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UNIVERSITÀ DEGLI STUDI DI MILANO

IQC component II

or

«How to estimate the random source of measurement uncertainty»

Elena Aloisio
UOC Patologia Clinica
ASST Fatebenefratelli - Sacco

13th International Scientific Meeting
THE INTERNAL QUALITY CONTROL IN THE TRACEABILITY ERA
Milan, November 28th 2019

QUALITY CONTROL

INTERNAL QUALITY CONTROL (IQC)

COMPONENT I:

System alignment verification

COMPONENT II:

Estimation of measurement uncertainty

EXTERNAL QUALITY ASSESSMENT PROGRAMME

MEASUREMENT UNCERTAINTY

Parameter characterizing the dispersion of the quantity values being attributed to a measurand

$$\text{Result} = x \pm u$$

quantity value — measurement uncertainty

The value of the measurand is assumed to lie within the interval $x - u$ to $x + u$ units, with a stated level of confidence.

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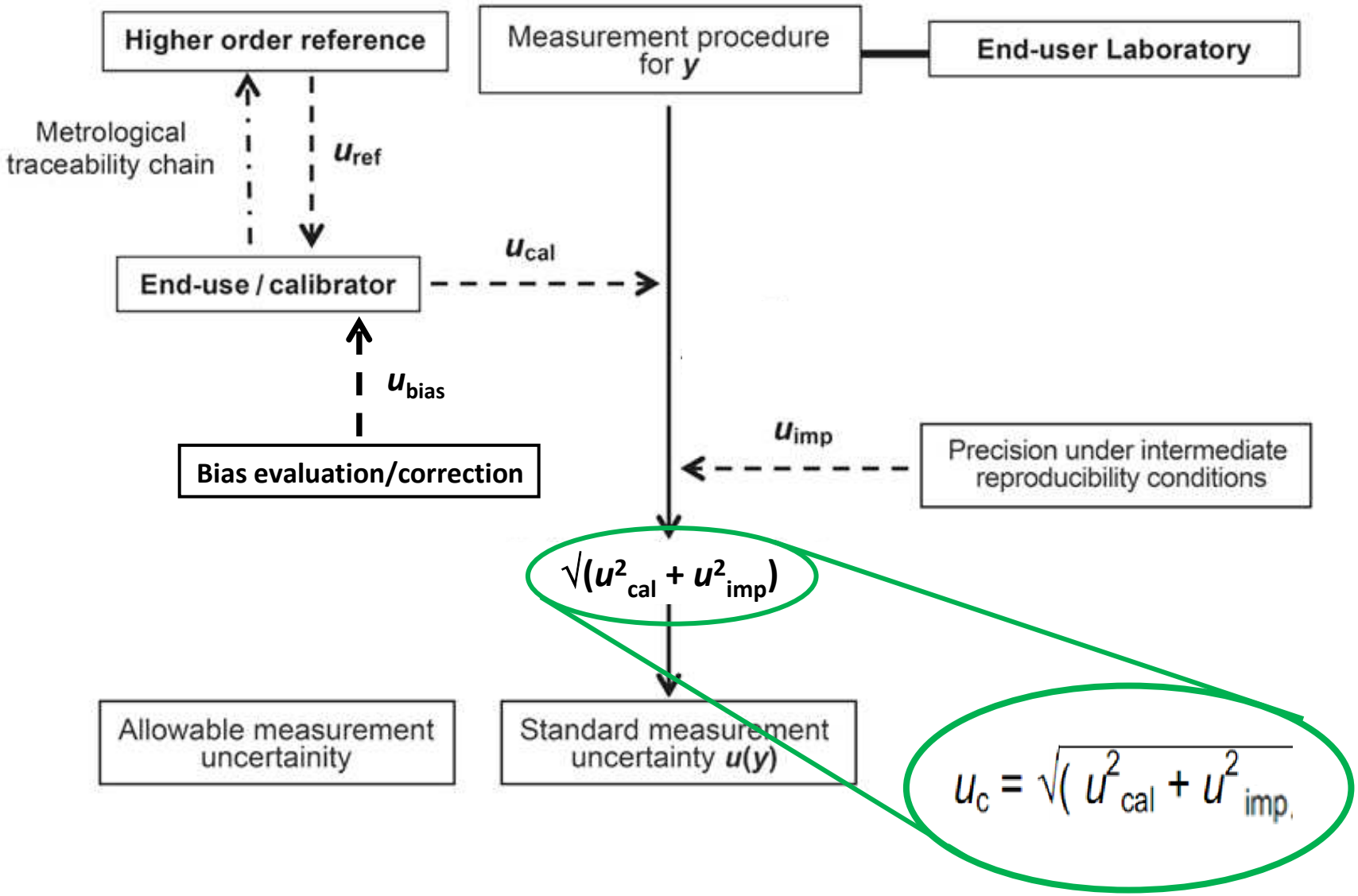
[International Vocabulary of Metrology Basic and general concepts and associated terms (VIM). 3rd ed. 2012]

