Performance criteria for internal QC – how to define a significant deviation from the expected results

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OSPEDALE SAN RAFFAELE

Internal CQ

- "part of quality management focused on fulfilling quality requirements" (ISO 9000:2005)
- Set of procedures intended to monitor the performance of a test procedure to ensure reliable results
- 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

Steps for IQC implementation according CLSI C24-A3

1. Define the quality specification for the test
2. Select the appropriate control materials
3. Determine the stable (in control) performance characteristics of the measurement procedure
4. Identify candidate quality control strategies
5. Predict the likelihood that candidate quality control strategy will detect out-of-specification performance
6. Specify desirable goals for the QC performance characteristics
7. Select a quality control strategy whose predicted performance meets or exceeds the quality control performance goals

1. Define the quality specification

- Performance criteria based on true and false classification: e.g. total cholesterol or cholesterol fractions, HbA1c, glucose, etc.;
- Biological variation: components with good homeostatic control e.g. electrolytes, substrates, etc;
- State of the art: analytes where BV targets are presently impossible to meet or where they are not completely reliable (too wide).

3. Determine the stable (in control) performance characteristics of the measurement procedure

Use the **uncertainty approach**

- Calculate the measurement uncertainty of your method at different concentration levels

Measurement uncertainty: the theory

From the metrological standpoint:

- In general, the **result of a measurement** is only an approximation or **estimate** of the value of the measurand and thus is complete only when accompanied by a statement of the **uncertainty** of that estimate.

Measurement uncertainty: definition

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

[VIM 2012, 2.26]

NOTE 1 Measurement uncertainty includes components arising from systematic effects, such as components associated with **corrections** and the assigned quantity values of **measurement standards,** as well as the **definitional uncertainty.** Sometimes estimated systematic effects are not corrected for but, instead, associated measurement uncertainty components are incorporated.

Uncertainty approach

- Assumes that the information from measurement only permits assignment of an interval of reasonable values to the measurand;
- Assumes that all significant systematic errors can be identified and corrected within some defined uncertainty, so that all uncertainty components can be treated in the same manner.

How to calculate the measurement uncertainty in a clinical lab: the top-down approach

- All the sources of random variability (operators, reagents, analyzer's performance, etc.) contribute to the imprecision measured by a well performed Internal Quality Control [$u(R_w)$]
- An estimation of the uncertainty due to the bias [*u(bias)*] can be derived from the measurement of a value assigned trueness material.

How to estimate uncertainty related to random variability [$u(R_w)$]

- Calculate the overall CV (CV_{pooled}) a weighted mean the CV of various time intervals (e.g. 6 months) according to the following formula:

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

- Calculation to be performed at different concentration levels

How to calculate the systematic component of the uncertainty

- **The bias from the assigned value of the manufacturer's trueness material can be calculated with the following formula:**

$$u(bias) = \sqrt{(bias)^2 + \left(\frac{S_{bias}}{\sqrt{n}}\right)^2 + u(Cref)}$$

- **Unfortunately the expanded uncertainty around the assigned value of the control material [*u(Cref)%*] usually is not available . As a surrogate it can be used the uncertainty of the value assigned to the calibrator:**

$$u(Cref) = \frac{U_{CAL}}{2} \qquad u(Cref)\% = \frac{u(Cref)}{\text{CAL}} \times 100$$

Calculation of the expanded uncertainty

- The square root of the sum of the squares of the two components of the uncertainty gives the **combined uncertainty**

$$u = \sqrt{u(R_w)^2 + u(bias)^2}$$

- **Expanded uncertainty**

$$U = u \times k$$

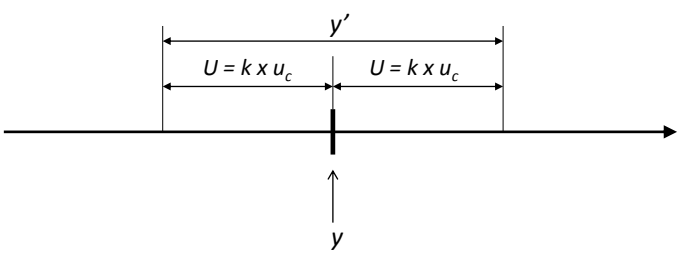
where k = 2 for 95.5% probability

4. Identify quality control strategies

- The most commonly used approach is the sigma metrics as proposed by Westgard, based on the "total error" theory.
- Question: is a model based on ***measurement uncertainty*** applicable?

