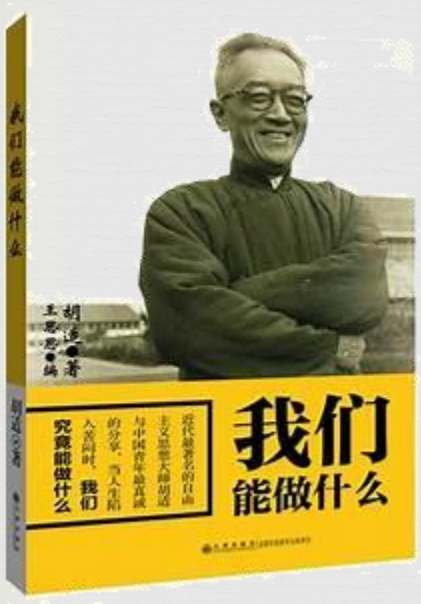
How often is “right” for QC frequency?

Richard Pang
PhD, FAACC

大胆假设、小心求证

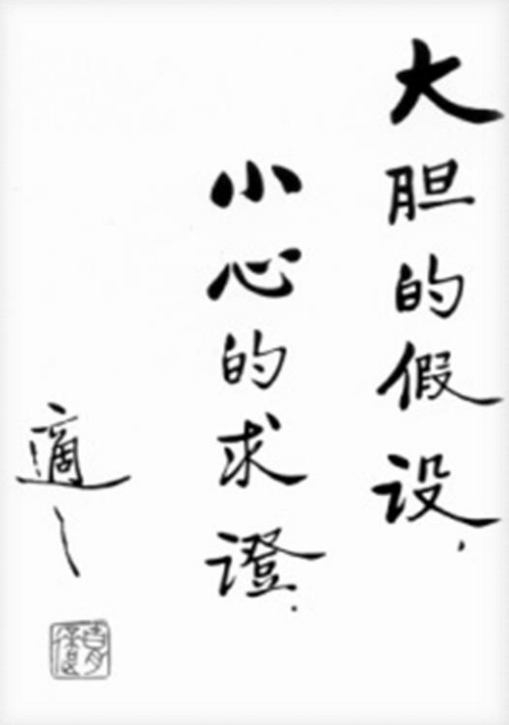
如何在生活中不因循旧规



- 胡适先生在1919年提出「大胆假设，小心求证」的治学方法。几乎每个人都知道小心求证的重要，但往往忽略了小心求证前的大胆假设。……若我们只走别人走过的路，那社会将失去活力而停滞不前，如何在生活中不因循旧规，是每个人都该学习的功课……

http://phtv.ifeng.com/program/kjbfz/detail_2012_04/20/14036880_0.shtml

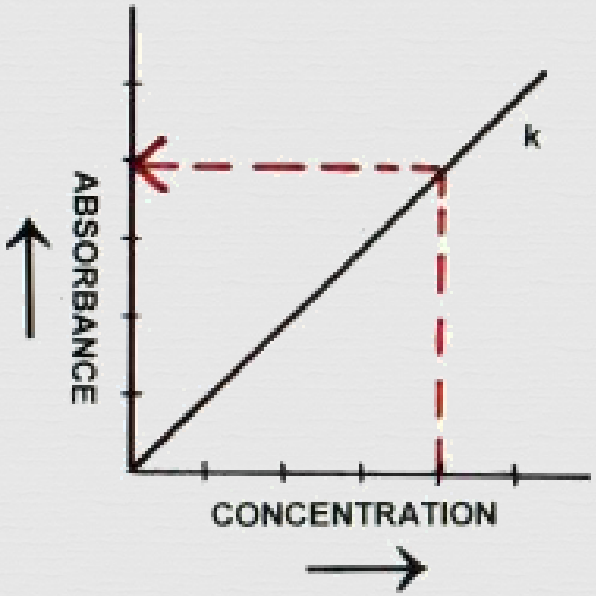
What is the purpose(s) of Quality Control?