MEASUREMENT UNCERTAINTY

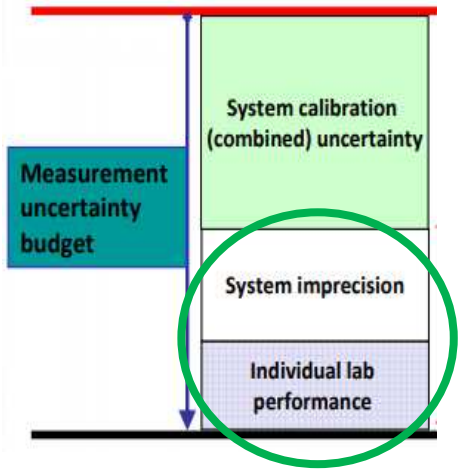


RANDOM UNCERTAINTY (u_{imp})

Portion of measurement uncertainty accounting for random sources of error

It gives information about the stability of the measuring system over time and its variability when employed by an individual laboratory

Measuring system → **RANDOM UNCERTAINTY** ← **Individual laboratory**



u_{imp} is often the **main contributor to the combined standard uncertainty** of a measurement result in medical laboratories

RANDOM UNCERTAINTY (u_{imp})

System imprecision

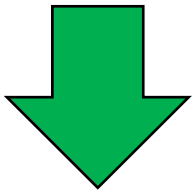
- Reagent lot variability
- Calibrator lot variability
- Reagent/Calibration stability
- Measuring equipment

Individual lab performance

- Environmental conditions
- Different operators
- Instrument maintenance
- Material preparation

MEASURING SYSTEM IMPRECISION

System Imprecision



Characteristic of the measuring system

Responsibility of the manufacturer

MEASURING SYSTEM IMPRECISION

Alinity c

Glucose Reagent Kit

en
Glucose
07P55
G71245R04
B7P550

Within-Laboratory Precision

Serum/Plasma

A study was performed based on guidance from CLSI EP05-A2.[15] Testing was conducted using 2 lots of the Alinity c Glucose Reagent Kit, 2 lots of the Alinity c Multiconstituent Calibrator Kit, 2 lots of commercially available controls and 2 instruments. Three controls and 3 human serum panels were assayed in a minimum of 2 replicates (target of 3 replicates) at 2 separate times per day on 22 different days.

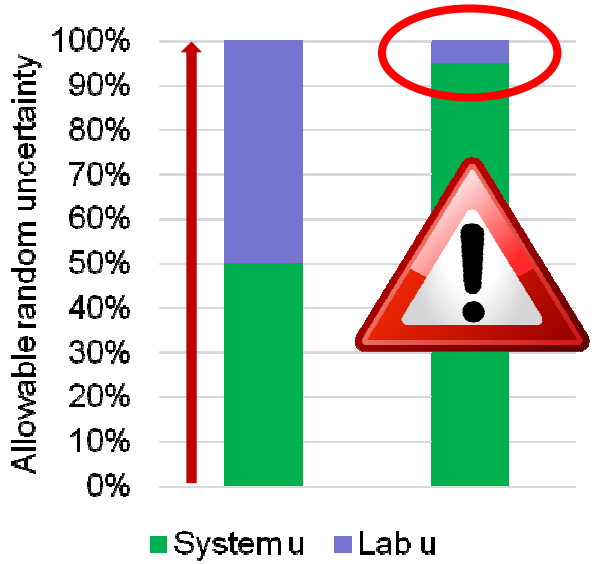
				Within-Run (Repeatability)		Within-Laboratory (Total)[a]	
Sample	Control Lot	n[b]	Mean (mg/dL)	SD	%CV	SD (Range[c])	%CV (Range[c])
Control Level 1	1	264	55	0.6	1.1	0.7 (0.5-0.8)	1.2 (1.0-1.4)
	2	264	55	0.5	0.9	0.6 (0.5-0.7)	1.1 (0.9-1.2)
Control Level 2	1	264	128	1.1	0.8	1.3 (1.1-1.4)	1.0 (0.9-1.1)
	2	263	128	0.9	0.7	1.3 (1.1-1.4)	1.0 (0.9-1.1)
Control Level 3	1	264	315	2.2	0.7	2.8 (2.5-3.1)	0.9 (0.8-1.0)
	2	260	311	2.1	0.7	2.5 (2.1-2.9)	0.8 (0.7-0.9)
Panel A	N/A	527	7	0.1	1.9	0.1 (0.0-0.2)	1.9 (0.0-2.8)
Panel B	N/A	528	106	0.8	0.8	1.0 (0.8-1.2)	0.9 (0.7-1.2)
Panel C	N/A	523	728	5.6	0.8	5.9 (4.4-7.6)	0.8 (0.6-1.1)