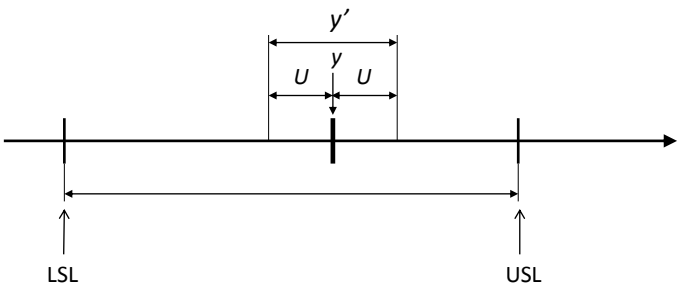
How to apply the uncertainty approach to IQC: the theory

- Estimated measurement uncertainty shall be taken into account to prove the conformity or nonconformity with the given specification.
- The complete measurement result, *y'*, is represented by the measurement result ± measurement uncertainty (*U*).



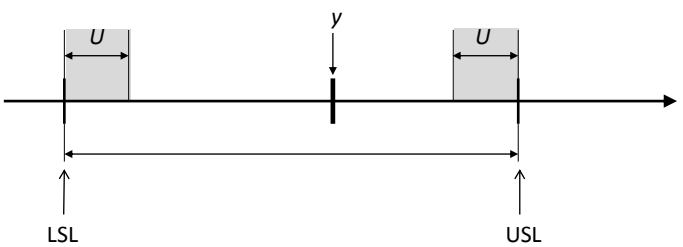
- Conformity with a specification is proved when the complete measurement result, *y'*, falls within the zone defined by a Lower Specification Limit (LSL) and an Upper Specification Limit (USL) (maximum permissible error).

LSL ≤ *y* - *U* and *y* + *U* ≤ USL



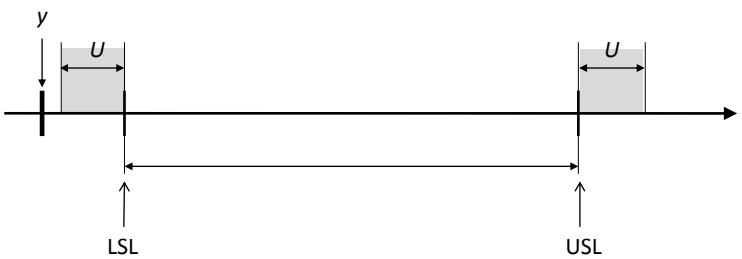
- The same conformity can be proved similarly when the measurement result, *y*, falls within the zone of maximum permissible error reduced on either side by the expanded measurement uncertainty.

LSL + *U* ≤ *y* ≤ USL - *U*

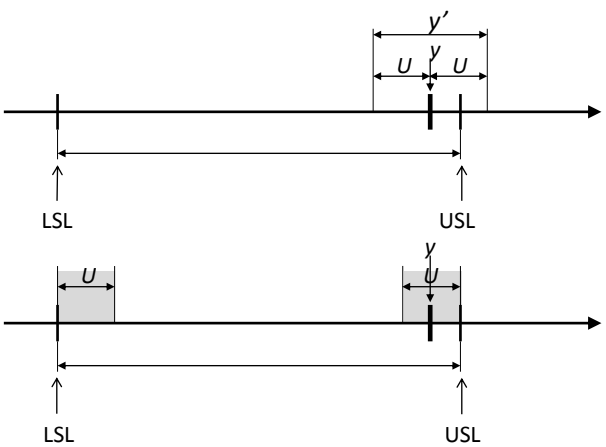


- Nonconformity of a specification is proved when the complete measurement result, *y'*, falls outside the maximum permissible error

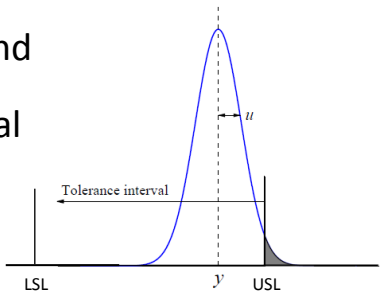
$$y + U \leq LSL \text{ or } USL \leq y - U$$



- The problem arises when the complete measurement result, *y'*, includes one of the limits (or *y* falls outside the limits reduced by *U*).



