International Scientific Meeting

URement Uncertainty

Edical Laboratories:

Friend or Foe?

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Deriving proper measurement uncertainty from Internal Quality Control data: a mission impossible?

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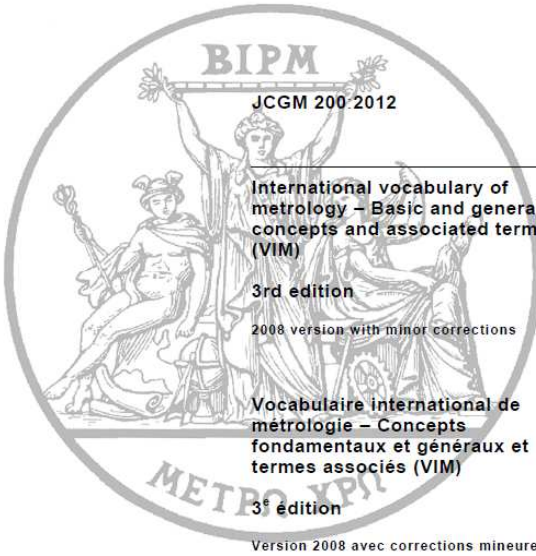
Measurement uncertainty

"non-negative parameter characterizing the dispersion of the quantity values being attributed to a measurand, **based on the information used**"

