CIRME

UNIVERSITÀ DEGLI STUDI DI MILANO

Centre for Metrological Traceability in Laboratory Medicine (CIRME)

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

13th International Scientific Meeting

THE INTERNAL QUALITY CONTROL IN THE TRACEABILITY ERA

MILANO, ITALY
November 28th, 2019

IQC component I or how to check the alignment of measuring systems

Sara Pasqualetti

Laboratory Medicine is clinically effective when the provided information can be interpreted in a reliable and consistent manner

LABORATORY RESULTS

ACCURATE

Tolerable measurement error without jeopardizing patient safety

EQUIVALENT

[For long term] No matter where they are performed

TRACEABILITY IMPLEMENTATION

Results obtained by the calibrated commercial procedure expressed in terms of the values obtained at the highest available level of the calibration hierarchy

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 IVD manufacturers to ensure traceability of their measuring systems to recognized higher-order references

CIRME

UNIVERSITÀ DEGLI STUDI DI MILANO

CE

Roles and responsibilities of IVD manufacturers

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

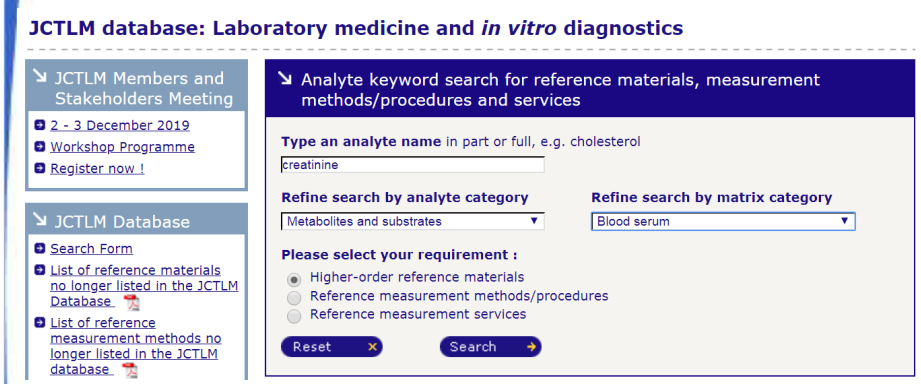
CIRME

UNIVERSITÀ DEGLI STUDI DI MILANO

- Identification of higher-order metrological **REFERENCES**
- Definition of a **CALIBRATION HIERARCHY** to assign traceable values to their system calibrators and bias correction during trueness transfer process
- Estimation of combined **MEASUREMENT UNCERTAINTY (MU)** of calibrators
- Fulfillment of **MU GOALS**, which represent a proportion of the uncertainty budget allowed for clinical laboratory results

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

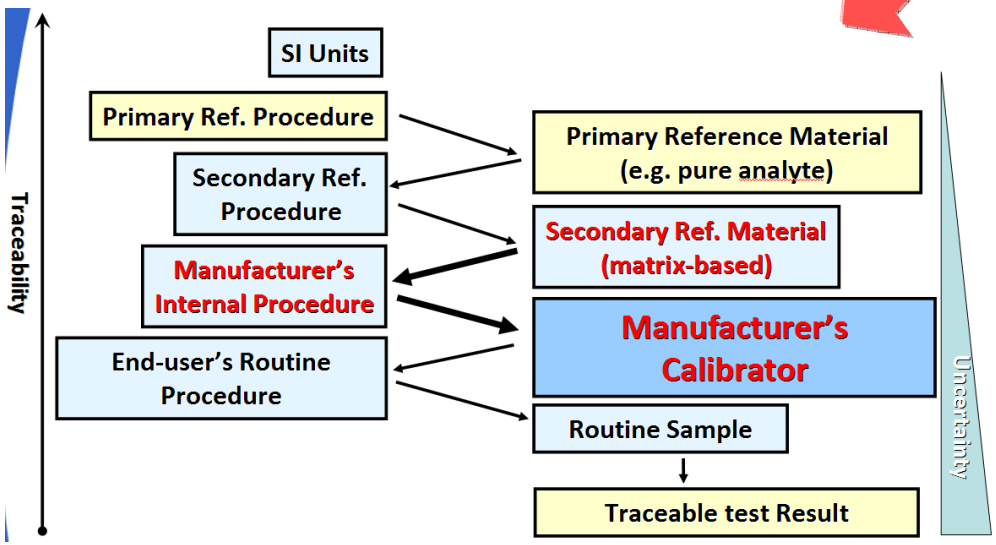
Identification of higher-order REFERENCES and definition of a CALIBRATION HIERARCHY to assign traceable values to the system calibrators



JCTLM
Accurate results for patient care

Joint Committe for Traceability in Laboratory Medicine (JCTLM)

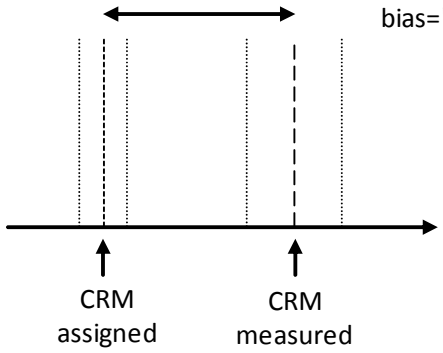
https://www.bipm.org/jctlm/



CIRME

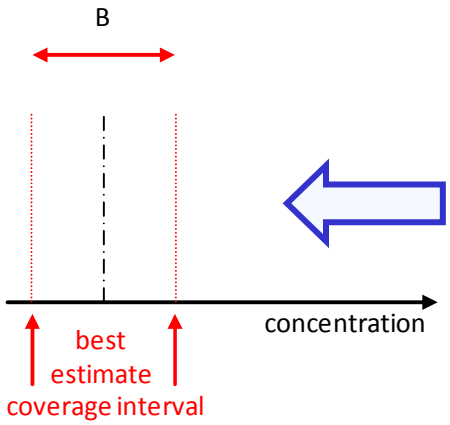
UNIVERSITÀ DEGLI STUDI DI MILANO

BIAS CORRECTION during trueness transfer process



***Bias,* systematic measurement error, due to e.g. inappropriate model for the calibration curve, incorrect values assigned to the calibrators, matrix related bias, etc.**

