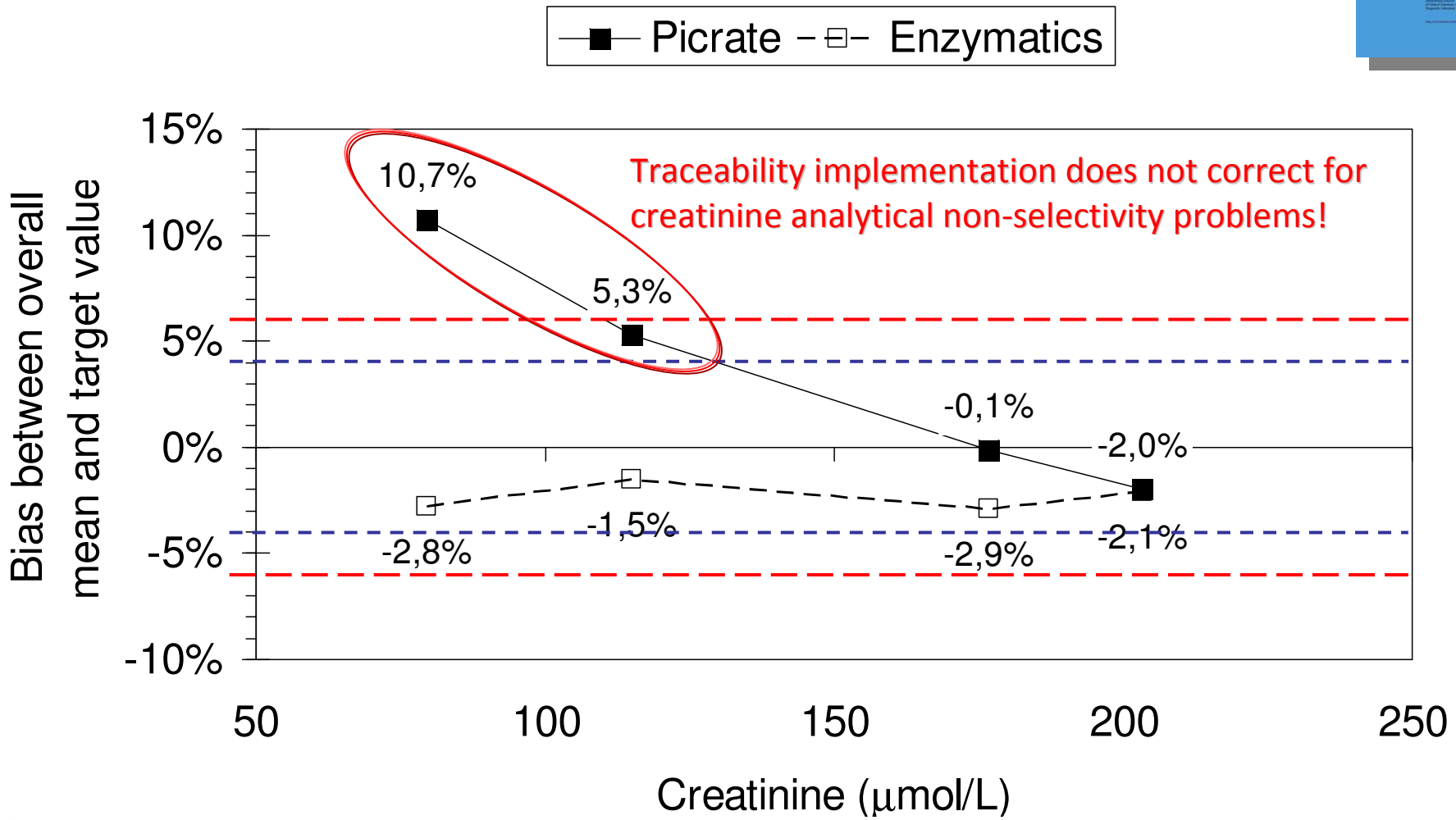
Panteghini M et al., Clin Chem Lab Med 2006;44:1187



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.