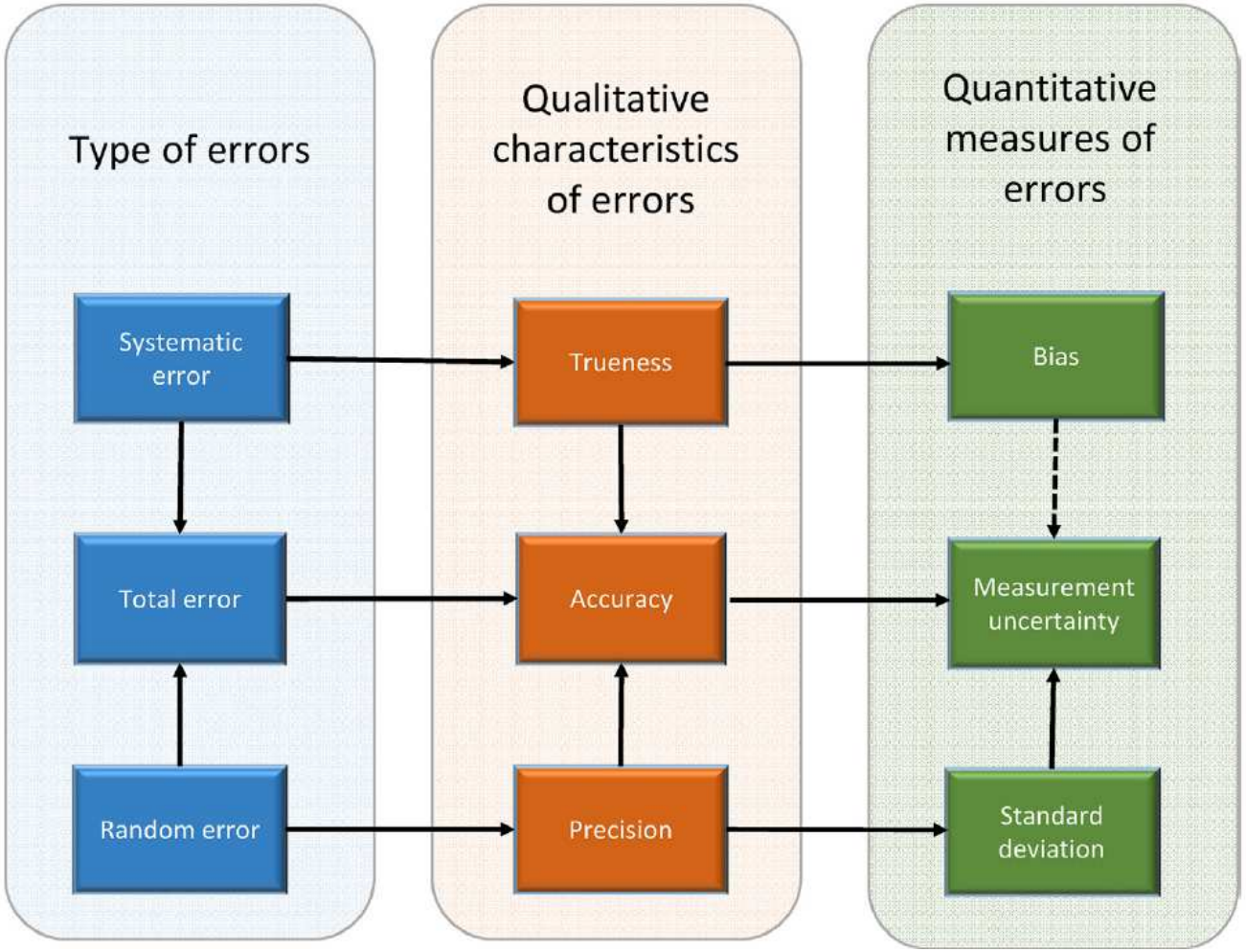


•NOTE 4. In general, for a given set of information, it is understood that the measurement uncertainty is associated with a stated quantity value attributed to the measurand. A modification of this value results in a modification of the associated uncertainty.

Sources of variability of a measured quantity value (that contribute to measurement uncertainty)

- Repeatability of the analytical system
- Calibration
  - Uncertainty of the value assigned to the calibrator
  - Frequency of calibration
  - How calibration is performed
- Stability of the reagents on board
- Lot to lot variability
- Frequency of maintenance
- Operators
- Environmental conditions

Components of error and measurement uncertainty



Which source introduce random error (imprecision)?
Which one introduce systematic error (bias)?

Sources of variability of a measured quantity value (that contribute to measurement uncertainty)

- Repeatability of the analytical system
- Calibration
  - Value assigned to the calibrator (and its uncertainty)
  - Frequency of calibration
  - How calibration is performed
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Random errors

