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# Analytical Quality in the Medical Laboratory – The ASAP Concept Part 2: Internal Quality Control

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**SUMMARY**
This essay tries to put the very basics of internal quality control (IQC) into a nutshell. First, IQC is a necessary part for obtaining a valid result for a patients' specimen. Establishing an effective IQC strategy requires basic statistical knowledge (mean, standard deviation and their confidence intervals). It also requires basic knowledge of power functions. The selection of an IQC-rule is always a compromise between power for error detection and probability of false reactions. Application of the allowable total error concept may be helpful in deciding about the most effective control rule for a specific analyte. This, however, requires decent knowledge about establishing analytical quality specifications. Practical considerations may lead the laboratory to deviate from the ideal IQC concept: i) working with the „wrong" mean because several systems/modules have to be controlled for an analyte; ii) working with the „wrong" standard deviation because lot-to-lot variation needs to be accommodated. Common problems associated with those practices are presented. It may be useful to add monitoring of patient percentiles to IQC monitoring.
*Keywords:* probability of false reaction, power function, allowable total error, lot-to-lot variation, wrong target.

**SOUHRN**
**Stepman H., Stöckl D.: Analytická kvalita v lékařské laboratoři – Koncept ASAP. Část 2: Interní kontrola kvality.**
Tato práce vysvětluje základy vnitřní kontroly kvality v kostce. V prvé řadě je IQC nezbytnou součástí získání spolehlivého výsledku měření pacientských vzorků. Vytvoření účinné IQC strategie vyžaduje základní statistické znalosti (průměr, směrodatná odchylka a jejich intervaly spolehlivosti). K tomu jsou také potřebné základní znalosti o silových funkcích. Výběr IQC-pravidel je vždy kompromisem mezi danou schopností systému detekovat chyby a pravděpodobností falešného zamítnutí. Použití konceptu přípustné celkové chyby může být užitečné při rozhodování o nejúčinnějších kontrolních pravidlech pro daný konkrétní analyt. To však vyžaduje též základní znalosti o analytických požadavcích na kvalitu. Praktické faktory však mohou někdy vést laboratoř k odchylkám od ideálního IQC konceptu: i) použití a práce s „nevhodným" průměrem, protože je souběžně kontrolováno několik systémů / modulů pro stanovení téhož analytu, ii) použití a práce s „nevhodnou" směrodatnou odchylkou, protože se musí zohlednit a respektovat variabilita mezi jednotlivými šaržemi. V práci jsou prezentovány běžné problémy spojené s těmito postupy. Tyto postupy mohou být i užitečné pro aplikování pacientských percentilů jako nástroje provádění IQC.
*Klíčová slova:* pravděpodobnost falešného zamítnutí; přípustná celková chyba; variabilita mezi šaržemi; chybná kritéria

## Introduction

The importance of Internal Quality Control (IQC) has nicely been described by Westgard [1]:

An analytical process has two major parts: the measurement procedure is necessary to obtain a measurement on a patient's sample; the control procedure is necessary to assess the validity of a measurement result.

Thus, analytical measurements should be controlled, or as other disciplines say, should be under Statistical Process Control (SPC). The basis of the control procedures shall be two paradigms:

The „analytical-paradigm": Analytical procedures give results ($x_i$) that are independent from other results and $x_i$ comes from a Gaussian distribution with a mean $\mu$ and a standard deviation $\sigma$. Note: An experimentally determined standard deviation (finite number of measurements) is denoted by SD. We assume that analytical procedures have periods of stable performance. The performance characteristics (mean, SD) of the stable process can be estimated from sufficiently frequent measurements under stable conditions. We assume that, in the course of time, analytical procedures tend to instability:

- Measured means deviate from the „true" mean due to the occurrence of systematic error
- Measured SD is >„true" $\sigma$ due to increased random error

The „IQC-paradigm": IQC can detect process deterioration (increased systematic or random error) at a sufficiently early stage:

- By repeated measurement of the same sample
- Investigation of the results by statistical methods

Statistical methods (control rules) indicate, for example, whether

- The actual mean deviates from the „true" mean
- The actual SD is > than the „true" $\sigma$

## Basic statistical aspects of IQC

The target value of a control material and the SD of the assay are typically estimated by 20 repeated measurements. Thus, the uncertainty of the mean is determined by the *t*-statistics and the uncertainty of the SD by the $CHI^2$-statistics. Both will be addressed later in a „statistics“ essay. Important for the selection of an IQC rule is its „power“, which can be visualized by a so-called power function graph [2].

### The power function graph

Fig. 1 indicates:

- the power of a rule for error detection ($P_{ed}$)
- the probability of false rejection ($P_{fr}$).

*Note: Separate graphs must be constructed for systematic and random error.*

- The x-axis plots the size of error in multiples of the analytical standard deviation
- The y-axis plots the probability of error detection ($P_{ed}$) (rejecting a run) against the size of error on the x-axis.
- The probability of false rejection ($P_{fr}$) can be read at the point ΔRE = 1 or ΔSE = 0.

The generation of a power curve shall be graphically explained for the 1-3s rule and the occurrence of systematic error.

*Note: Generally, we strive for an IQC rule with 90 % $P_{ed}$ and < 1 % $P_{fr}$.*

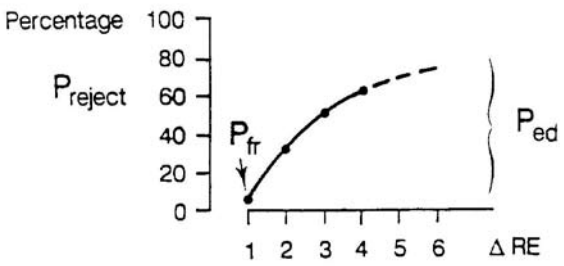


**Fig. 1.**

### Power function graph

Fig. 2 shows the relationship between the systematic error (SE) and the power function of the $1_{3s}$-rule [2]. The shadowed areas show the increase of the probability of rejection when changing the systematic error. This probability is then projected to the plot below, the power function graph. $P_{fr}$ is the point where no error (ΔSE=0) is present.

*Note: A power function of an IQC rule is characterized by 2 important points: Ped AND Pfr. Choose the IQC-rule with LOWER Pfr when 2 IQC rules have the same power. Typically, the rule selection possibilities are limited by your software. Often used rules are the 1-3s rule, the 1-3s/2-2s rule and exponentially weighted moving average rules. The reader is referred to Westgard software (for example, EZ-Rules) in case he/she is responsible for setting up a laboratory IQC system.*

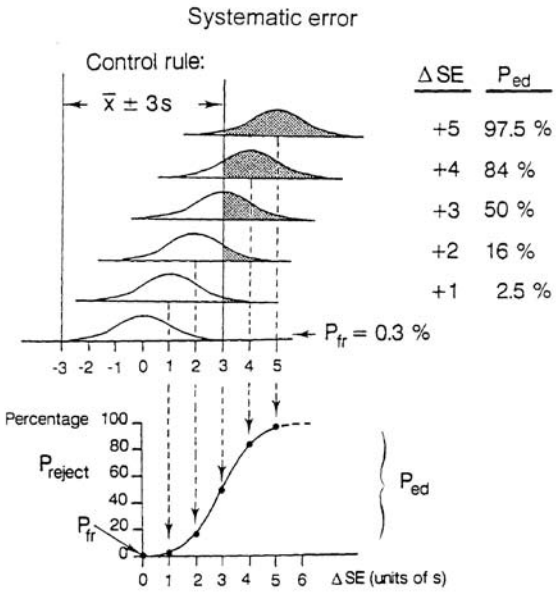


**Fig. 2.**

## Basic medical aspects of IQC – IQC and allowable total error (TEa)

**Observation:** The statistically defined „stop-limit“ of IQC ($TE_{IQC}$; e.g., 3s) may be much lower than medically relevant (e.g., triglycerides).