"Check"

Post-marketing surveillance

The role of the end-users

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

2. Daily surveillance of IVD system traceability

3. Estimating the measurement uncertainty due to the random effects

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

Daily surveillance of IVD system traceability

1. **Verification of the consistency of declared performance during routine operations performed in accordance with the manufacturer's instructions**
(checking of system alignment by *IQC component I*)

2. **Participation to appropriately structured EQAS**
("that meet metrological criteria")

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

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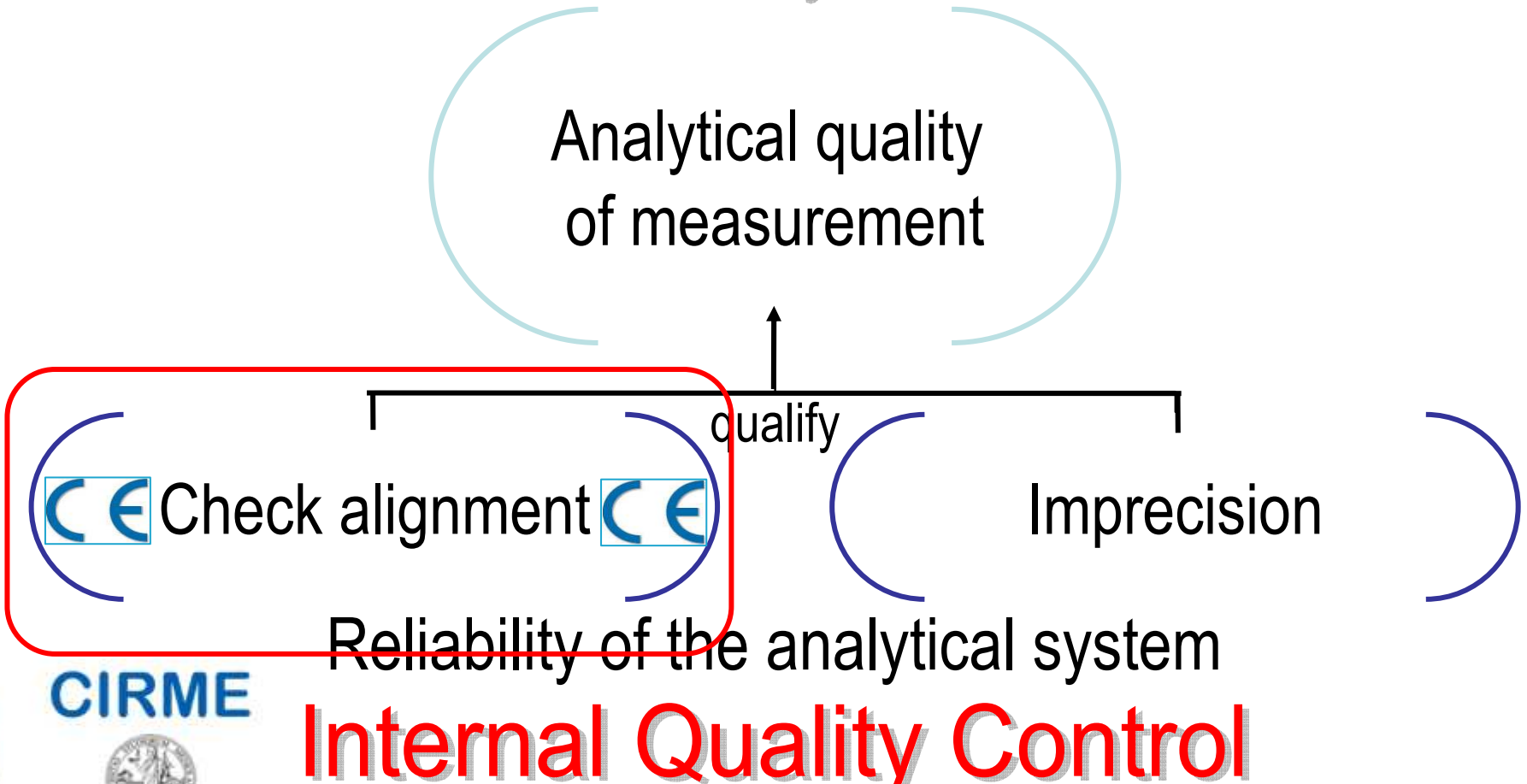
Analytical Quality Control in the Traceability Era