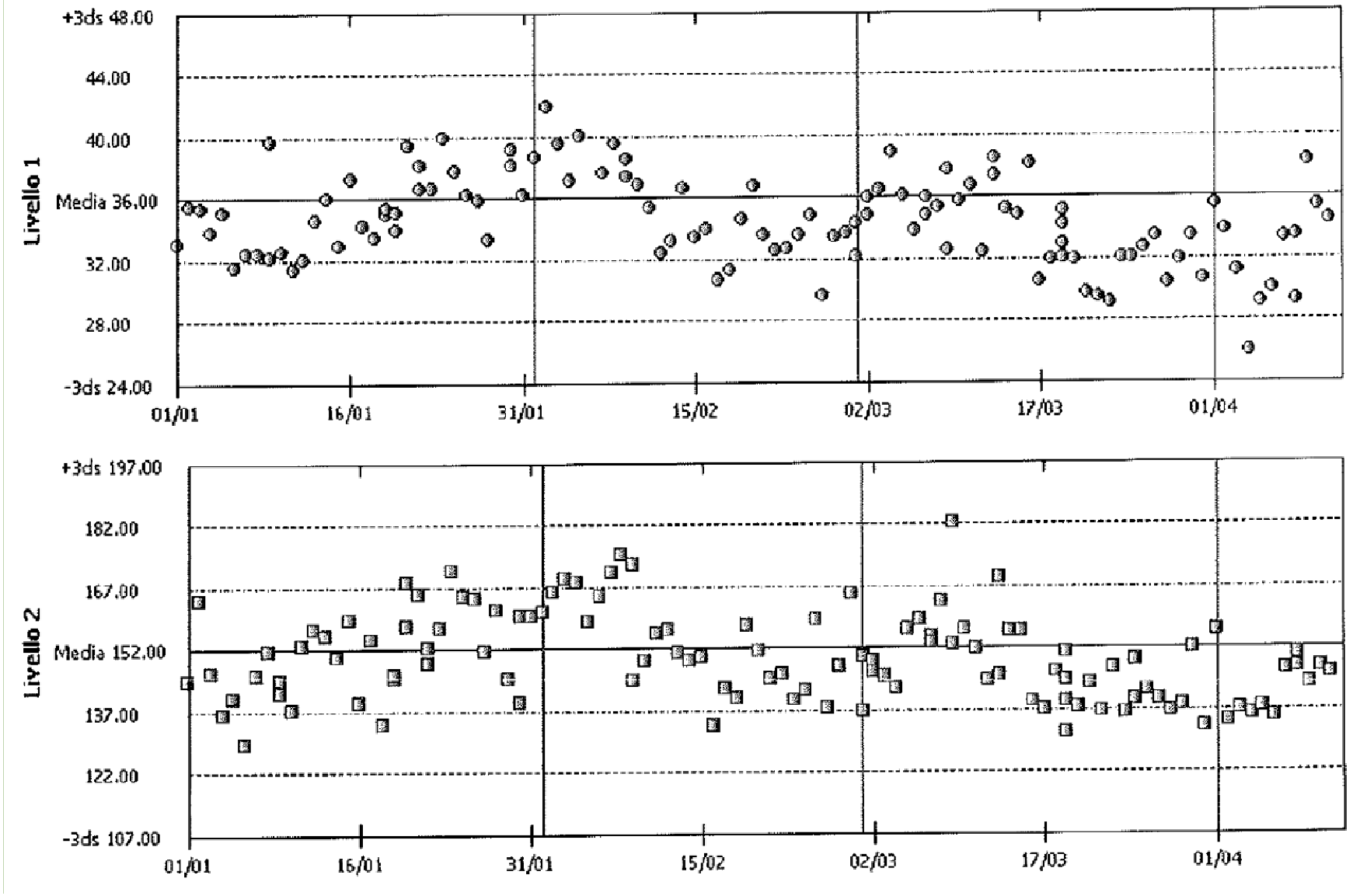
Both random and systematic errors

Systematic errors

Internal quality control (IQC)

- IQC represents the whole set of activities performed to assure the constant monitoring of the performances of an analytical system with the aim of providing an alarm as soon as the analytical process fails to meet the predefined analytical goals.
- *“ The laboratory shall design internal quality control procedures that verify the attainment of the intended quality of results ”* (ISO 15189, par. 5.6.1)