***Bias correction*, realignment of measuring system by adjusting the value assigned to the calibrator**



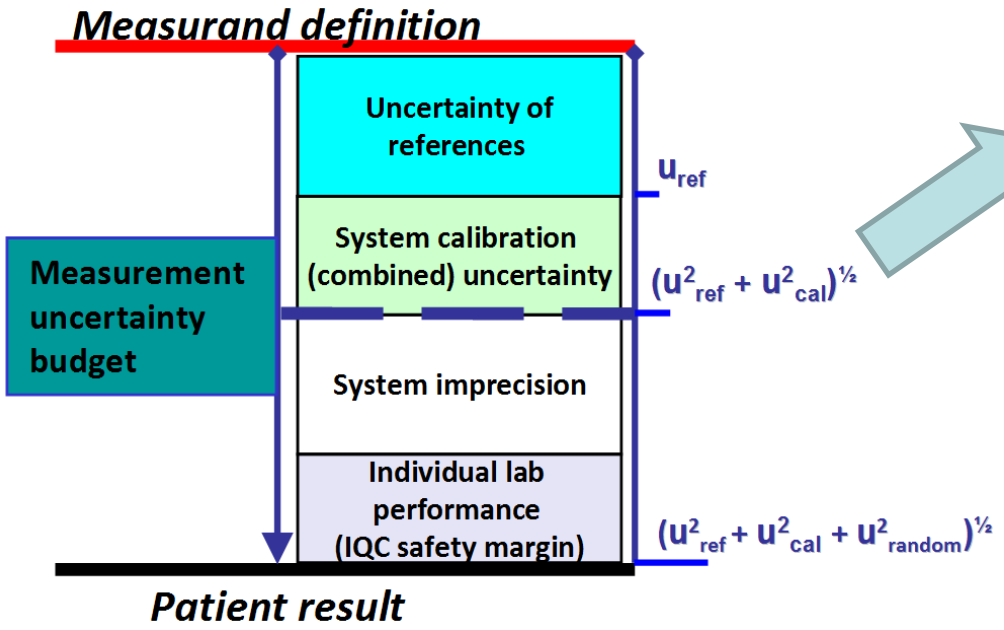
Uncertainty of calibrator

Provide unbiased clinical results

CIRME

UNIVERSITÀ DEGLI STUDI DI MILANO

Estimate combined MEASUREMENT UNCERTAINTY (MU) of calibrators and fulfill MU GOALS, which represent a proportion of the uncertainty budget allowed for clinical laboratory results



Manufacturers

- ✓ **Combines the uncertainty derived from the previous steps of the metrological chain**
- ✓ **Leaving enough uncertainty budget usable by individual laboratories warranting the production of clinically suitable results**

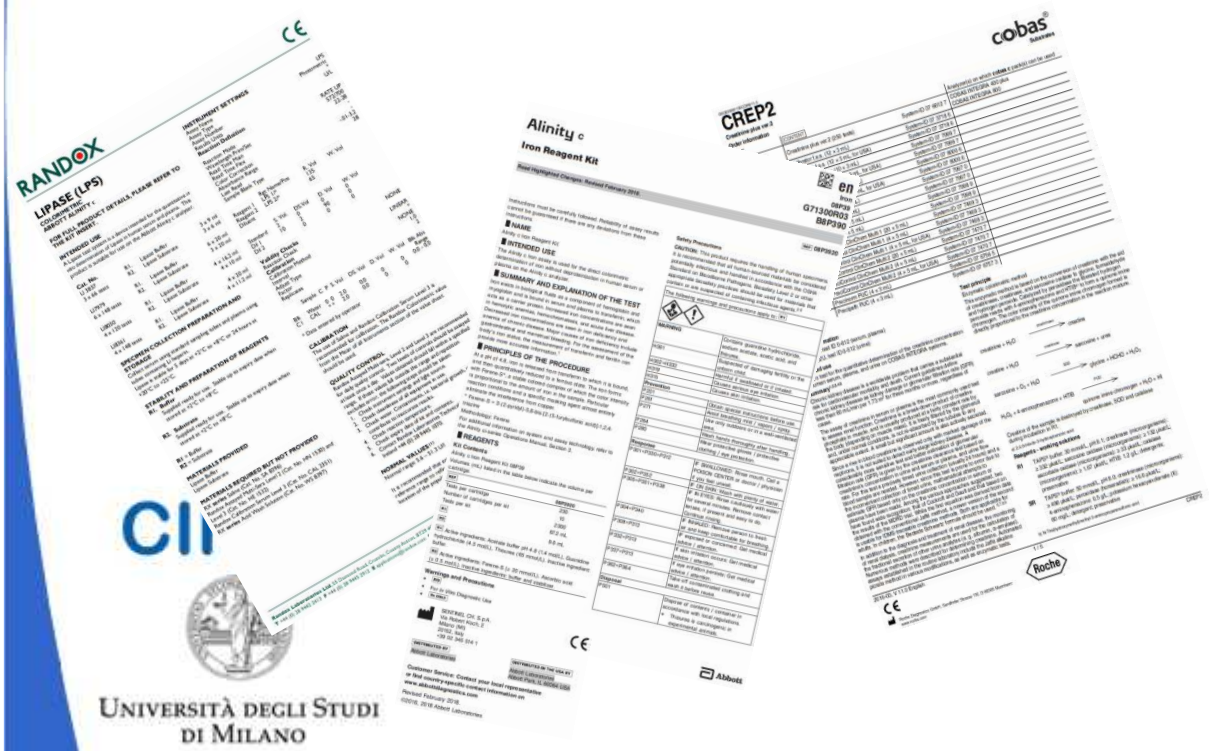
CIRME

UNIVERSITÀ DEGLI STUDI DI MILANO

Furthermore, IVD manufacturers should provide:

- **Technical documentation**
- **Instructions for use**
- **Quality control suitable for post-market traceability surveillance (system alignment)**

Only working according to the manufacturer's instructions the declared performance of measuring system can be warranted