External Quality Assessment



Internal Quality Control

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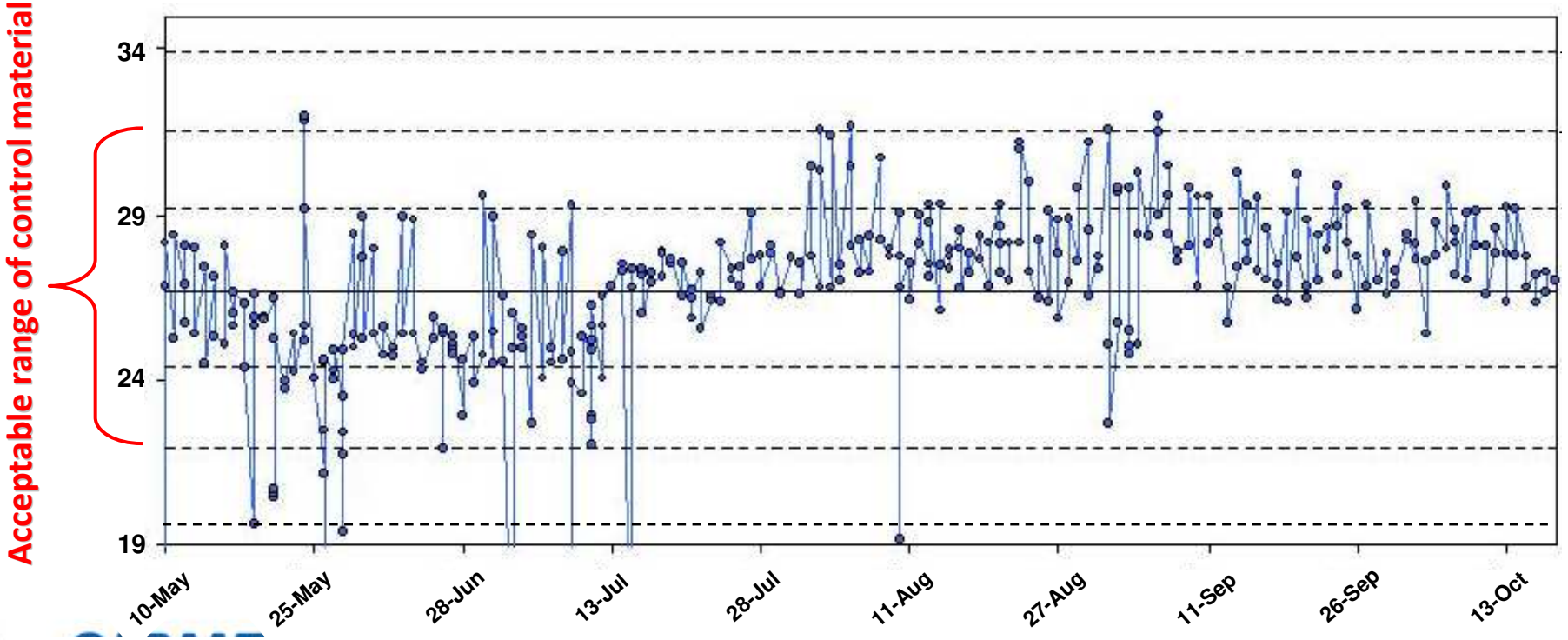
Panteghini M, Clin Chem Lab Med 2010;48:7
Braga F & Panteghini M, Clin Chim Acta 2014;432:55

Monitoring the reliability of the measuring system through IQC: Component I. Check alignment ("system traceability")

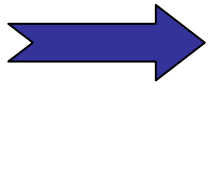
This program checks whether in the course of an analytical run the performance of a measuring system complies with the set goals, represented by the acceptable ranges of control materials.