Calibration vs Quality Control

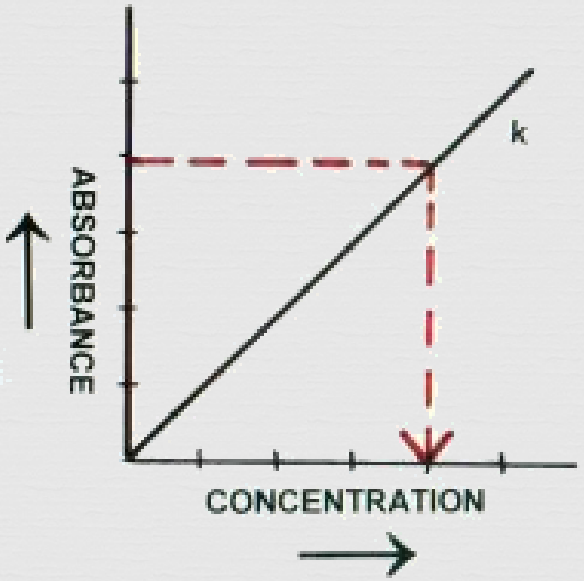
- There is confusion in regarding the terms "calibration" and "quality control", or QC.
- The processes of calibration and QC are two sides of the same coin: they complement each other.
- The calibration establishes an initial point of measurement or data point in a reaction; the QC **checks that the calibration is correct**. Together, they determine the reliability of the method, i.e., the accuracy and precision of the method.

Calibration vs Quality Control



Calibrators

校准品



QCs/Patient samples

质控品/病人样本

What's the meaning of Calibration?

- Standard curve of the measurement system
  - linearity
  - curve fitting
- (re)Adjustment of variations in e.g.
  - energy of the source lamp
  - probe position
  - sampling volume
  - reagent volume
  - incubation temperature
- Deterioration of the reagent (ingredients)

Problem: Calibration frequency

- **Question:**
  - Can the lab decide on their own the calibration frequency on different assay?
  - In the eyes of ISO 15189 assessor, is it OK if customer change/ modify the vendor suggested procedure (in this case, the calibration frequency). If yes, how it should be probably done?

What is the "right" frequency for running QC samples in your laboratory?

- It is widely accepted that laboratories should perform QC at least every day of patient testing.
- However, is this the right QC frequency for every assay and for every laboratory? Is running QC once per day really sufficient?
- What is the "right" frequency for running QC samples in your laboratory?

ISO 15189 regulations don't state a recommended QC frequency but they do recommend that:

- **5.6.2.2 Quality control materials** *"Quality Control materials shall be periodically examined with a frequency that is based on the stability of the procedure and the risk of harm to the patient from an erroneous result."*

- ISO 15189 understands that differing tests and situations will require differing QC frequencies. So how do you use this advice to work out the correct QC frequency for the assays in your lab?

Manufacturer's Recommendations

- The minimum frequency for QC testing is the frequency defined by the manufacturer or the frequency defined by the regulatory agency that inspects or assesses your laboratory, whichever is more stringent.
- Other factors may cause the laboratory to decide to test controls more frequently. These factors include:

Other Factors

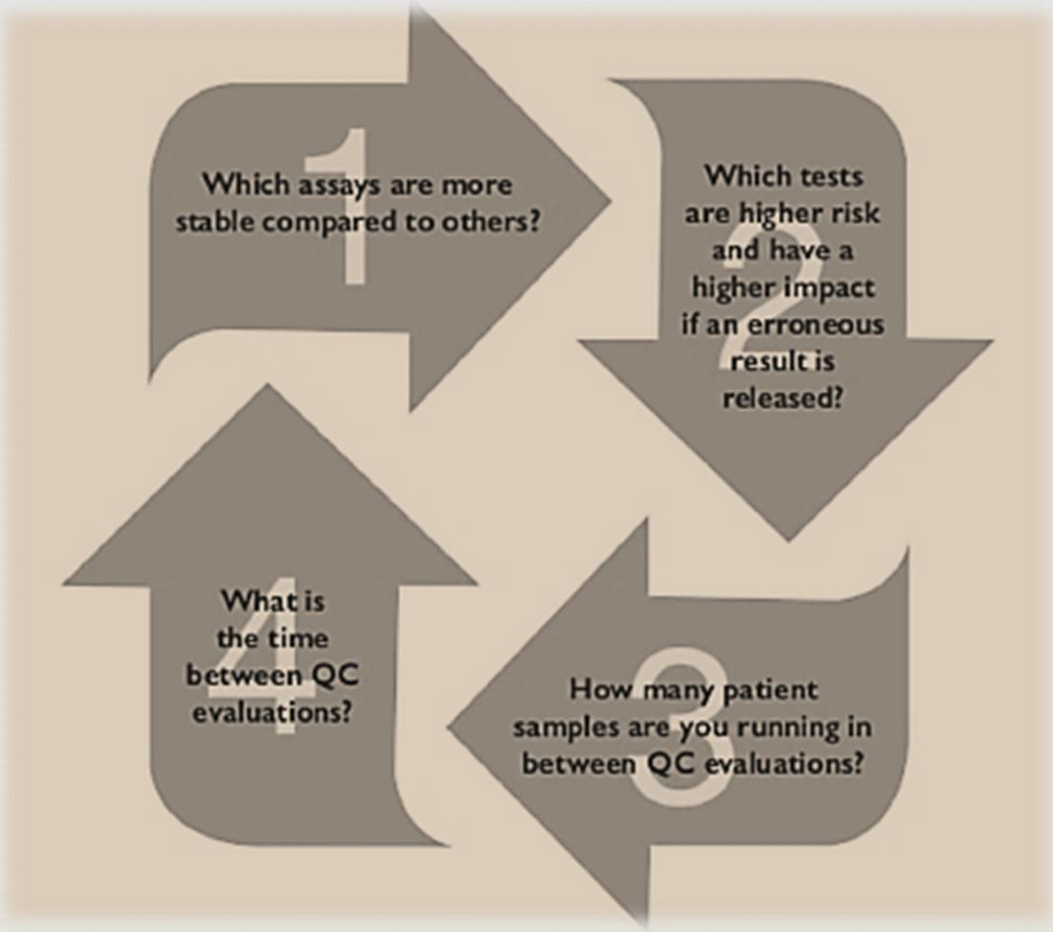
- Stability of the analyte and the method system
- Number of patient tests that are routinely performed
- Change of instrument operators at change of work shift
- Change of reagent Lots
- Recalibration

How often is “right” for Quality Control?

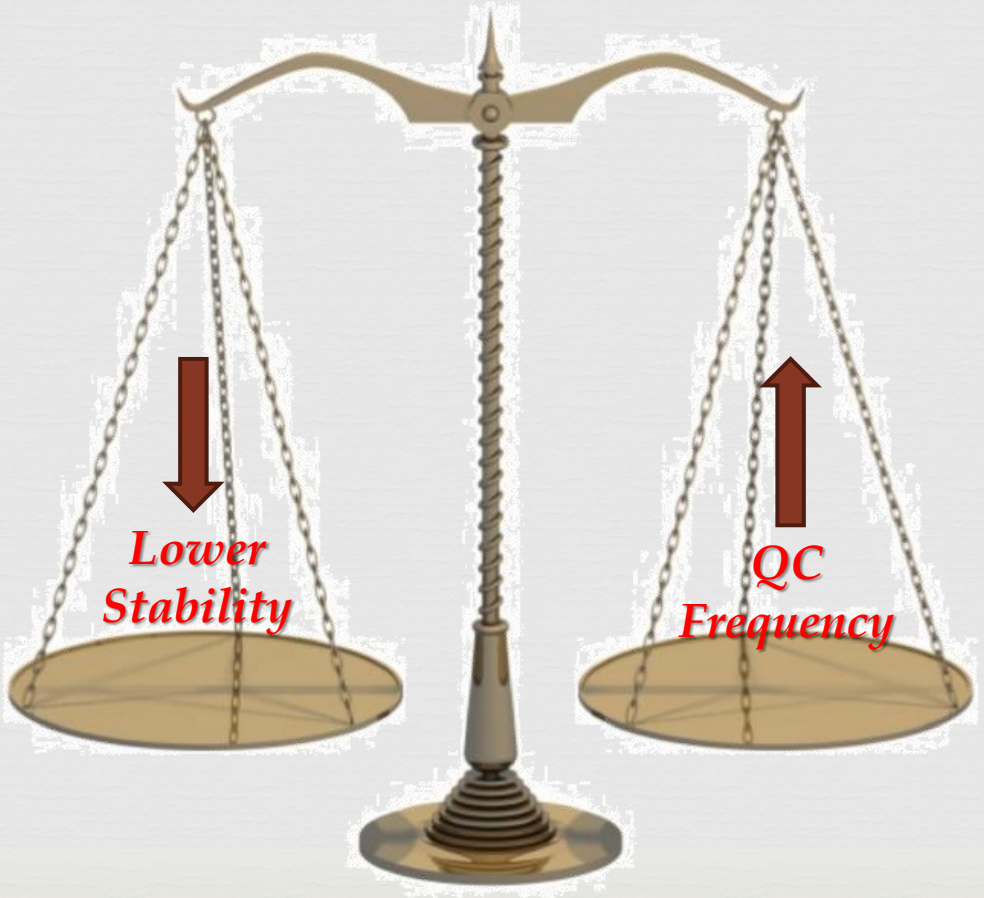
There are various factors that you need to consider when deciding an appropriate QC frequency. A good place to start is by asking the following questions:

- Which assays are more stable compared to others?
- Which tests are higher risk and have a higher impact if results are erroneous?
- How many patient samples are you running in between QC evaluations?
- What is the time between QC evaluations?

A good place to start is by asking the following questions:



Which assays are more stable compared to others?



Which assays are more stable compared to others?

- Some assays naturally perform better than others, giving consistently better results. On the other hand, some assays perform inconsistently, having a higher rate of error and much lower stability.
- It's important that laboratories can recognize which assays are more stable and consistent in comparison to others and ensure that they are running QC at an appropriate frequency.

Higher rate of error and much Lower stability

PT/EQAS

- By utilizing a PT scheme and/or peer group reporting programme, method validation and peer performance comparison can be monitored, helping laboratories to assess their performance over time and easily identify which tests generally perform better or worse.
- Do this to determine which assays are more unstable and run QC more frequently for those assays.

Which tests are higher risk and have a higher impact for an erroneous result?

Patient Safety

- A different approach would seem appropriate to establish guidelines for QC frequency in the context of patient safety.
- In this case we need to look at the whole process wherein an erroneous lab test result may occur and can compromise patient safety.

Patient Safety

- It's important that you run QC more frequently for higher risk tests.
- With higher risk tests there is a greater risk of harm to the patient, therefore it's of utmost importance that the results released are both accurate and reliable.

Faster is NOT necessarily Better

Any tests that have the following characteristics should be considered high risk and QC should be run more frequently in these instances.

- A test where there could be a detrimental consequence, should the wrong test results be released
- A test that supports the clinician's decision in isolation
- A test that is acted upon immediately
- A test that is performed on a specimen that is difficult/painful to collect

How many patient samples are you running in between QC evaluations?

- Lab A tests 10 patient samples a day, whereas Lab B tests 1000 patient samples a day.
- Is performing QC once per day still sufficient for each lab? Say an error occurred in the test system after 50% of the samples had been tested.
- Neither labs would recognize any QC failure until the next day, meaning erroneous patient results may have been released.
- In both cases, they will have to re-evaluate the patient samples from the last successful quality control event as recommended by ISO 15189.
- Potentially Lab B will have to repeat 1000 patient samples, meaning a significant wastage of both time and resources.

How many patient samples are you running in between QC evaluations?

- Ideally patient samples should be run in batches, perhaps every 50 or 100 patient samples, starting and ending with a QC evaluation.
- This will ultimately save time and money, and most importantly will reduce the risk of harm to the patient.

Question: Why 50-100?

What is the time between QC evaluations?

