A Self-instructional Course for
Laboratory Professionals.

P.A.C.E. Approved
Contact Hours: **3**

Basic Applications in Clinical Laboratory Quality Control

P.A.C.E. Approved Workbook

Skill Level: **Basic**

Challenge or refresh knowledge and understanding of quality control practices.

Written by Sten Westgard MS

TECHNOPATH
CLINICAL DIAGNOSTICS

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Introduction

Congratulations! You've been selected, or volunteered, or been volunteered, or been ordered to learn about Quality Control (QC). Maybe you're having problems sleeping at night and think this will cure your insomnia. Maybe you've lost a bet on how much time you can spend reading about statistical quality control.

Regardless, you're here now. And we're happy to have you.

The good news is that we don't intend to be boring. And we don't intend to teach you the same old lessons you learned about Quality Control in the past.

Quality Control is the very lifeblood of the laboratory – the daily signs that tell us our results are safe. Perhaps you haven't felt this way about Quality Control in the past. It's often viewed as a drudgery, a hassle, and, at worst, a frustration.

For many medical technologists, QC is a daily struggle – they know they have to do QC, but they don't know why, or the reasons behind the practices that are in place. QC is often done by rote, by tradition, by a set series of habits that have been in place for decades.

The purpose of this book is to CHANGE how you do QC so you can do it more efficiently in your laboratory, do it more easily for your staff and colleagues, and do it more effectively to ensure patients are safer from the possibility of erroneous results.

So, let's begin, shall we?

Goals for this workbook

- Illustrate the purpose and practice of statistical QC
- Outline the setup, implementation and interpretation of single statistical rules as well as "Westgard Rules"
- List useful troubleshooting techniques

Explain the fundamental aspects of control materials that are critical to the success of quality control

Throughout the book, we will provide you with self-assessment quizzes along with the answers to verify your understanding. At the end of this process, you can take a final exam to get continuing education / contact hours.

Also, throughout this book we will be quoting from various references, standards, and regulations. These may be the hardest to read; seemingly the aim of such documents is to be as scientific, precise, and boring as possible. We will provide a "real world" definition along with an official definition to help you keep your sanity.

For example, here's the official definition of Quality, according to ISO 9000:

> *"Quality is the degree to which a set of inherent characteristics fulfills requirements"*

That's exactly what you were thinking, right? It's safe to say, the official definitions of these concepts are not how the average laboratorian will describe these terms if you walk up to them and ask.

The Regulations and Requirements:

CLIA (Clinical Laboratory Improvement Amendments), passed in 1988, provides the US regulatory framework. Updates are added to the Federal Register regularly. Washington, DC.

CLSI (Clinical Laboratory Standards Institute) These guidelines provide recommendations on best practices and detailed protocols for processes that aren't explicitly defined in the CLIA regulations.

ISO: International Standards Organization, Geneva Switzerland. These are international guidelines for quality, basically the global standard for quality. Each standard has a different number. ISO 9000 is the general quality standard. ISO 15189 is the specific quality guideline for the laboratory. Other important guidelines include ISO 17593 and ISO 22869.

At the end of this document you can find more specific references.

ISO/TR 22869 has a more detailed definition of Quality:

> *"A set of well-defined and well-executed processes that create a system for the collection, examination, and reporting of human samples that supports diagnosis, preventions, and management of disease states, generates information having clinical utility and optimal impact on health outcomes, meets predetermined targets for accuracy, reproducibility, and traceability; strives to minimize error, is timely, safe efficient, cost effective, and focuses on client satisfaction and continual improvement."*

This definition has the virtue of being far less abstract than the first definition, but the weakness of being so multi-faceted as to remain completely amorphous.

This is why labs frequently hire consultants to help them comply with regulations – the consultant explains in normal language how to meet these arcanely-written goals and requirements.

If you can't afford a consultant, you may end up reading a workbook instead.

Quality Control

Definitions

Let's start with what Quality Control is and what it means for the clinical laboratory.

"Quality Control" often refers to many activities in the normal world.

From ISO we can get a general definition:

> *"operational techniques and activities that are used to fulfill requirements for quality."*

Again, so high level as to cause altitude sickness.

But in the lab, "QC" often means something much more specific – it means running controls, examining data plotted on Levey-Jennings charts, and interpreting control rules to decide whether a run is "in" or "out", troubleshooting, cursing, etc. A more specific term is frequently invoked: "Internal Quality Control" or IQC, referring to an activity that a laboratory performs by itself, looking at their own tests' performance.