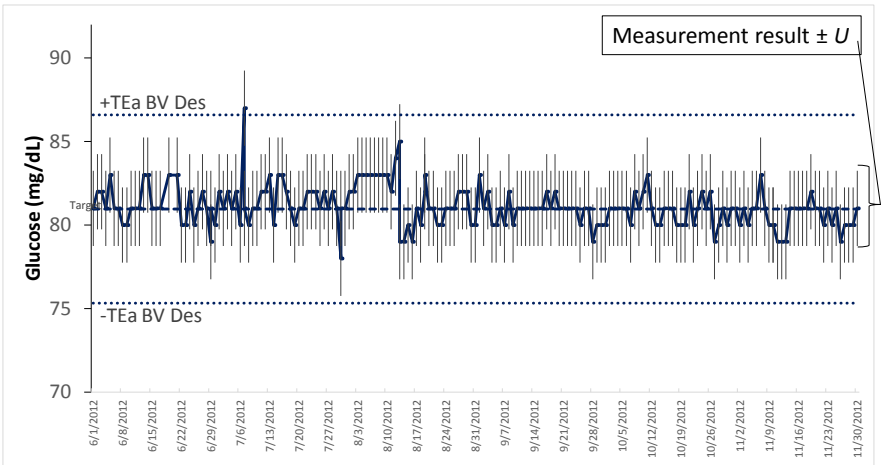
In this case the knowledge of the possible values of the measurand can be encoded and conveyed by a probability density function or a numerical approximation of such a function. An assessment of conformity with specified requirements is thus a matter of probability.



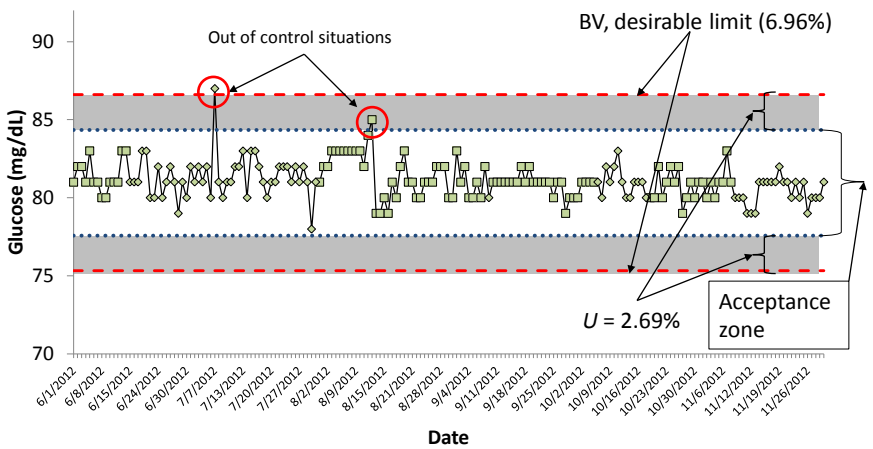
The probability of conformity, assuming a symmetrical distribution, falls to 50% when the measurement result equals the tolerance limit.