INSTRUMENT SETTINGS

CALIBRATION MATERIALS

- PREPARATION
- STABILITY
- FREQUENCY
- TRACEABILITY
- UNCERTAINTY

QUALITY CONTROL MATERIALS

- PREPARATION
- STABILITY
- FREQUENCY
- ACCEPTABILITY RANGE

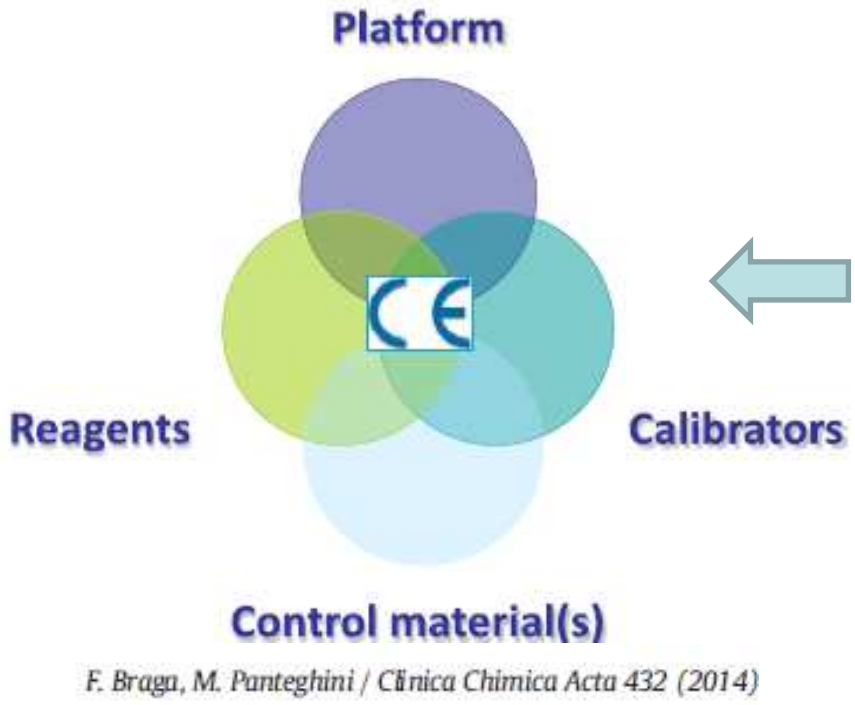
SPECIMENT TYPES ACCORDING TO THE INTENDED USE

REAGENT

- PREPARATION
- STORAGE
- STABILITY (unopen/onboard)

Measuring System Components in the Traceability Era

The Paradigm Shift



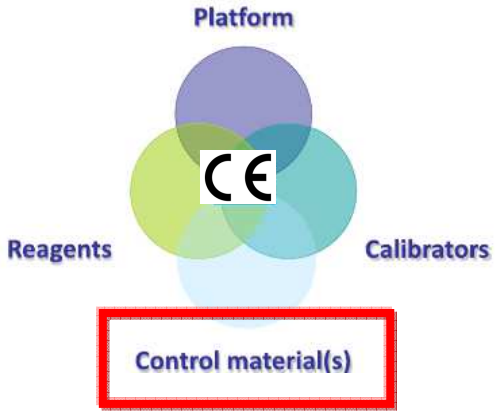
F. Braga, M. Panteghini / Clinica Chimica Acta 432 (2014)

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.

Changes 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.

Quality control suitable for post-market traceability surveillance (system alignment)

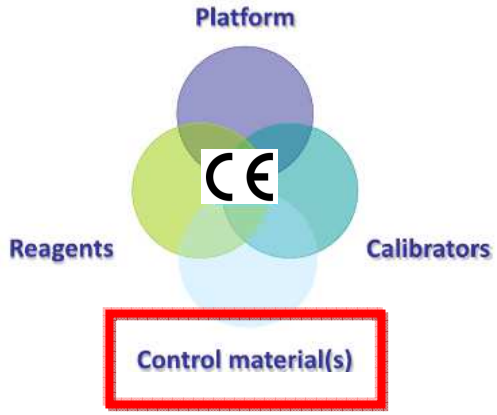
The verification of the consistency of declared performance in terms of measuring system alignment (i.e. system traceability) during daily operations must be performed in accordance with the instructions of manufacturer, which has total responsibilities about the declared performance of marketed measuring system.



Control materials from the IVD manufacturers as a part of the CE-marked measuring system (System alignment verification IQC component I)

CIRM

UNIVERSITÀ DEGLI STUDI DI MILANO



Control materials from the IVD manufacturers as a part of the CE-marked measuring system (System alignment verification IQC component I)

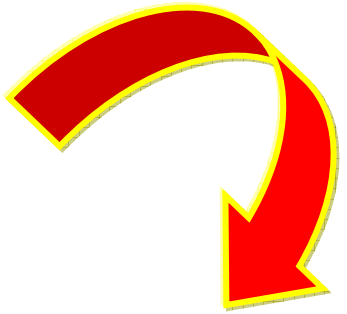
BASIC PREMISE

If the traceability of the measuring system to higher-order references is granted, control materials from the IVD manufacturers have to be a good surrogate of the employed (and declared) reference to permit checking the correct system alignment to this reference

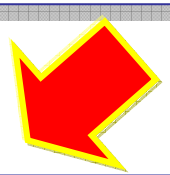
Internal Quality Control
CHARACTERISTICS

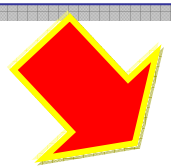
- Monitoring the reliability of analytical measurements according to defined rules for QC acceptability, with the identification of out-of-control conditions in real time
- Identifying situations when the measurement system may not be provide results suitable for use in medical decisions

[Adapted from CLSI C24-A3]
Statistical Quality Control
for Quantitative Measurement
Procedures: Principles and Definitions



Plan IQC strategies based on the performance needed to support the intended medical use of results





Select appropriate IQC material

Define appropriate interpretative criteria

CIRME

UNIVERSITÀ DEGLI STUDI DI MILANO

Internal Quality Control
CHARACTERISTICS

[Adapted from CLSI C24-A3]

- Monitoring the reliability of analytical measurements according to defined rules for QC acceptability, with the identification of out-of-control conditions in real time
- Identifying situations when the measurement system may not be provide results suitable for use in medical decisions

Plan IQC strategies based on the performance needed to support the intended medical use of results

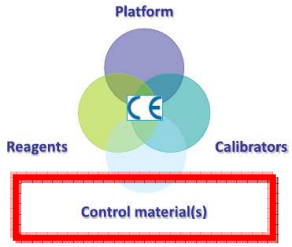
Select appropriate IQC material

Define appropriate interpretative criteria

CIRME

UNIVERSITÀ DEGLI STUDI DI MILANO

MAIN CHARACTERISTICS OF QUALITY CONTROL MATERIAL FOR SYSTEM ALIGNMENT VERIFICATION



- ✓ Concentration levels in line with clinically relevant thresholds
- ✓ Unbiased target value (e.g. possibility of correction of bias due to matrix-related effect resulting from the interaction of reagents and ”matrix-modified” material) – Commutable materials not needed
- ✓ Acceptability range according to the suitable application of test results in clinical setting
- ✓ Enough stability to monitor the performance of the measuring system under the influence of components potentially deteriorating it

Concentration levels in line with clinically relevant thresholds

Accurate calibration of hs-cTn assays in the low range of concentrations is of the utmost importance for this application that relies on a single troponin measurement @ patient admission.