MEASURING SYSTEM IMPRECISION

System imprecision

NOT CONTROLLABLE BY END-USERS

If too high, it may cause u_{imp} to exceed the **IQC safety margin**, leaving no room for uncertainty related to the end-user



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Letter to the Editor

Novel generations of laboratory instruments should not worsen analytical quality: The case of GEM Premier 5000

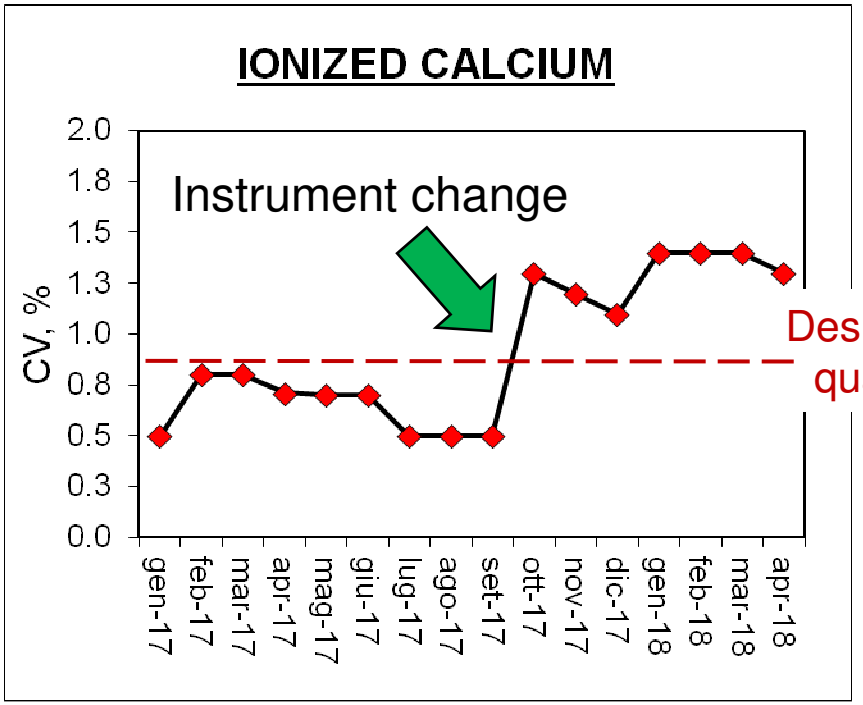
Elena Aloisio[a,*], Assunta Carnevale[b], Alberto Dolci[b], Mauro Panteghini[a,b]

[a] *Research Centre for Traceability in Laboratory Medicine (CIRME), University of Milan, Milan, Italy*

[b] *Clinical Pathology Unit, ASST Fatebenefratelli-Sacco, Milan, Italy*

From GEM 4000 to GEM 5000:

- Same environment
- Same operators
- Both are closed systems (no manual interventions)