**The idea:** Let‘s stop the process at a medically relevant allowable total error: TEa.

**Advantages:** If TEa >> $TE_{Stable}$, „very loose“ IQC-rules can be selected.

**CAVE:** There is little consensus in laboratory medicine about what is a medical allowable total error. Therefore, CLIA limits are often used; those, however, are typically large. On the other hand, some use TEa values established as GOALS from biological variation. Those are too small for analytes such as sodium, calcium, or chloride. A 1-3.5s rule does a good job for analytes which are controlled easily (such as triglycerides); a 1-3s/2-2s combirule does a good job for more difficult analytes (such as calcium). Moving average rules are recommended when your software offers them.

## Modern IQC – A reality check

(see also www.westgard.com/dietmar-qc-1.htm)

### Purposely working with the „wrong target“

*QC practice 1*

We are an organization with several laboratories. We use the same assays (instruments, reagents and calibrator lots) and the same IQC materials. Therefore, we use the same target value for the IQC material.

*QC practice 2*

We have a high volume analyzer with 3 different modules (channels). We use the same IQC material for all modules and we apply the same target value.

*Reasoning*
Convenience, for both.
*What are the challenges?*
Laboratories which use the same controls, calibrator lots and analyzers will NOT produce the same results. 3 different channels (or modules) on 1 instrument, so within 1 laboratory, will also NOT produce the same results. Hereby comes that instabilities will turn up at different points in time on different channels.
*„Message"*

- If one uses the same target for different laboratories (modules, channels) one has to expand the range (= changing the „stable SD") if one does not want to increase the false positives. Also, one has to be careful with Xbar and moving average rules.
- Expansion of ranges, however, should be very carefully thought about (see purposely working with the „wrong standard deviation").

**Purposely working with the „wrong standard deviation"**
*QC practice 1*
We have several immunoassays that regularly have instabilities that have no clinical consequences. Therefore, we use the mid-term standard deviation (= SD over different lots) for calculating control limits.
*QC practice 2*
We have significant lot-to-lot variation of several immunoassays: however, we do not consider them clinically relevant. Lot durations are relatively short (1 to 3 months), therefore, we consider the establishment of lot-specific SDs and target values not as cost-effective. We calculate control limits with standard deviations that account for lot variations.
*Problem*
„We are violating the 10Xbar rule - which CLIA is concerned about".
*Reason for the violation*
A stable SD (SDstable) can be smaller than the SD used for the definition of the control limits (SDrule). As a result, even medium-sized shifts/drifts will lead to violations of all rules that work with a mean (average rules) or with a location relative to the target (e.g., the 10Xbar-rule).
*Solution*
If SDstable << SDrule, average rules and X-bar rules are not a good choice for controlling the process.

## Take-home messages

Understand the basic statistics related to IQC (mean, SD, power). IQC rules have different power for error detection and different percentages of false rejections! When two IQC rules have the same power, choose the rule with the lower percentage of false rejections.

The medically allowable total error has to be defined CAREFULLY. Do not pressurize your assay (and your personnel) by IQC when the actual quality of your assay does not satisfy quality GOALS derived, for example, from the biological variation of the analyte. The stable quality of your assay is „what it is". Do not „fool yourself" by taking very generous TEa values.

The IQC reality may tempt you to deviate from the „ideal" IQC scenario (for example, deliberately working with a wrong target); if you do so, please be aware of the consequences (for example, do NOT use Xbar rules).

**CAVE:** Do not forget: what you see in your IQC, typically, is reflected in your patient data. If IQC differs, your patients differ!

Setting laboratory-specific targets will **NOT** help for patient data! Shifts/drifts on the IQC, will still been reflected into the patient data. However, laboratory-specific targets allow a better process control by minimizing the amount of false rejections!

## References


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