Even relatively small analytical variations in practice may misclassify patients with suspected acute coronary syndrome.

CIRME

UNIVERSITÀ DEGLI STUDI DI MILANO

Tools that labs would need to use to check the performance at the low end of measuring range of hs-cTn assays

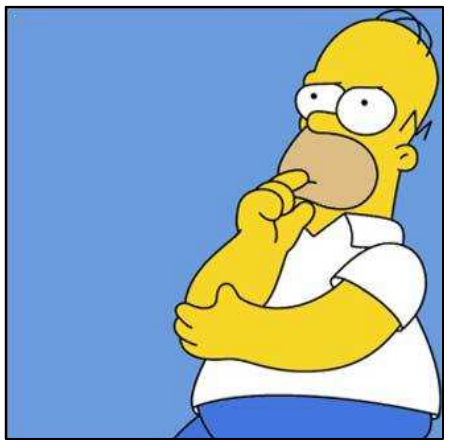
- A control material with an hs-cTn concentration near the LoD to monitor baseline drifts (IQC component I)
- A low-level QC material with cTn concentration close to 99th percentile limit to monitor assay performance at cut-off (IQC component II)
- Calibration frequency to be determined based on the imprecision performance and drift characteristics of the assay

CIRME

UNIVERSITÀ DEGLI STUDI DI MILANO

[Adapted from Panteghini M. Clin Chim Acta 2009;402:88; Panteghini M. Clin Chem 2018;64:621]

However, commercial IQC materials available as part of the hs-cTn measuring systems do not cover such low concentrations, leaving the assay vulnerable to potential drifts that could remain unnoticed.



CIRME

UNIVERSITÀ DEGLI STUDI DI MILANO

DE GRUYTER Clin Chem Lab Med 2019; x(x): xxx–xxx

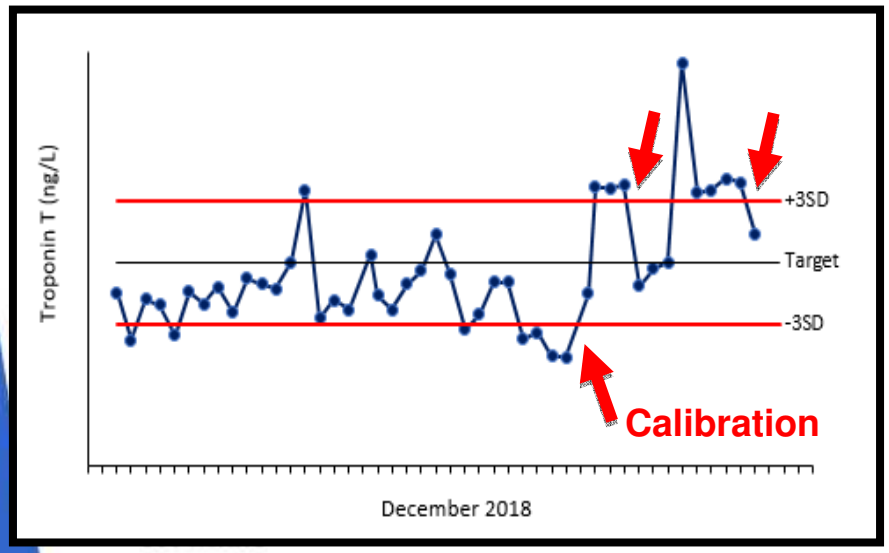
Letter to the Editor

Elena Aloisio*, Sara Pasqualetti, Alberto Dolci and Mauro Panteghini

Daily monitoring of a control material with a concentration near the limit of detection improves the measurement accuracy of highly sensitive troponin assays

Use of an in-house made serum pool with hs-TnT ~5 ng/L (LoD) as a third material, besides commercial Roche materials, to check calibration of the measuring system

- **Target value:** mean of 10 preliminary measurements, performed in optimal conditions.
- **Acceptability range:** ±30% of target value.



If QC results are “out of control”, immediate corrective actions are undertaken before further reports related to the patient samples are issued and measurements repeated.

Unbiased target value

The values provided in the data sheet were derived from replicate analyses and are specific for a particular lot of product. These values have been generated using third party manufacturers' instrument systems and are specific to one measurement procedure. Technopath make no accuracy claims regarding these values. Tests were performed by the control manufacturer and/or by independent laboratories, for various methods and instrument systems. As a tool to assist in establishing their own mean, laboratories can import the values into their Alinity c system. For more details and to register for access to this file please visit www.technopathcd.com.

Values are provided only as guidelines, each laboratory should establish its own statistical limits. Laboratory means may vary from the values listed during the shelf life of the control. Technopath monitors the values over the shelf life of the control and provides update(s) at www.technopathcd.com or contact your local Abbott customer service representative.