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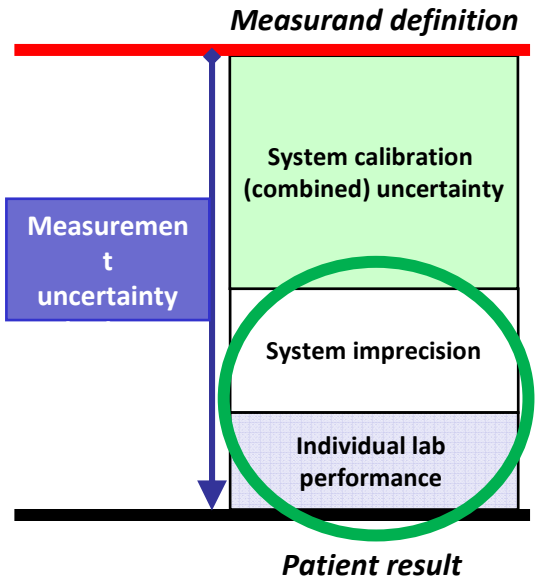
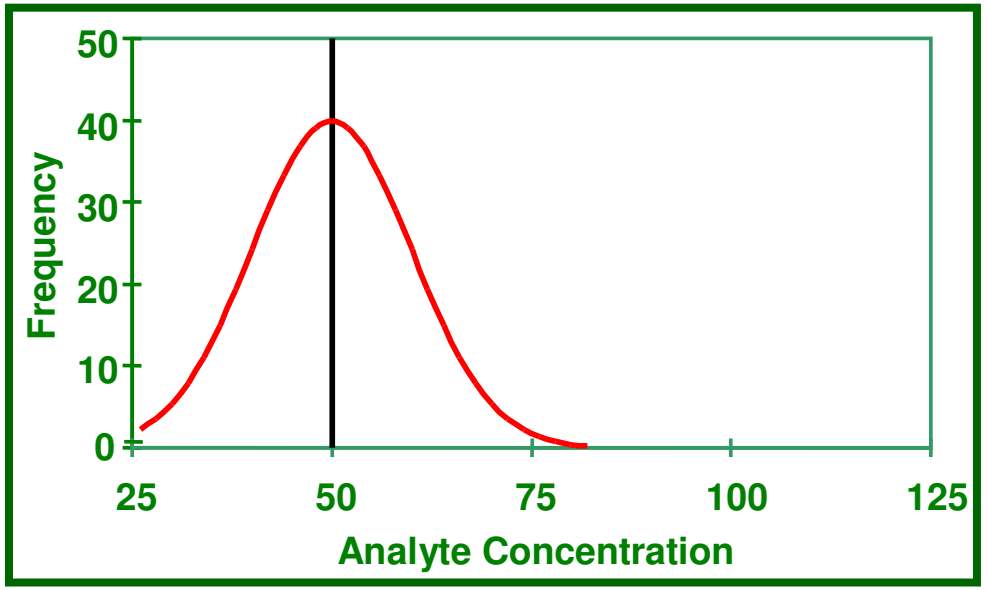
RANDOM UNCERTAINTY (u_{imp})



Through IQC Component II, the individual laboratory estimates the measurement uncertainty due to random effects (u_{imp})

How to estimate u_{imp}



Dispersion of repeated measurements which can be expressed as a **standard deviation (SD)** or a **coefficient of variation (CV)**

How to estimate u_{imp}

CONTROL MATERIALS:

- Third Party
- Commutable
- Clinically relevant concentrations

How to estimate u_{imp}

1) THIRD-PARTY MATERIALS

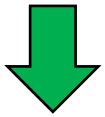
The materials **must be different from those used for the verification of system alignment (IQC component I)** [better if produced by a different manufacturer].

How to estimate u_{imp}

WHY DIFFERENT MATERIALS?

The two IQC components need to be kept separate

Materials for IQC Component I are used to validate the analytical run and must have specific characteristics, described in the previous presentation. If the IQC fails, no other measurements can be performed until the situation is brought back under control



On the contrary, measurements for random uncertainty estimate must be part of an already validated analytical run

How to estimate u_{imp}

NON-EXHAUSTIVE LIST OF MATERIALS IN USE AT THE "LUIGI SACCO" UNIVERSITY HOSPITAL

Commercial controls:

- Bio-Rad Liquichek Unassayd Chemistry Control, Level 1;
- Bio-Rad Liquichek Hematology Control X, Level 1 & Level 2;
- Bio-Rad Liquichek Blood Gas Plus EGL, Level 2;
- Randox Unassayed Urine Control, Level 3;
- Randox Liquid Cardiac Control, Level 2;
- IL-Werfen Plasma Coagulation Control, Level 1.