Clinical laboratories must verify the consistency of declared performance during routine operations performed in accordance with the manufacturer's instructions, by checking that values of control materials provided by the manufacturer as component of the measuring system are in the established control range, with no clinically significant changes in the assumed traceable results.

Internal Quality Control (Component I)

Acceptance/rejection of the analytical run in "real time"



Any "out of control" signal must be made available with sufficient time to allow immediate corrective actions to bring again the situation under control (virtually "unbiased") and before reports related to the samples analyzed in the affected analytical run are issued.

Daily surveillance of IVD system traceability

1. **Verification of the consistency of declared performance during routine operations performed in accordance with the manufacturer's instructions**
(checking of system alignment by *IQC component I*)

2. **Participation to appropriately structured EQAS**
("that meet metrological criteria")

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

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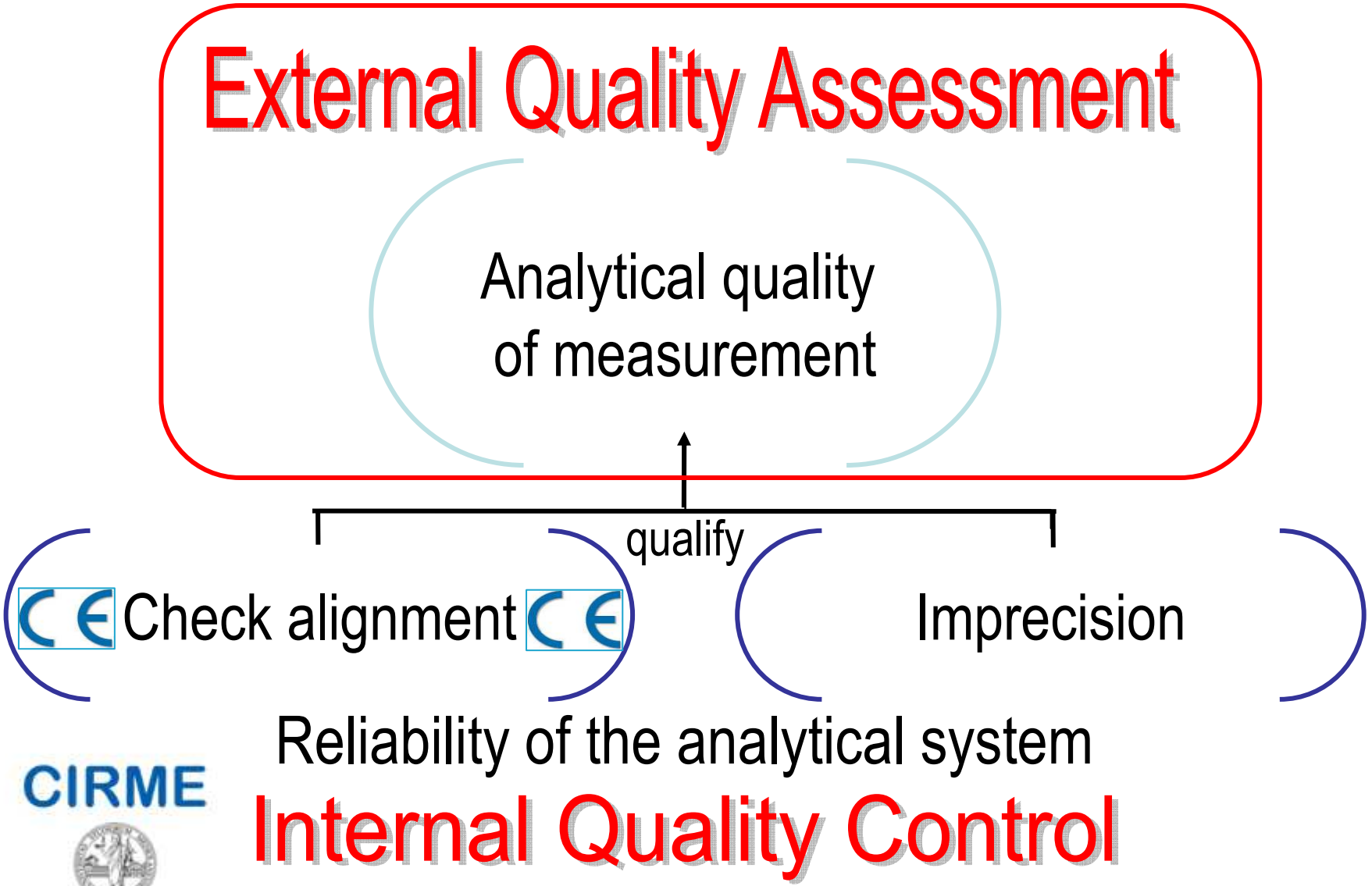
Analytical Quality Control in the Traceability Era