… Mean value derived from replicate performed by independent laboratory

… Data from interlaboratory program are included in the determination of some ranges

… Values/Range provided only as guides

… Values listed are approximate targets and are provided only for convenience

… No accuracy claims regarding mean value

… Values update during the shelf life of the material available @website

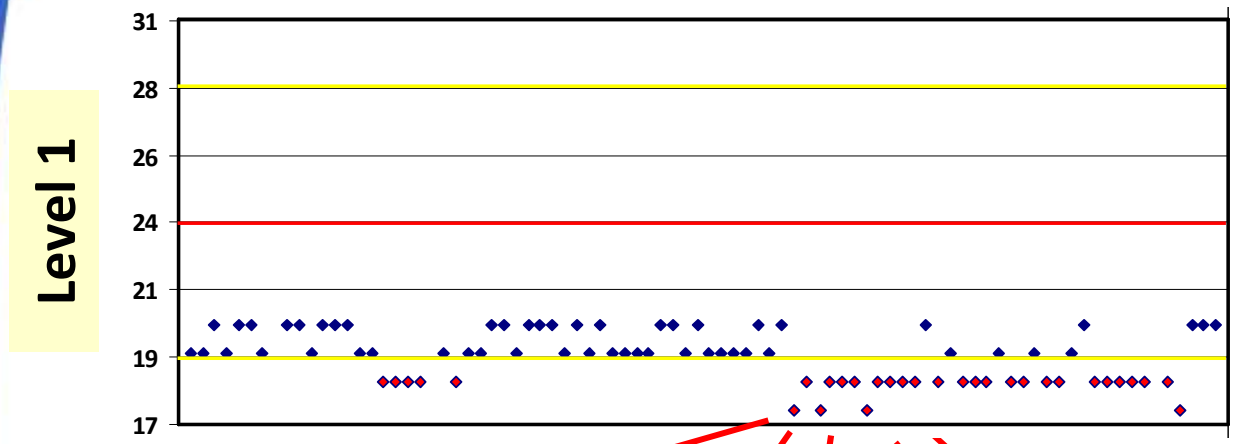
… Each laboratory should establish its own statistical limits

CIRME

Università degli Studi di Milano

Who's taking care of the metrological quality of the assigned value?

ALINITY c ALT, System alignment verification



Liquid Frozen Multiparametric IQC

Target mean= 23.3 U/L
Acceptability= 18.7-28.0 U/L (±20%)

Reagent= Activated ALT, P5P

IFCC traceable calibration factor= 7658

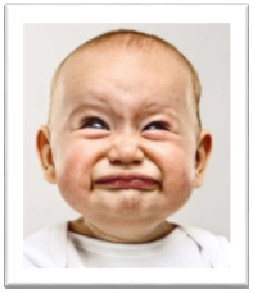
First determination

Repetition

Calibration and then repetition

Change of reagent lot, recalibration and then repetition

Technical intervention



CIRME

UNIVERSITÀ DEGLI STUDI DI MILANO

Are the repeated out-of-control results in ALT measuring system due to a real system misalignment from the declared IFCC reference?

BIAS ESTIMATION

Note that:

- *Bias estimation is not a part of IQC*
- *Need of a dedicated experimental protocol (e.g. CLSI EP09)*

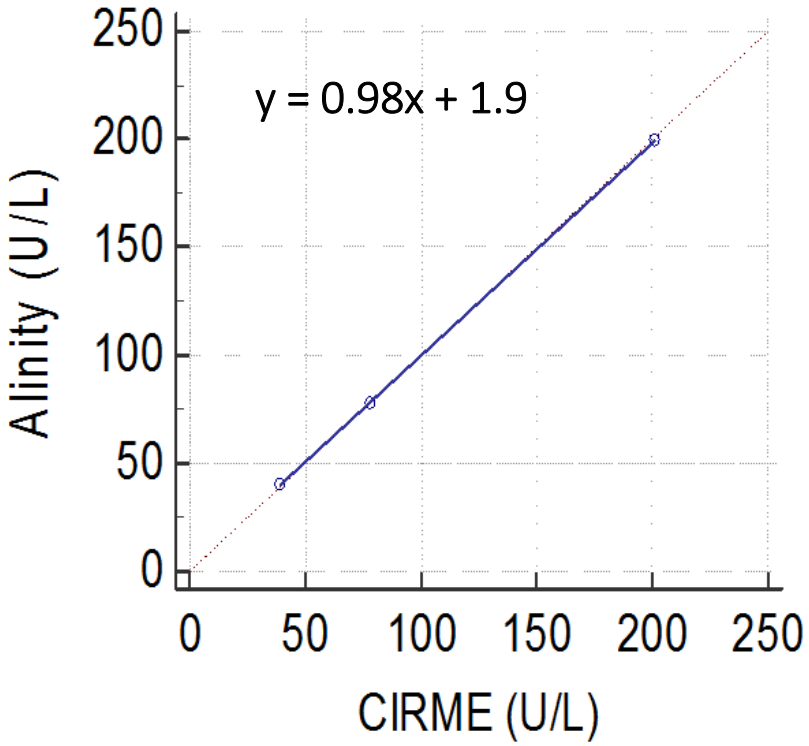
To investigate the persistent systematic misalignment of ALT Alinity measuring system → Correlation between Alinity and IFCC reference procedure

CIRME

UNIVERSITÀ DEGLI STUDI DI MILANO

	Alinity						
	rep 1	rep 2	rep 3	media	CIRME	Bias	Bias %
Pool 40	40	40	40	40.00	38.87	1.13	2.9
Pool 80	78	77	78	77.67	78.13	-0.46	-0.6
Pool 200	199	199	200	199.33	201.28	-1.95	-1.0

Optimal Bias

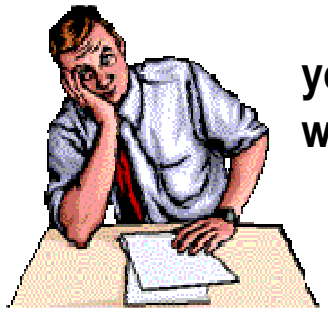


Traceability to the declared reference
CONFIRMED !!

Technopath make no accuracy claims regarding these values. Tests were performed by the control manufacturer and/or by independent laboratories, for various methods and instrument systems.

CIRME

UNIVERSITÀ DEGLI STUDI DI MILANO



Abbott

you have a problem with control material!

A POSITIVE EXAMPLE

Serum Albumin DiAgam IQC Component I

QUALITY CONTROL

reproducibility: analytical performances can be checked with the internal quality control serum of the laboratory or with the Liquichek™ (BIO-RAD) Control sera

Calibration: calibration curve and stability of calibration curve can be validated with the DiAgam calibration control (MPCON-002, MPCOS-002 and MPCOX-002). In case of analytical performances modification, calibrate the method again and contact the manufacturer if modifications are subsisting.