Some practical examples

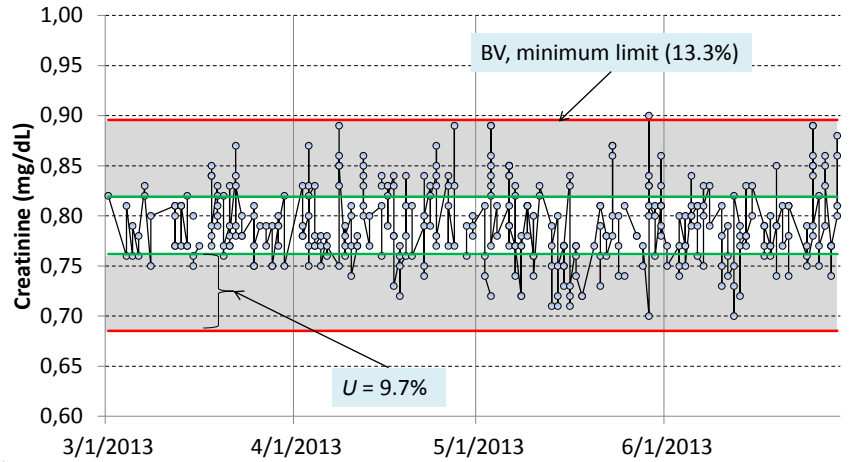
Glucose



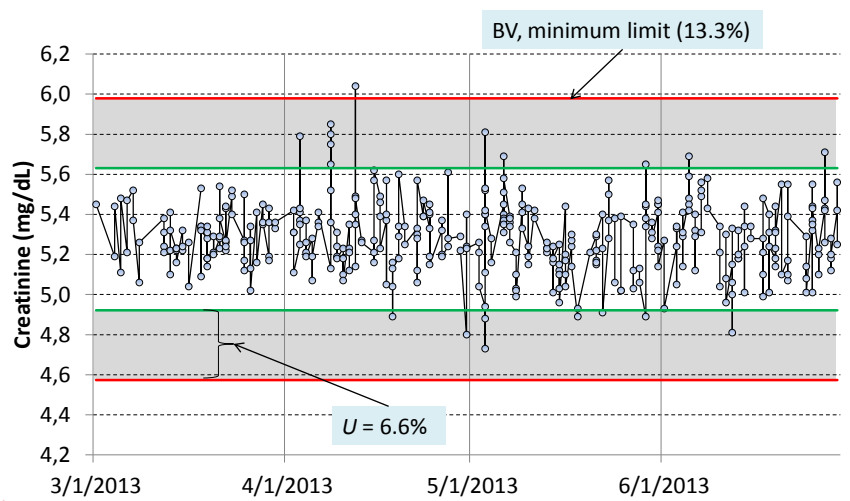
Glucose



Creatinine Level 1



Creatinine Level 2



Considerations on the 3 examples

- **Glucose**: the described situation is close to 6 sigma (imprecision = 1.2%, TEa = 6.96%), very easy to detect out of control situations
- **Creatinine level 1**: below 3 sigma (imprecision = 4.6%, TEa = 13.3%) no way to guarantee the respect of the target quality 95% of the time
- **Creatinine level 2**: slightly more than 4 sigma (CV = 3.0%, TEa 13.3%), more strict and frequent control needed

Conclusions (1)

The model is based on the following assumption:

- The control materials respond to the modifications in the analytical system in a manner similar to the patients' samples.
- The measurement uncertainty has been defined correctly, taking into consideration all the possible sources of variability, including bias or its correction.

Conclusions (2)

- The model is well applicable **only** if the defined quality goal is greater than the measurement uncertainty (*U*) otherwise no “acceptance zone” can be defined. If *U* is larger than the quality goal the probability of producing a result within the quality specification is always lower than 95%, so one has to adopt (and communicate to the customers) a lower level of target quality (or change or modify the analytical method).
- The measurement uncertainty should be periodically verified to assure its stability with time.

Conclusions (3)

- The definition of concentration dependent measurement uncertainty provides the reference for detecting significant deviations from expected results.
- The relationship between the measurement uncertainty of a method and the quality goal is the key for the definition of the ability of the method of providing results of the desired quality.

References

- JCGM 106:2012 Evaluation of measurement data – The role of measurement uncertainty in conformity assessment.
- ISO 14253-1:2013 Geometrical product specifications (GPS) – Inspections by measurement of workpieces and measuring equipment – Part 1: decision rules for proving conformity or nonconformity with specification. ISO Geneve, 2013.
- Eurachem/Citac Guide "Use of uncertainty information in compliance assessment". Ellison SRL and Williams A Editors; first edition 2007.