Home-made pools:

- CRP;
- Ferritin;
- HCG;
- Serum Indices;
- HbA1c;
- Troponin T & Procalcitonin.

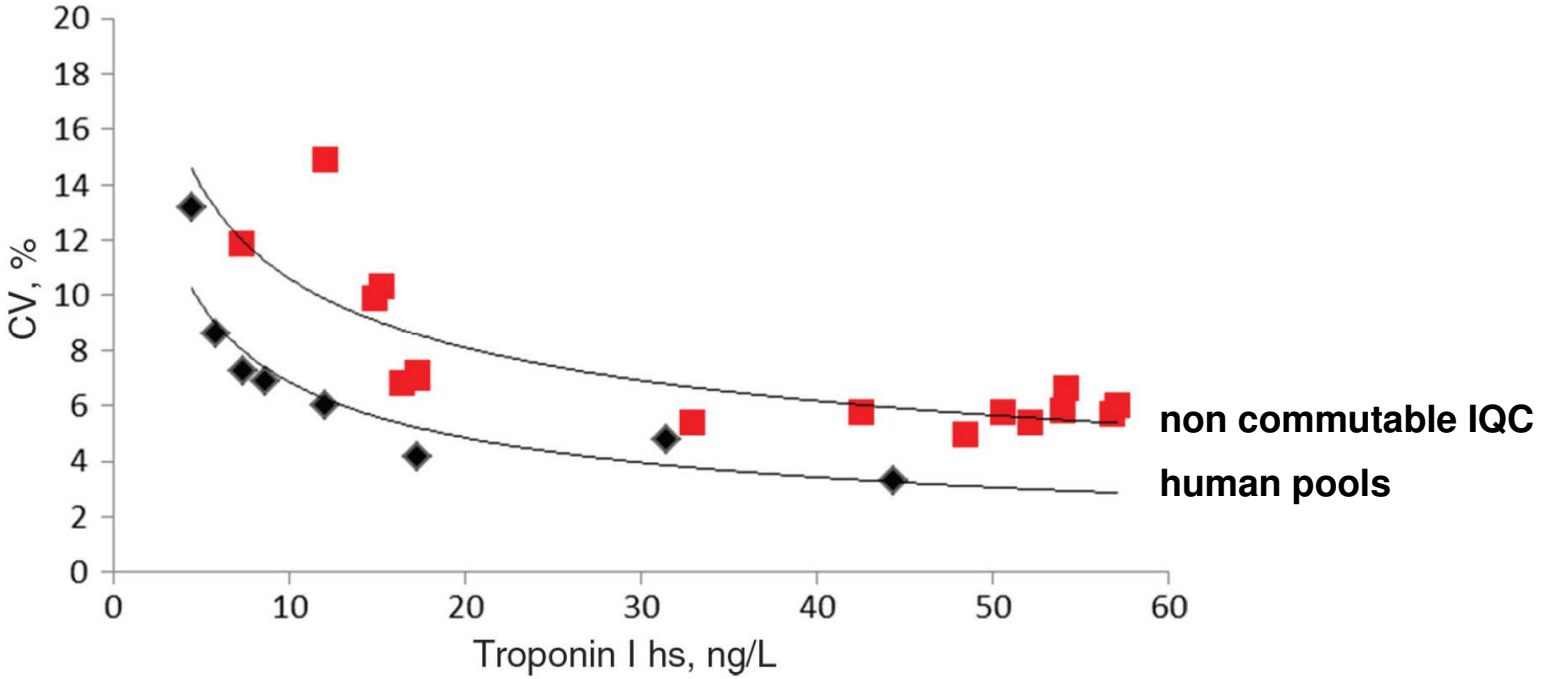
How to estimate u_{imp}

2) COMMUTABLE MATERIAL

Results obtained on non-commutable materials may not reflect performances achieved by the same measuring system on biological samples in terms of random uncertainty.