Multiparametric Control

✓ ***REFERENCE***

Multiparametric Low Control	MPCOS-002	1 x 2 ml	2-8°C
Human multiparametric biological fluid standardized from the reference ERM-DA470k/IFCC, sodium azide (< 1g/l)			
Lot #		18E29	
Expiry date		05/2020	
Control date		31/07/2018	
Quality control report #		DGM-QAC-REP-18065	
Document prepared and signed by		L. Ginneberge	

Proteins:	CONTROL	
	g/l	
	Target	Range
Albumin	25,0	20,00 - 30,00
Alpha1-Antitrypsin	0,81	0,65 - 0,97
Alpha1-Acid Glycoprotein	0,51	0,41 - 0,61
Alpha2-Macroglobulin	1,21	0,97 - 1,45
Antithrombin III*	0,17 ***	0,14 - 0,20 ***
Complement C3	0,94	0,75 - 1,13
Complement C4	0,16	0,13 - 0,19
Ceruloplasmin*	0,30 **	0,24 - 0,36 **
Haptoglobin	0,80	0,64 - 0,96
IgA	1,35	1,08 - 1,62
IgG	6,09	4,87 - 7,31
IgM	0,57	0,46 - 0,68
Prealbumin	0,16	0,13 - 0,19
Transferrin	1,58	1,26 - 1,90

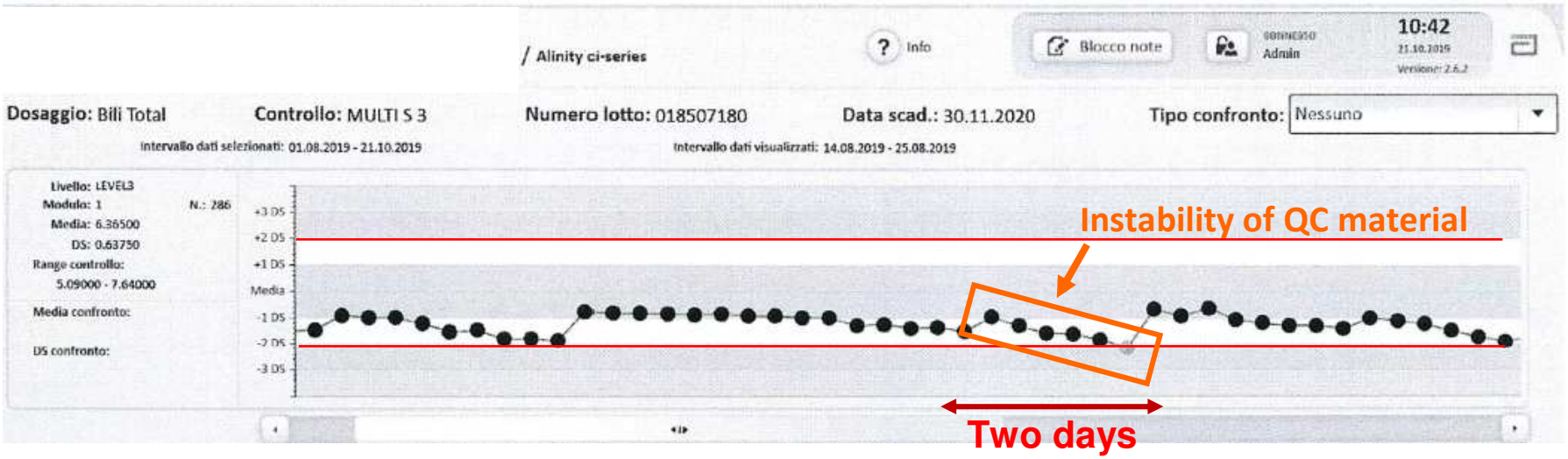
Values assigned from the reference ERM-DA470k/IFCC.
**AT-III and Ceruloplasmin are referenced to external controls.*
*** Values compatible with the new Ceruloplasmin reagent (since 17H24) and the calibrant MPREK (since 17H28). In case of dou*
**** Values compatible with calibrant MPREK (since Lot17H28). In case of doubt, contact the manufactu*

DiAgam Avenue Louis Lepoutre 70 – 1050 BRUSSELS Belgium mail@diagam.com Tel: +32 (0) 68 5

UNIVERSITÀ DEGLI STUDI DI MILANO

Enough stability to monitor the performance of the measuring system

EXAMPLE



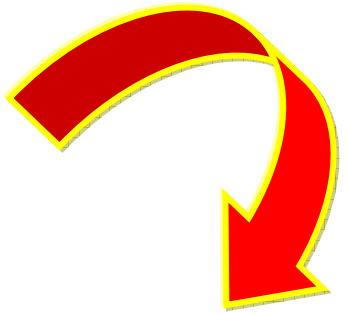
CIRME

UNIVERSITÀ DEGLI STUDI DI MILANO

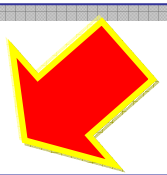
Internal Quality Control
CHARACTERISTICS

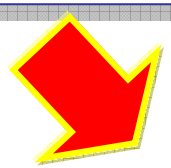
[Adapted from CLSI C24-A3]

- Monitoring the reliability of analytical measurements according to defined rules for QC acceptability, with the identification of out-of-control conditions in real time
- Identifying situations when the measurement system may not be provide results suitable for use in medical decisions



Plan IQC strategies based on the performance needed to support the intended medical use of results





Select appropriate IQC material

Define appropriate interpretative criteria

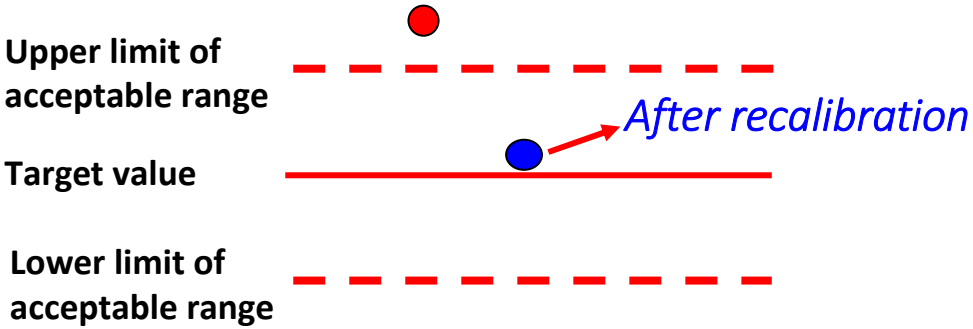
CIRME

UNIVERSITÀ DEGLI STUDI DI MILANO

1) MACROEVALUATION

THIS IS A ROLE OF END-USERS

Checking that the single control value is in the ACCEPTABLE RANGE.