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Panteghini M, Clin Chem Lab Med 2010;48:7
Braga F & Panteghini M, Clin Chim Acta 2014;432:55

Requirements for the applicability of EQAS results in the evaluation of the performance of participating laboratories in terms of traceability of their measurements

Feature	Aim
EQAS materials value-assigned with reference procedures by an accredited ref. laboratory	To check traceability of commercial system to reference system
Proved commutability of EQAS materials	To allow transferability of participating laboratory performance to the measurement of clinical samples
Definition and use of the clinically allowable measurement error	To verify the suitability of laboratory measurements in clinical setting

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Panteghini M, Clin Chem Lab Med 2010;48:7
Infusino I et al., Clin Chem Lab Med 2010;48:301
Braga F & Panteghini M. Clin Chem Lab Med 2013;51:1719
Braga F & Panteghini M, Clin Chim Acta 2014;432:55

Table 1: Unique benefits of External Quality Assessment Schemes meeting metrological criteria.

– Giving objective information about quality of individual laboratory performance
– Creating evidence about intrinsic standardisation status/ equivalence of the examined assays
– Serving as management tool for the clinical laboratory and IVD manufacturers, forcing them to investigate and eventually fix the identified problem
– Helping those manufacturers that produce superior products and systems to demonstrate the superiority of those products
– Identifying analytes that need improved harmonisation and stimulating and sustaining standardisation initiatives that are needed to support clinical practice guidelines
– Abandonment by users (and consequently by industry) of nonspecific methods and/or of assays with demonstrated insufficient quality

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[Ferraro S, Braga F, Panteghini M. Clin Chem Lab Med 2016;54:523]

"Check"