How to estimate u_{imp}

COMMUTABLE vs NON-COMMUTABLE MATERIAL



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

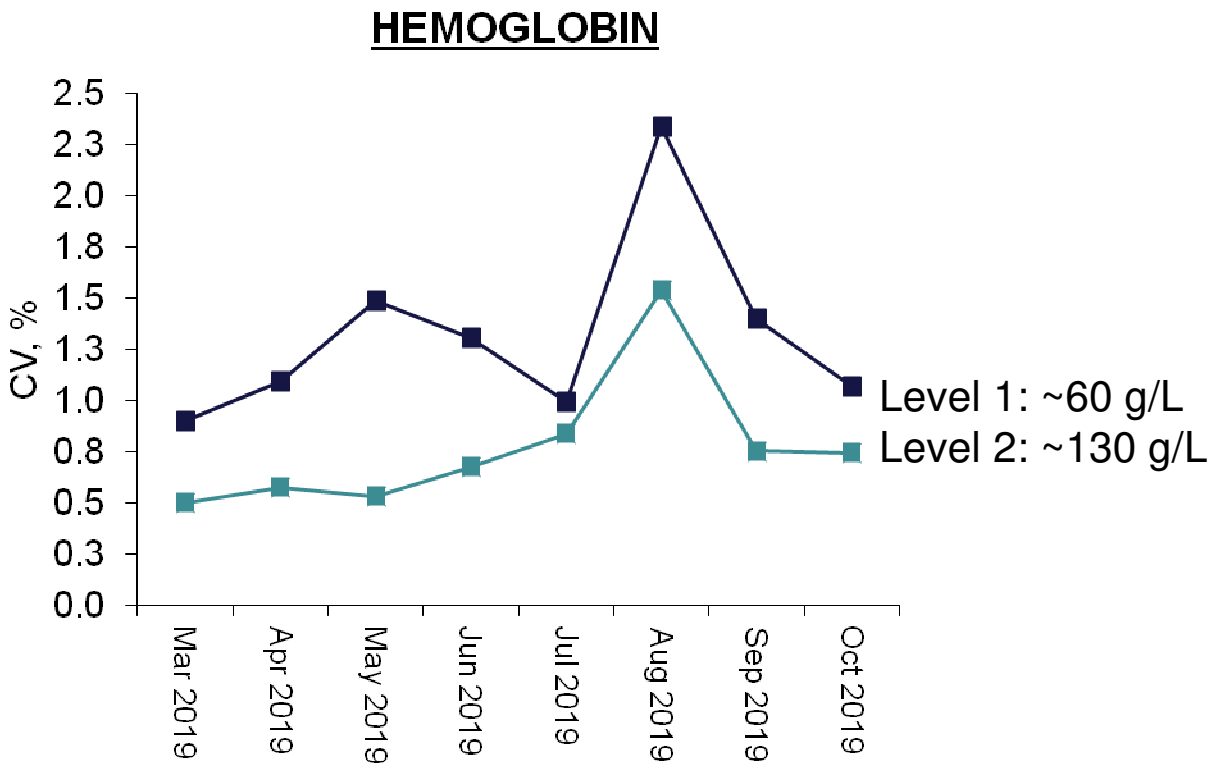
How to estimate u_{imp}

3) RELEVANT CONCENTRATIONS

Imprecision may vary with analyte concentration, so that the material concentration should be chosen in relation to the clinical application of the test → **concentration close to decision limits or reference limits**