Can the IQC provide enough information on all these sources of variability?
Is the information reliable?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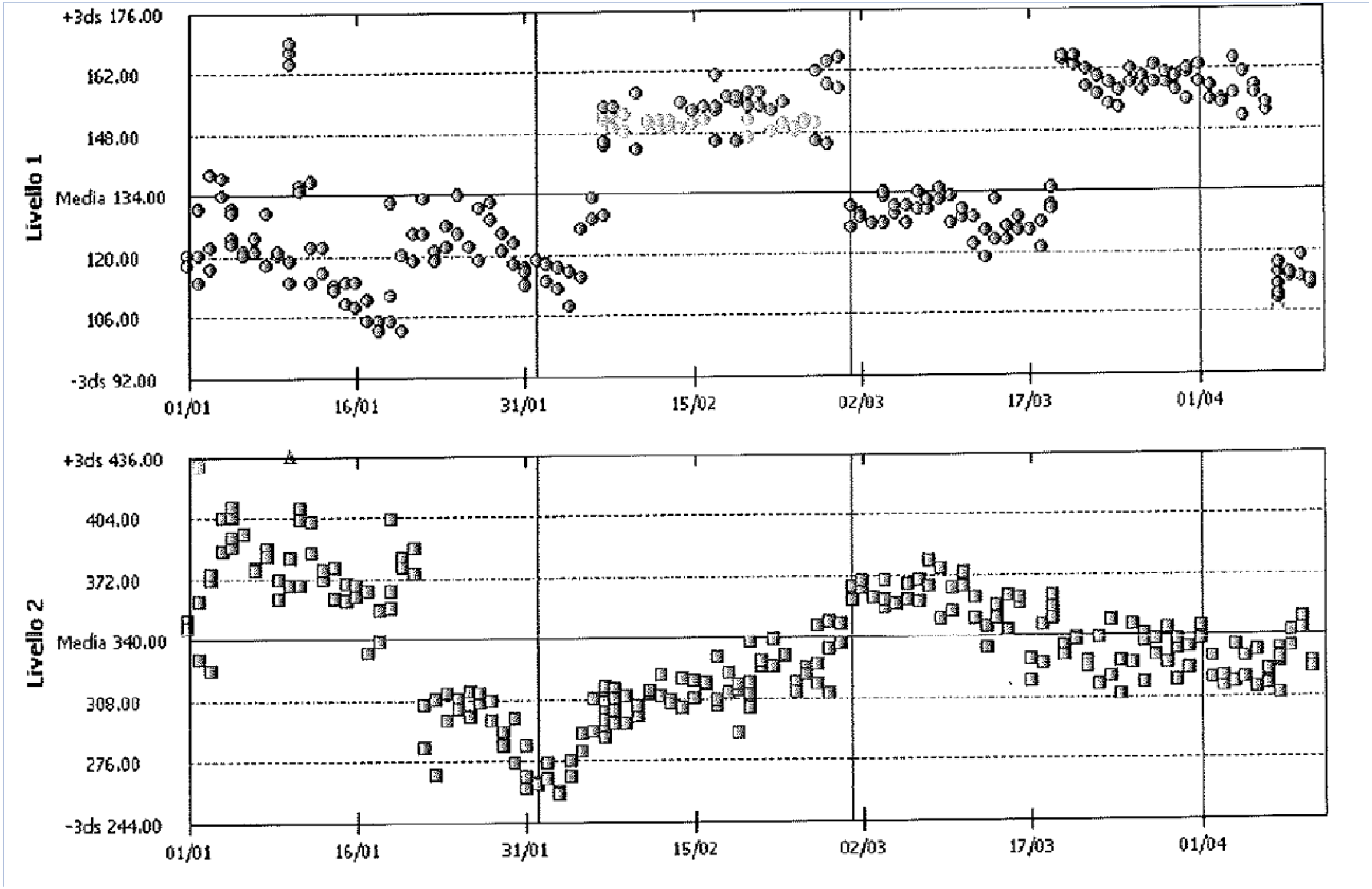
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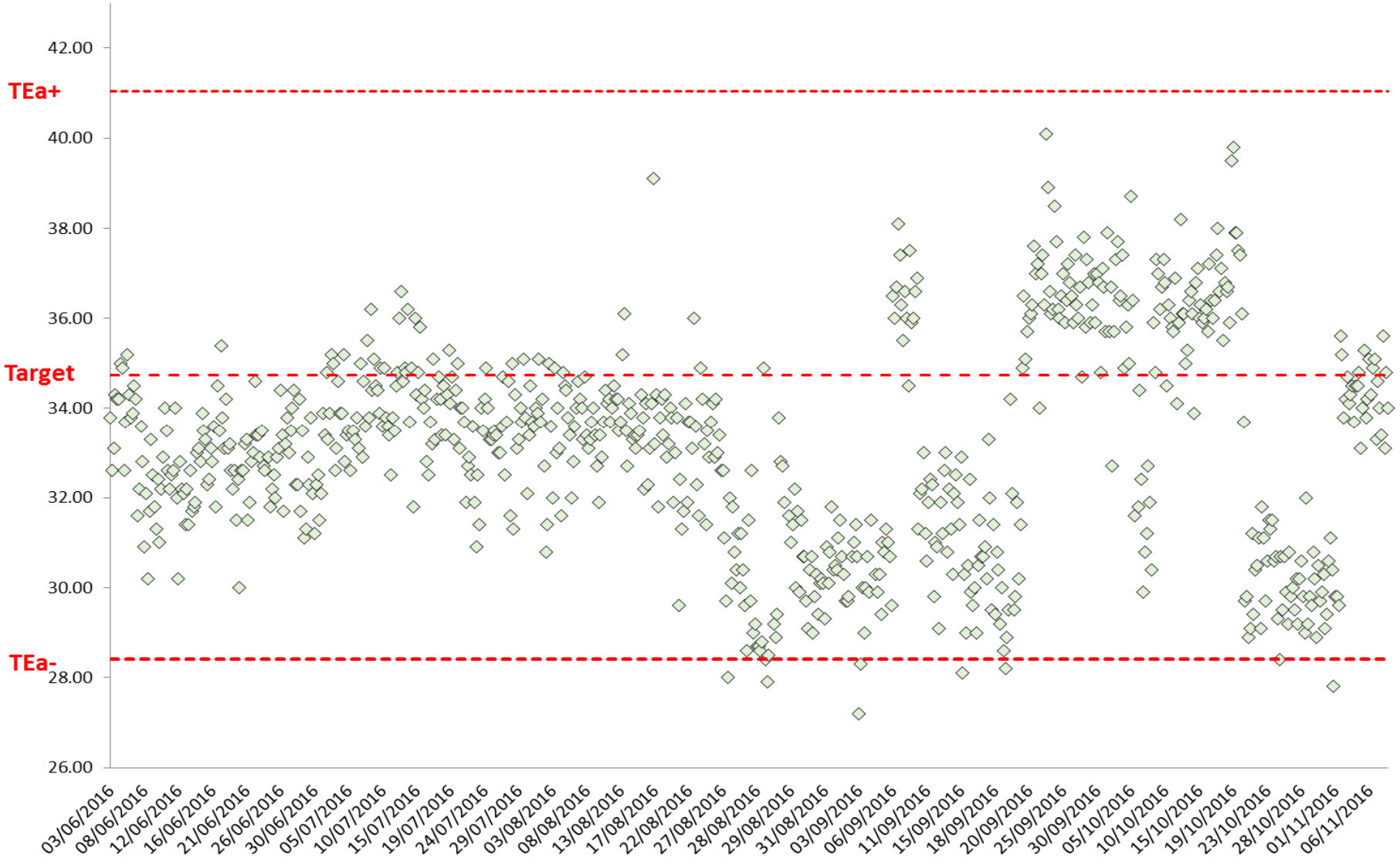
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Information from IQC