Post-marketing surveillance

The role of the end-users

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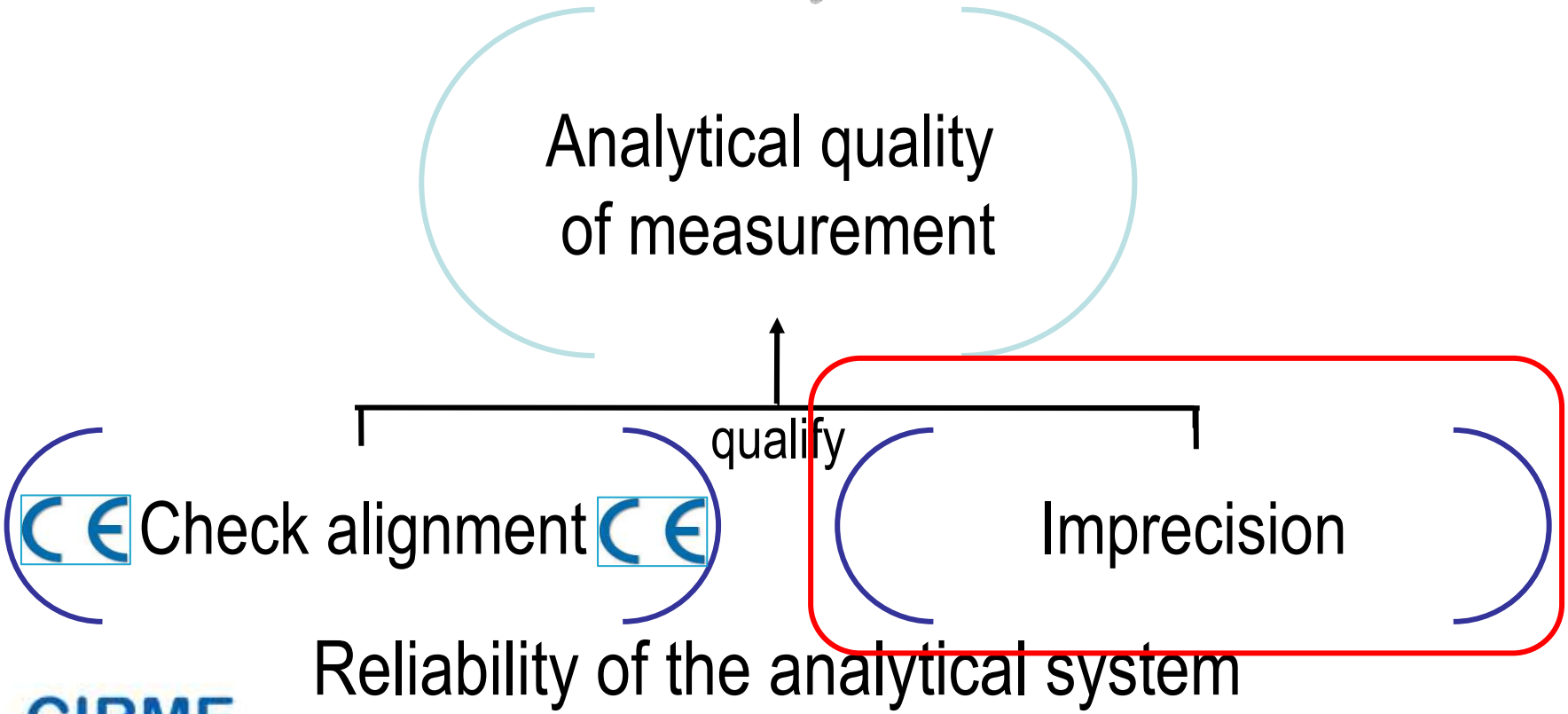
Braga F & Panteghini M, Clin Chim Acta 2014;432:55

Analytical Quality Control in the Traceability Era

External Quality Assessment



Internal Quality Control

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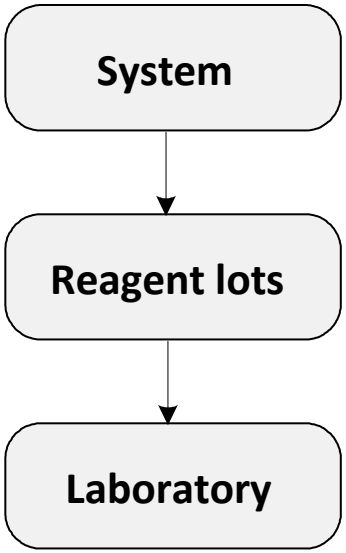
Panteghini M, Clin Chem Lab Med 2010;48:7
Braga F & Panteghini M, Clin Chim Acta 2014;432:55

Internal Quality Control (Component II)