- Let's consider another scenario.
- Both Lab A and Lab B now decide to change their QC strategy to run QC every 100 patient samples.
- Great news, right? This perhaps is a good move for Lab B as QC will be run more frequently, reducing risk for their patients. However, it's not good for Lab A.

Let's consider another scenario

- Let's say that an error occurs after 50 patient samples have been run.
- For Lab B, they will detect the problem straight away on day 1 and will be able to investigate the problem preventing the release of erroneous patient results.
- For Lab A, the error will have occurred on day 5 of their patient testing, but the problem won't be recognized until day 10!
- This could spell disaster for any laboratory, with the release of potentially erroneous results causing misdiagnosis, incurring cost and resulting in a negative impact on patient care.

A good rule of thumb

- Therefore, it's vital to consider the time between QC evaluations in correlation to the number of patient samples being tested.
- Keep the time between QC evaluations shorter than the time needed to undertake any corrective action in the case of an erroneous result.
- This is a good rule of thumb to ensure you select an appropriate QC frequency.

No straightforward answer to how frequently you should run QC

1. Make sure you are running QC more frequently for high risk and unstable tests;
2. Ensure you start and end patient testing with a QC evaluation; and
3. Make the time between QC evaluations shorter than the time needed to take corrective action in the case of an erroneous result.

Additional QC Requirements

- Finally QC samples should also be tested before and after any event that has the potential to adversely affect the testing process e.g.
  - change of reagent batch,
  - instrument maintenance and calibration.
- Testing prior to the event provides confidence that patient results since the last successful QC check are reliable.
- Testing QC samples immediately after the event ensures the test system is in control prior to running more patient samples.

What is the Solution?
大胆假设，小心求证

Brainstorming

- Strategic Planning vs Strategic Thinking

Practical QC Design Process

1. Define TEa for test of interest
2. Estimate SD or CV from routine QC data
3. Estimate Bias from comparison of methods, PT survey, Peer Comparison
4. Calculate Sigma =(%TEa-%Bias)/%CV
5. Use QC software or paper charts to translate Sigma into Statistical QC (control rules, N)

James Westgard, PhD

Ideas for QC Strategy that Don't Require Math Calculations

1. Always end patient testing with a QC.
2. Make the time between QC's shorter than the time needed to correct results.
3. Compare CV's to your peers, if you're not in the top 20% - get there.
4. Set the QC Target to the group mean for multiple instruments.
5. Know your number of patient tests between QC's.
6. Estimate the magnitude of the Out-of-Control condition before correcting it.
7. Use a realistic TEa: What magnitude will cause patient harm?
8. If running a 1:2s rule, and you have a failure, repeat it. Just ONCE.
9. Divide analytes into High/Low sigma groups
    a. High sigma rules goal: reduce false rejection rate
    b. Low sigma rules goal: increase frequency of QC

Curtis Parvin, PhD

Basic QC Requirements

- Start up QC
- End-of-Run QC
  - end of batch
  - end of shift
  - end of day
- Event (adverse effect) changes
  - change of reagent batch
  - instrument maintenance and calibration