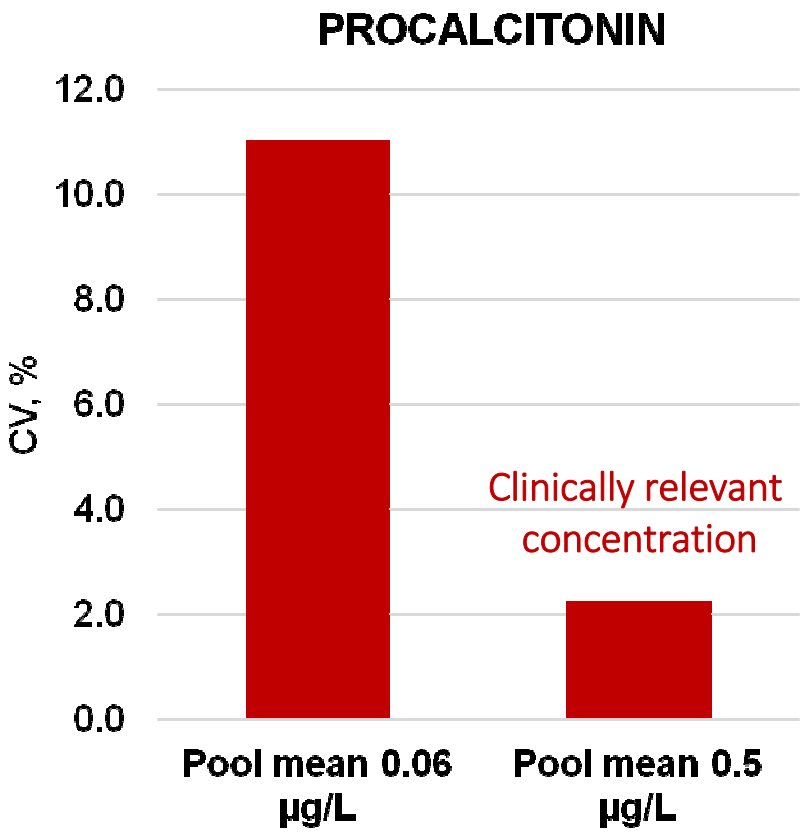
How to estimate u_{imp}

IMPRECISION OFTEN VARIES WITH ANALYTE CONCENTRATION



How to estimate u_{imp}

IMPORTANCE OF CLINICALLY RELEVANT CONCENTRATIONS



How to estimate u_{imp}

Replicate measurements should be performed under **intermediate precision conditions**:

ISO 20914:2019 → condition of measurement, out of a set of conditions that includes the same measurement procedure, same location, and replicate measurements on the same or similar objects over an extended period of time but may include other conditions involving changes.
The changes can include new calibrations, calibrators, operators, and various platforms.

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How to estimate u_{imp}

Measurements should be performed over an **extended period that includes all or most changes in measuring conditions** (e.g., reagent lots, calibrators, instrument maintenance, etc.)

INTERMEDIATE IMPRECISION

How to estimate u_{imp}

WHAT IS THE IDEAL EVALUATION TIME?

Consecutive 6-month evaluation

Time span for covering significant sources of random uncertainty, while still being clinically relevant

How to estimate u_{imp} using IQC Component II

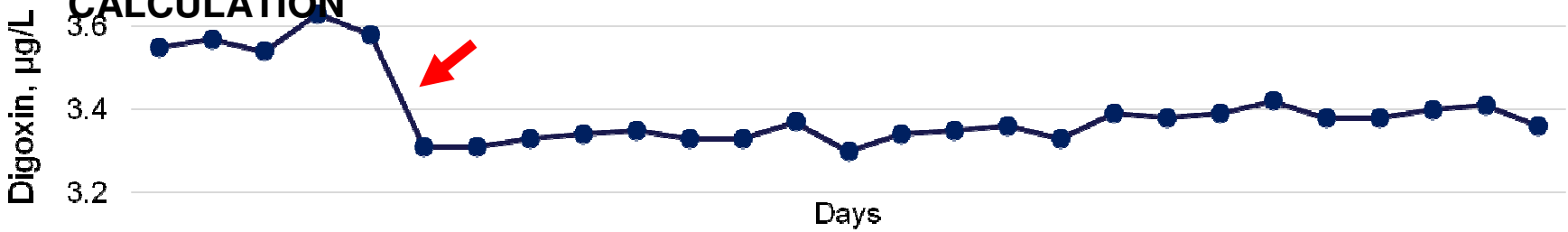
- Provide that your measuring system is running properly and is correctly aligned (IQC Component I);
- Run control material randomly inside the routine analytical run (same analytical conditions of clinical samples);
- Repeat measurements at least daily;
- Do not include gross outliers in your uncertainty estimate, but check the measuring system and explain the outlier IQC result;
- At the end of the evaluation period, collect all results and revise the data (exclude explainable outliers, separate data obtained with different lots of control materials, etc.);
- Calculate mean and SD of replicates;
- Calculate u_{imp} as CV: $\frac{SD}{Mean} x\ 100$