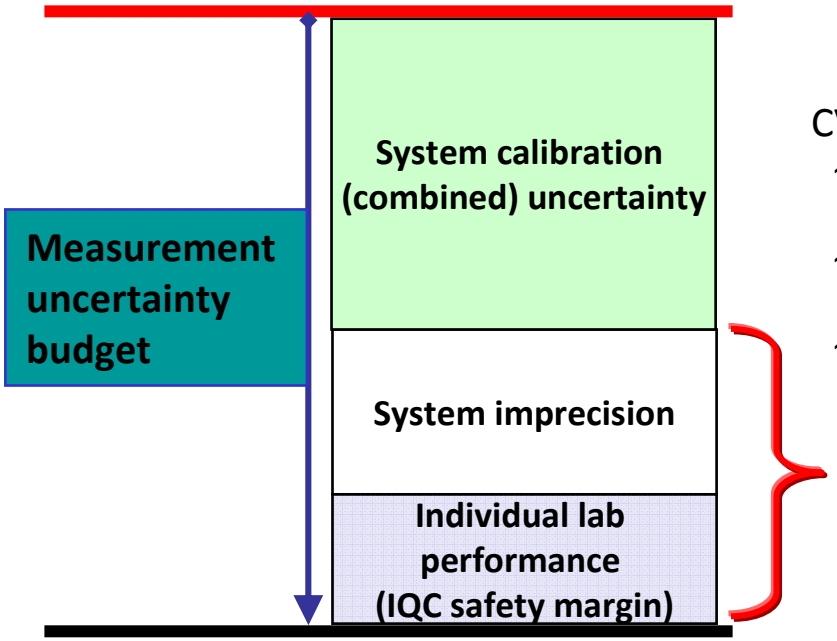
System stability at medium/long term

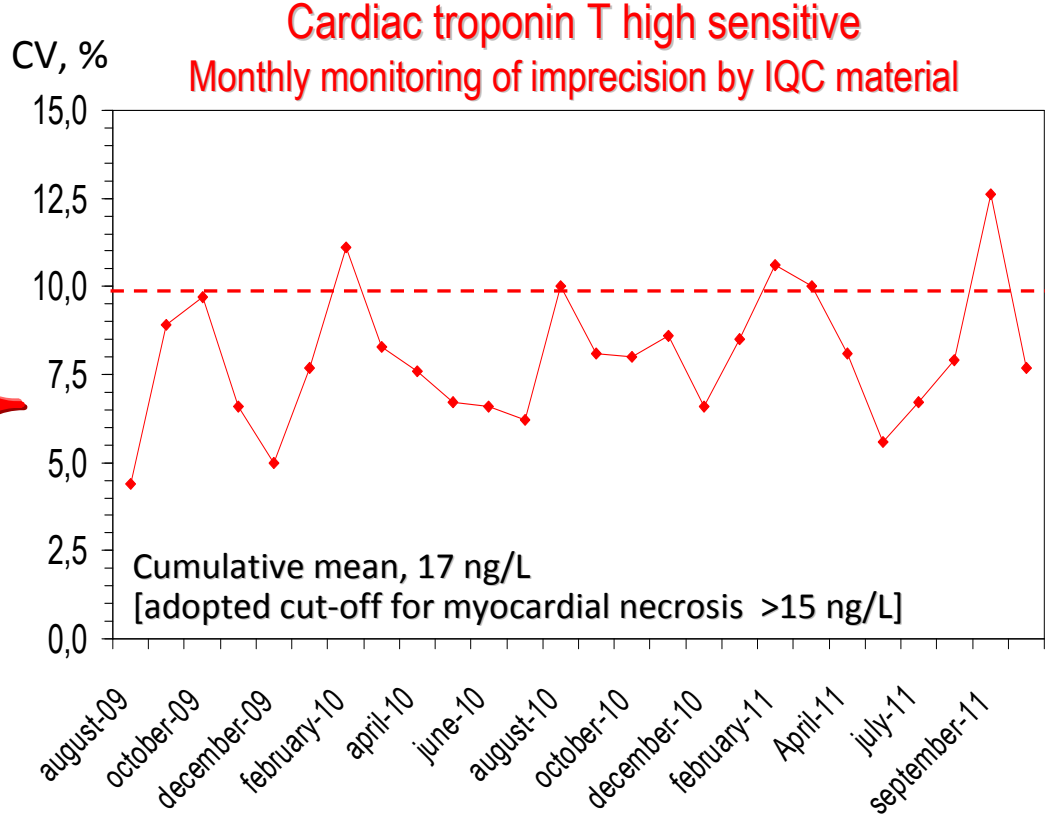
→ *Testing the uncertainty due to the random effects ("imprecision")*

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



Monitoring the reliability of the measuring system through IQC: Component II. 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 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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University of Milan, Milan, Italy**

http://users.unimi.it/cirme/home/index.php

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