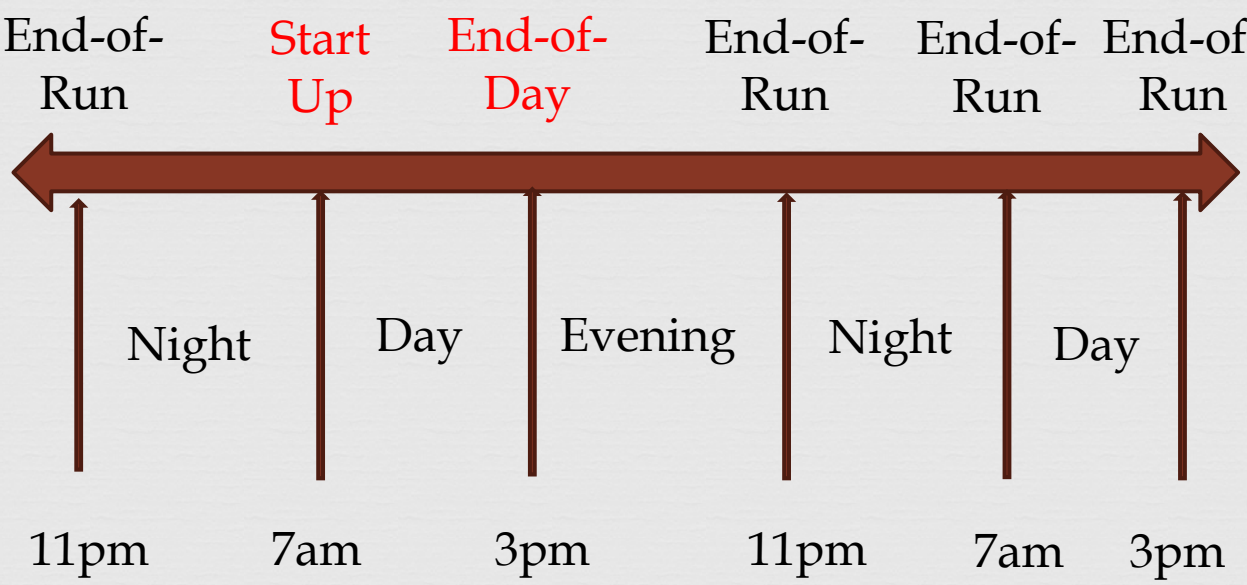
QC Frequency
(Collective Opinion Paper)

- >6σ (excellent performance) – evaluate with one QC per day (alternating levels between days) and a 1-3.5s rule.
- 4σ–6σ (suited for purpose) – evaluate with two levels of QC per day and the 1-2.5s rule.
- 3σ–4σ (poor performance) – use a combination of rules with two levels of QC twice per day.
- <3σ (problematic) – maximum QC, three levels, three times a day. Consider testing specimens in duplicate.

Clin Chem Lab Med 2011; 49: 793-802.

QC Frequency

Common Sense Approach



Every *8 hours* of operation

Assumption(s)
大胆假设，小心求证

- Most autoanalyzers presumably, run 60 tests per hour
- If Sigma Value:
  - =6 run 1 additional QC every 60 samples
  - =5 ……..every 50 samples
  - =4 ……..every 40 samples
  - =3 ……..every 30 samples
  - =2 ……..every 20 samples

Adverse Factors that would affect QC frequency

- Sigma Value (actual number)
- Clinical Alert (0.1, 0.2, 0.3 ; low, moderate, high)
- Calibration Stability (0.3, 0.2, 0.1 ; low, moderate, high)
- Reagent Stability (0.3, 0.2, 0.1 ; low, moderate, high)
- Error Rates (0.1, 0.2, 0.3; low, moderate, high)
- Risk Scores

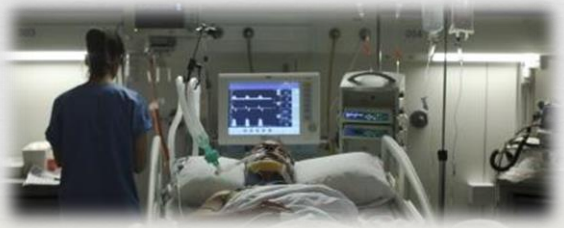
Clinical Alert Level

- For an outpatient service, one can estimate this cycle time to be as long as 2-3 days or even one month.
- For a non-acute hospital setting, the test repeat cycle may be perhaps 4 hours.
- For an intensive care setting, the cycle time may be as short as 1 hour for chemistry tests and 30 minutes for blood gases.