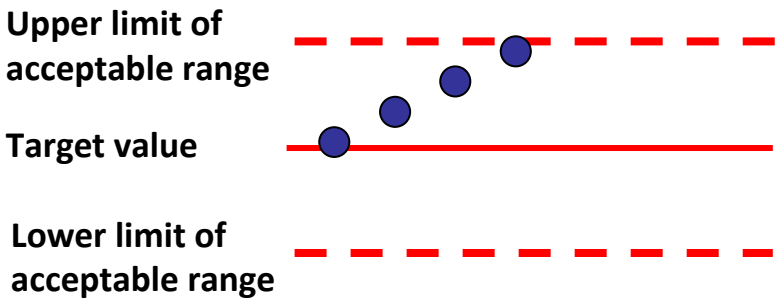


- ✓ Acceptance/rejection of the analytical run in 'real time'.
- ✓ Any "out of control" signal must promote immediate corrective actions to bring again the situation under control (i.e. within the acceptance range) and before results related to the samples analyzed in the affected analytical run are released.

2) LONGITUDINAL EVALUATION

THIS IS A ROLE OF END-USERS

Checking the temporal trend of control values.



Frequency of control measurements:

If measurements are performed in batches → Before and at the end of each analytical run

If measurements are performed continuously h24 → Every 8 hours

2) LONGITUDINAL EVALUATION

a. Check for significant trend

b. Evaluate the influence on random source of measurement uncertainty

CIRME

UNIVERSITÀ DEGLI STUDI DI MILANO

2) LONGITUDINAL EVALUATION

a. Check for significant trend

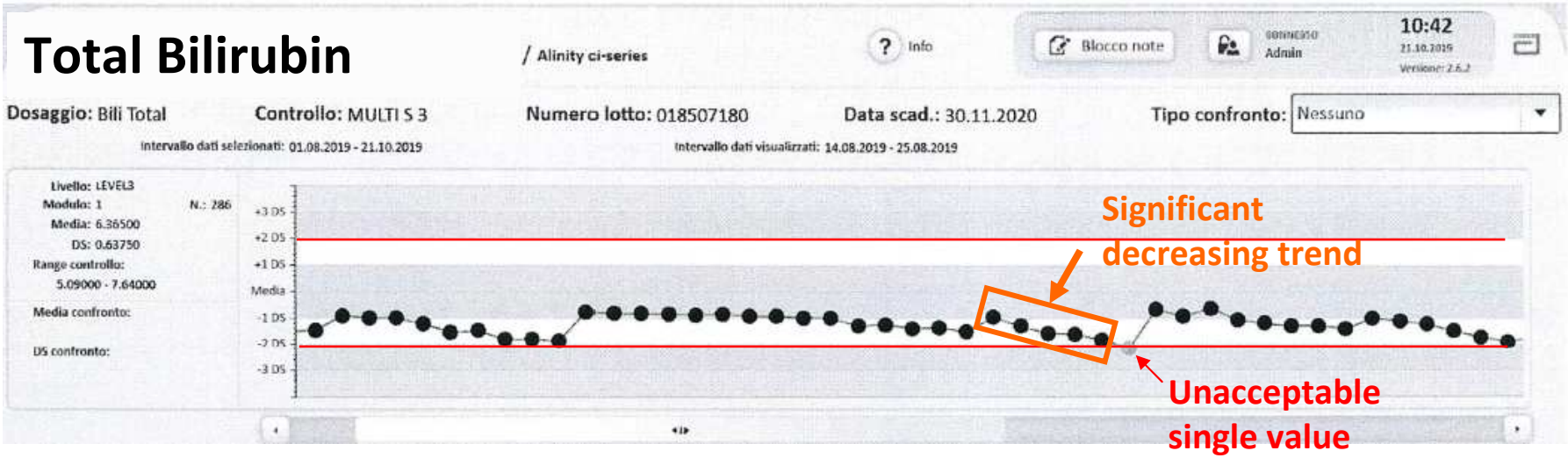
b. Evaluate the influence on random source of measurement uncertainty

CIRME

UNIVERSITÀ DEGLI STUDI DI MILANO

EXAMPLE

Check for significant trend



MACRO EVALUATION: Single control values are acceptable

LONGITUDINAL EVALUATION: The decreasing trend of two days data indicates an ongoing problem that becomes definitively evident at the macroevaluation only at the sixth measurement of the control material