DATA EVALUATION - EXAMPLES

EXPLAINABLE OUTLIER: TO BE EXCLUDED

SHIFT DUE TO THE NEW BATCH OF CONTROL MATERIAL: SEPARATE u_{imp} ESTIMATE

SHIFT DUE TO A NEW CALIBRATION: KEEP ALL RESULTS IN THE CALCULATION



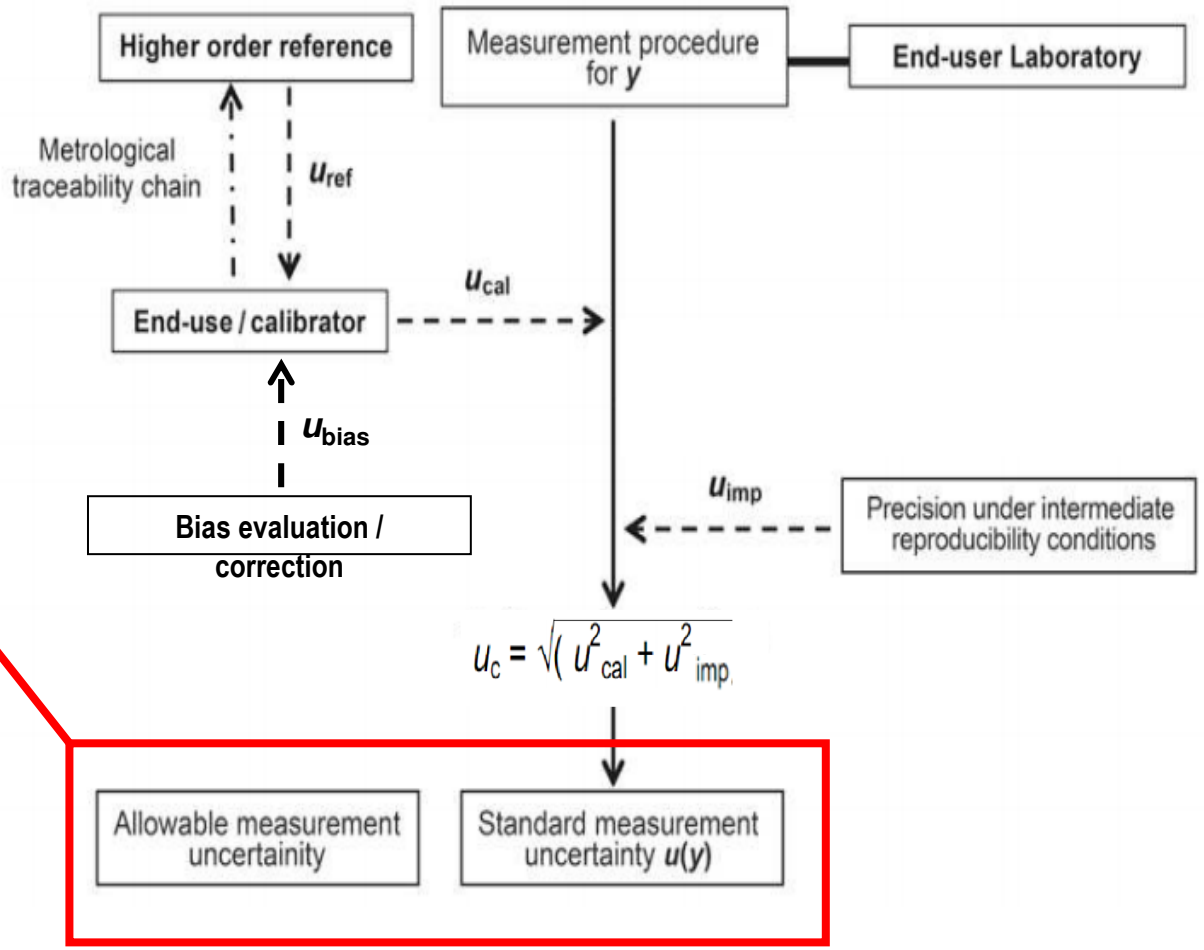
AND DO NOT FORGET !

u_{imp} ***MUST be combined with*** u_{cal} → $u_c = \sqrt{(u^2_{cal} + u^2_{imp.}}$

All commercial calibrator assigned values have an uncertainty that contributes to the overall uncertainty of measurement results.

AND, MORE IMPORTANTLY, ASCERTAIN IF MEASUREMENT UNCERTAINTY AFFECTS THE INTERPRETATION OF LABORATORY RESULTS

Comparison with analytical performance specifications



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Key messages

- **Select an adequate control material;**
- **Manage their measurements as similarly as possible to clinical samples;**
- **Medium/long term evaluation is necessary in order to account for most sources of analytical variation;**
- **Critically review the data during/at the end of the evaluation period;**
- **Combine random uncertainty to calibrator uncertainty;**
- **Compare results with objectively defined performance specifications.**

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