- If performed properly it can provide information on repeatability and intermediate precision
- Intermediate precision **includes sources of bias** (relative bias) like those introduced by reagent **lot changes**, different **calibrations**, progressive decrease of the performance of a reagent etc.
- This information is available at different concentration levels and thus it is possible to evaluate if different uncertainty values are needed
- No information on “absolute” bias, unless a material with certified value assigned is used.

Limits of the IQC information

- If the IQC material is not commutable
- If the concentration of the IQC material is far away form the clinically relevant concentrations
- If the results are too few or the time interval is too short
- If the IQC material is not sufficiently stable or it is used not properly

The problem of bias

- “absolute” bias:
  - bias form the most reliable estimate of the quantity value (reference method value): Type 1 or 2 EQAS, commutable CRMs, direct comparison with a reference measurement procedure on clinical samples;
- “relative” bias:
  - bias form the laboratory mean in the previous months
  - bias from the “peer group mean” (type 3-5 EQAS, interlaboratory IQC)

The problem of bias

- Lack of absolute references for the vast majority of measurands: few type 1/2 EQAS, few commutable CRMs;
- Poor reliability of the relative references: peer group means of inter-laboratory IQC may be biased by heterogeneity of laboratory classification; EQAS results are few (usually maximum of 12 / year) so statistically weak and require long periods to get the information;
- **Trueness materials from the manufacturers**: if the traceability to the reference measurement system is granted, it should be a good surrogate of an absolute reference, but usually it does not have an uncertainty value.

How many uncertainty values?

- It depends upon two considerations:
  - The precision and bias profile of the method
  - The clinically relevant concentration value (decision limits)
- If the CV is relatively constant or the clinically relevant concentration value is close the value of one of the control materials, just one value may be sufficient;
- If the CV vary considerably with the concentration or if the clinically relevant concentration values are more than one (e.g. lower and upper limits of the reference intervals), more than one uncertainty value should be used.

How to use the IQC data to calculate measurement uncertainty (1)

- **Minimal requirement:**
  - Just consider intermediate precision (6 months of IQC data with at least 20 results) of one IQC material (concentration at decision level)

$$\boldsymbol{u = R_w = CV} \qquad \mathbf{CV \times 2 = U}$$

  - Just intermediate precision, but combining two (ore more) IQC materials

$$u_c = R_W = \sqrt{\frac{CV1^2 + CV2^2}{2}} \qquad R_w \times 2 = U$$

Limits of this approach

- It includes only the bias components that are considered into the intermediate precision
- It does not include the sources of uncertainty due to the previous steps of the traceability chain

but

- It can be sufficient for most of the tests lacking of absolute references or mainly used for monitoring

If this approach is used a note as the following one may be added to the report:

- *The reported measurement uncertainty was calculated by considering only the component due to the variability observed in the control materials over the last 4-6 months. Additional components, such as possible bias from reference values, may be provided on request.*

Including bias (or the uncertainty related to its correction) into the uncertainty value

- Problems:
  - The reference value and its uncertainty
  - Bias correction or inclusion into the calculation
  - How to avoid of overestimating the effect of bias (the bias has a sign, but when including it into the formula the sign disappears)
- Possible approaches
  1. Just consider the uncertainty of the value assigned to the calibrator
  2. Add the bias from a reference material (CRM or trueness material from the manufacturer)
  3. Add the bias calculated from EQAS or from interlaboratory IQC data
  4. Add the bias from the previous period (historical mean of the laboratory)

1. IQC + the uncertainty of the value assigned to the calibrator (COFRAC approach 4)

- *u(Rw)* = six months CV (single conc. level or as mean of two lev.)

- *u(bias)* = $u(\mathrm{cRef}) = \frac{U_{CAL}}{2}$ $\mathrm{u(cRef)\%} = \frac{\mathrm{u(cRef)}}{\mathrm{CAL}} \times 100$

$$\boldsymbol{U = 2\,x\,\sqrt{u(Rw)^2 + u(bias)^2}}$$

Note

- U_{CAL} not always easy to obtain;
- Calibrator concentration can be very different the one of the control;
- How to deal with multiple calibrators?

2. IQC + manufacturer trueness material

- $u(Rw)$ = six months CV (single conc. level or as mean of two lev.)
- $u(bias)$ = two components: the uncertainty of value assigned to the reference ($u(cRef)$) and the amount of bias
- $u(cRef) = \frac{U_{ref}}{2}$ (if available) $\quad bias = \bar{x} - Xref$
- $u(bias) = \sqrt{\left(\frac{bias}{\sqrt{3}}\right)^2 + u(cRef)^2}$

$$\boldsymbol{U = 2\,x\,\sqrt{u(Rw)^2 + u(bias)^2}}$$

Note: u(cRef) usually not available

3. IQC + EQAS or interlaboratory IQC (COFRAC proposal 3) (Nordtest report)

- $u(Rw)$ = six months CV (single conc. level or as mean of two lev.)
- $u(cRef) = \frac{SD_{group}}{\sqrt{n(group)}}$ $\qquad bias = RMS_{bias} = \sqrt{\frac{\sum(bias_i)^2}{n}}$
- $u(bias) = \sqrt{(RMS_{bias})^2 + u(cRef)^2}$

$$\boldsymbol{U = 2\,x\,\sqrt{u(Rw)^2 + u(bias)^2}}$$

Note: the calculation of $u(cRef)$ is based on the most common situation in which the reference value derives from a consensus mean.

There is the risk of overestimating the bias component, in fact $u(Rw)$ already includes some bias effects, moreover $u(cRef)$ may be significant in case of small groups.

4. IQC + bias from the mean of the previous period [Brugnoni et al. Biochim Clin 2015;39:108-15]

- **The bias component of intermediate precision is minimized by calculating $u(Rw)$ as weighted mean of monthly CV**

$$u(Rw) = CV_{pooled} = \sqrt{\frac{(n_A - 1)\times CV_A^{\,2} + (n_B - 1)\times CV_B^{\,2} + .. + (n_i - 1)\times CV_i^{\,2}}{(n_A + n_B + .. + n_i) - n_{periods}}}$$

- $u(cRef) = \dfrac{CV_{pooled}}{\sqrt{mean\ num\ of\ monthly\ QC\ results}}$ $\qquad bias = RMS_{bias} = \sqrt{\dfrac{\sum(bias_i)^2}{n}}$

- $u(bias) = \sqrt{(RMS_{bias})^2 + u(cRef)^2}$

$$\boldsymbol{U = 2\,x\,\sqrt{u(Rw)^2 + u(bias)^2}}$$

Note: it implies that an unbiased initial situation

Conclusions

- Deriving the uncertainty values from the IQC data **is not** an "impossible mission".
- It requires long term QC data, on commutable materials at proper concentrations.
- The decision on how to deal with the bias and how to calculate the bias related component of uncertainty is still under debate, no perfect solution is presently available.


Thanks for your attention!