CIRME

UNIVERSITÀ DEGLI STUDI DI MILANO

2) LONGITUDINAL EVALUATION

a. Check for significant trend

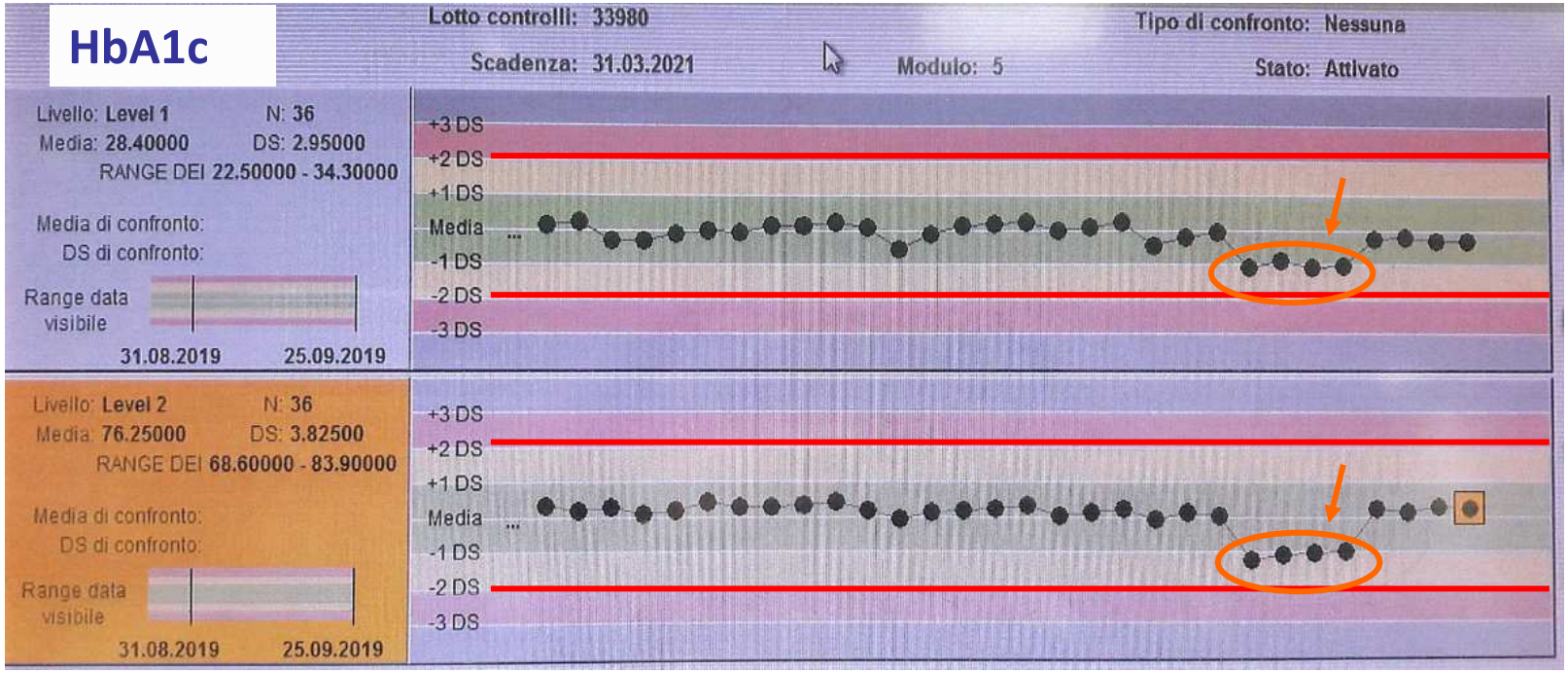
b. Evaluate the influence on random source of measurement uncertainty

CIRME

UNIVERSITÀ DEGLI STUDI DI MILANO

EXAMPLE

Impact of the influence of poor measuring system alignment on measurement uncertainty



MACRO EVALUATION: Single control values are always acceptable

LONGITUDINAL EVALUATION: The control shift has caused an unacceptable random MU

→ Monthly CV: 1.4% (vs 1.3% desirable goal)

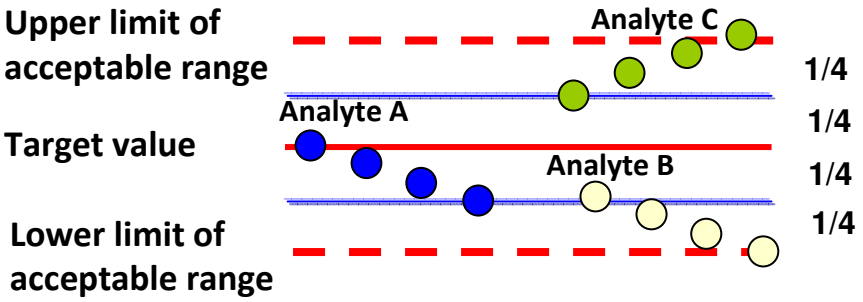
CIRME

UNIVERSITÀ DEGLI STUDI DI MILANO

Proposed criteria (I)

LONGITUDINAL EVALUATION

IQC TEMPORAL TREND: Considering at least 3 determination for reducing the influence of random error, it could be appropriate to consider an intervention when, after 4 measurements (e.g. 2 days), the IQC drift exceed 1/4 of the acceptability range.



CIRME

UNIVERSITÀ DEGLI STUDI DI MILANO

Proposed criteria (II)

LONGITUDINAL EVALUATION

SHIFT: Consider an intervention when after any change in the measuring system (e.g. reagent lot, calibration, technical intervention, etc.), a difference between two consecutive IQC results exceeds half of the performance specification for measurement uncertainty.

CIRME

UNIVERSITÀ DEGLI STUDI DI MILANO

Conclusions

According to the European Regulation, the CE marking should ensure the availability for end-users of measuring systems correctly aligned to higher-order references

IVD manufacturers therefore assume total responsibility in terms of traceability of commercial measuring systems, including the responsibility in providing a QC material suitable for traceability verification and alignment surveillance

On the other hand, end-users should improve IQC interpretative criteria to apply prompt corrective actions if the performance of measuring system is worsening and may jeopardize the fulfilment of performance specifications for measurement uncertainty.

UNIVERSITÀ DEGLI STUDI
DI MILANO


GENERAL INFORMATION

CONFERENCE VENUE
AULA MAGNA - LITA SEGRATE
Via Fratelli Cervi, 93 - Segrate, Milano

REGISTRATION FEES
€ 150,00 + 22% VAT = € 183,00

Special fee for students (including postgraduates)
€ 24,60 + 22% VAT = € 30,00
(a document certifying the position is requested)

The registration fee includes:
- Lunch buffet as indicated in the programme
- Certificate of attendance

Cancellations will be accepted by the organising secretariat strictly within (and no further than) 7 days before the event, entitling the registrant to a 50% refund of the fee paid. Although no reimbursements will be processed further to the cancellation deadline, registration may be turned over to another attendee, provided the name is communicated in advance to the organising secretariat.

To make your registration, please access the following link: https://eims.mzcongress.com/start/154/1/eng

ORGANISING SECRETARIAT
MZ CONGRESSI srl - Partners SPHF

MZ CONGRESSI
Via C. Farini, 81 - 20159 - Milano, Italy
Phone: +39 02 66802323 - Fax: +39 02 66866919
portale.sfsm@mzcongressi.com
www.mzcongressi.com

Supported by an unconditional grant by
Abbott

CIRME

UNIVERSITÀ DEGLI STUDI DI MILANO

https://sites.unimi.it/cirme/

CIRME

Centro Interdipartimentale per la Riferibilità Metrologica in Medicina di Laboratorio (CIRME)

Under the auspices of:

13th International Scientific Meeting

THE INTERNAL QUALITY CONTROL IN THE TRACEABILITY ERA

MILANO, ITALY
November 28th, 2019

AULA MAGNA - LITA SEGRATE
Via Fratelli Cervi 93 - Segrate, Milano

Thank you

for Your kind attention !!

CIRME

UNIVERSITÀ DEGLI STUDI DI MILANO

Sara Pasqualetti