0.1

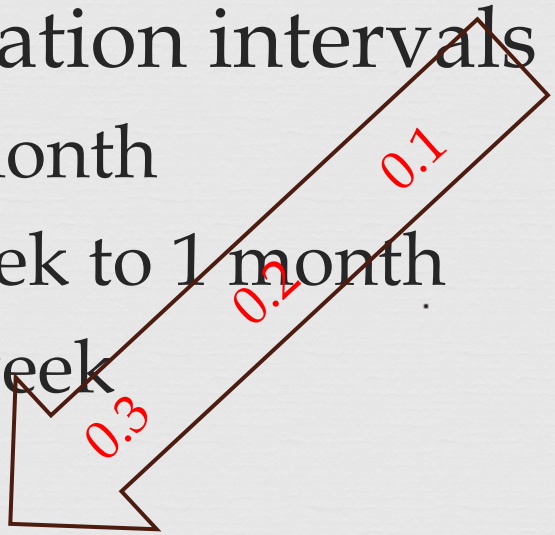
0.2

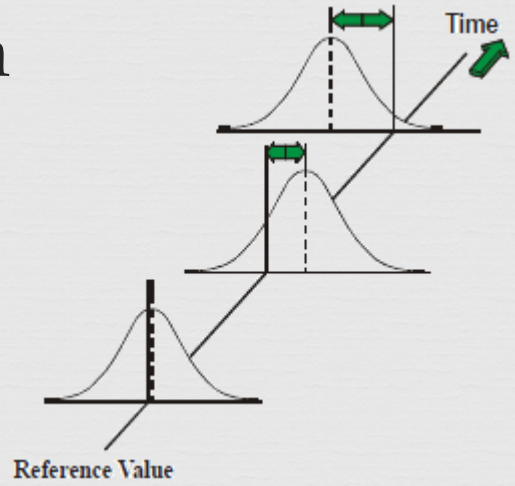
0.3



Calibration Stability

- Manufacturer's recommendations
- Calibration intervals
  - >1 month
  - 1 week to 1 month
  - <1 week





Reagent Stability

- Manufacturer's recommendations
- Once opened
  - >1 month
  - 1 week to 1 month
  - <1 week

Choosing OWN (Individualized) QC Rules Based on Error Rates

$SE_c = [(TEa\text{-}bias)/s] - z$

ΔSE_c	QC Rule		
	Low	Moderate	High
> 3	1-3.5s	1-3s	1-2.5s (D, I)
2-3	1-3s	1-2.5s	1-2s (D, I)
1-2	1-2.5s (D)	1-2s (D, +)	1-2s (D, +, I)
<1	1-2s (D, I)	1-2s (D, +, I)	1-2s (D, +, I)

D: examine QC chart Daily, **+**: Increase control frequency;
I: Initiate corrective action

Error Rate Categories

Low = method that experiences <3% QC flags/year

Moderate = method that experiences 3-10% QC flags/year

High = method that experiences >10% QC flags/year

By courtesy of
Alan Wu, PhD, FACB

Error Rates

- Error Rate Categories
  - Low = method that experiences <3% QC flags/year
  - Moderate = method that experiences 3-10% QC flags/year
  - High = method that experiences >10% QC flags/year

Per year or Per month

Risk Assessment Metrics

Adverse effects to Sigma Metric

Test	QC Level	Sigma Value	Clinical Alert Level	Calibration Stability	Reagent Stability	Error Rates	Risk Score	QC Frequency No. of Patient Samples per QC	Samples per Day	QC per Day
Serum K	1	5	0.3	0.1	0.1	0.1	4.4	44	500	11
ALT	2	6	0.2	0.1	0.1	0.1	5.5	55	500	9
Ca	1	4	0.3	0.3	0.3	0.3	2.8	28	300	11
Glu	3	6	0.3	0.1	0.1	0.1	5.4	51	200	4
FT4	2	3	0.2	0.3	0.2	0.2	2.2	21	100	5
AFP	3	3	0.1	0.1	0.2	0.2	2.4	24	50	2
TnI	1	4	0.3	0.2	0.2	0.1	3.2	32	20	-

大胆假设、小心求证

大胆假设、小心求证

- 科学精神在于寻求事实，寻求真理
- 科学态度在于撇开成见，搁起感情，只认得事实，只跟着证据走
- 科学方法只是「大胆的假设，小心的求证」十个字。没有证据，只可悬而不断；证据不够只可假设，不可武断；必须等到证实之后，方才奉为定论

大胆假设、小心求证