Here's the comprehensive definition of quality control according to CLSI:

> *"Quality Control: (internal) the set of procedures undertaken in a laboratory for the continual assessment of work carried out within the laboratory and evaluation of the results of tests to decide whether the latter are reliable enough for release to the requesting clinician.*
>
> *NOTE: The procedures should include tests on procedural control material and statistical analysis of patient data. The main object is to ensure day-to-day consistency of measurement or observation that is, if possible, in agreement with an agreed reference, such as control material with assigned values."*

Quality Control Notes

NOTE 1: This includes the operational techniques and activities used to fulfill requirements for quality;

NOTE 2: In health care testing, the set of procedures designed to monitor the test method

and the results to ensure appropriate test system performance;

NOTE 3: Quality control includes testing quality control materials, charting the results and analyzing them to identify sources of error, and evaluating and documenting any action taken as a result of this analysis;

NOTE 4: Quality control includes testing of normal and abnormal control materials, recording the results, identifying sources of error, and evaluating and documenting any corrective action taken;

NOTE 5: In clinical laboratory testing, quality control includes the procedures intended to monitor the performance of a test procedure to ensure reliable results;

NOTE 6: The set of procedures undertaken in a laboratory for the continuous assessment of work carried out in the laboratory and evaluation of tests to decide whether these are reliable enough for release of results to the requesting health care provider. The procedures should include tests on control material, results of which may be plotted on a quantitative control chart showing upper and lower standard deviation-based ranges, and may also include statistical analysis of patient data (e.g., moving averages). The main objective is to ensure day-to-day consistency of measurements or observations, if possible, in agreement with an indicator of truth, such as a control material with end-user assigned values;

NOTE 7: Quality control is also described as operational techniques and activities that are used to fulfill requirements for quality;

NOTE 8: The purpose of quality control is to ensure that all quality requirements are being met;

NOTE 9: The set of mechanisms, processes, and procedures designed to monitor the measuring system to ensure the results are reliable for the intended clinical use;

NOTE 10: More specifically, it is the set of procedures undertaken in a laboratory for the continuous assessment of work carried out in the laboratory and evaluation of tests to decide whether these are reliable enough for release of results to the requesting health care provider;

NOTE 11: In health care testing, the set of procedures based on measurement of a stable material that is similar to the intended patient specimen, to monitor the ongoing performance of a measurement procedure and detect change in that performance relative to stable baseline analytical performance;

NOTE 12: A system for ensuring maintenance of proper standards by periodic inspection of the results and the operational techniques that are used to ensure accuracy and reproducibility;

NOTE 13: In medical laboratory testing, quality control includes the procedures intended to monitor the performance of a test system to ensure reliable results."

That's a symphony of Notes! They've taken a very simple definition and added quite the chorus. We'll address all these notes in turn, in a more gradual approach. So, don't panic that you need to learn all these notes at once.

Let's distill all of those possible differences into a practical definition of QC:

> *"Set of procedures used in a laboratory for continually assessing laboratory work and the patient results achieved. This includes*

day-to-day monitoring of assay, operator and equipment performance."

Typically, every test in the laboratory requires some form of quality control. It's best practice to have QC on every test in your lab, even the ones where "traditional quality control" is not an easy fit.

In summary, quality control should include a set of procedures utilized in your laboratory that are suited to continually assess each test system's performance as well as the staff's processing, as it could impact the patient results. It is critical that the quality control processes used in the laboratory monitor any pre-analytical, analytical and post-analytical effects to the laboratory outcomes. However, the laboratory should also rely on feedback not only from their QC data management program but also their patient results and any communication from the clinicians on results.

In this workbook, we will use the terms analyte, assay, method, and test. They will be used interchangeably.

Sources of feedback on test system performance	Purposes
QC Data Management Program	Monitors test system bias and imprecision on a run-to-run basis via the use of quality control products and possibly quality assurance processes. Allows raw data analysis and/or charts
Patient samples	By tracking patient averages over time, the lab can use this as an internal check between QC sample events for test system performance
Clinician Feedback	How many times do you get calls from your doctors questioning why all their patient results are recovering in the abnormal range? While no one likes to get these types of calls; these are good checks on your test system.

Self-assessment Quiz

Question 1

1. What is Quality Control?

   a. Testing control materials

   b. Using control charts

   c. Ensuring that all quality requirements are met

   d. All of the above

Answer Key: page 42

Notes

What kinds of lab testing are there?

Before we even start talking about Quality Control, we need to talk about the type of tests we run in the laboratory, because the Quality Control you run will depend on the kind of test.

Quantitative Tests: these are tests that give results expressing a numerical amount or level (concentration) of an analyte in a specimen. In other words, it measures a quantity and reports it as a numerical value. The Quality Control techniques described in this workbook will most directly apply to this type of testing.

Qualitative Tests: these are tests that give results that are descriptive, not numerical. For example, "positive" or "negative", "present" or "absent", etc. The quality control requirements for qualitative testing are minimal because it's not possible to calculate things like mean, standard deviation (SD), coefficient of variation (CV), bias, etc. In qualitative testing, QC is usually reduced to truth tables.

Semi-Quantitative Tests: (wait, there's another kind of testing?) These are tests that have

> *"a dose-response gradient that may be included in the reported result, but for which no authoritative calibration scale exists to determine inaccuracy and imprecision; tests that yield results in an approximate range of values (e.g., trace, moderate)."*
> [ISO and CLSI].

Many serology, infectious disease tests are of this type, having signal-to-cutoff ratios (S/CO) that then are used to determine qualifications of "positive", "negative" and even "low positive" and "indeterminate" categorizations.

If you simply run qualitative tests, you can skip all the sections that involve math in this workbook. Congratulations!

If you run tests that are semi-quantitative or quantitative, sorry, there are no shortcuts. You must do QC including the math, the charting, the rules, the interpretation, and the troubleshooting. But we'll try to eliminate the frustration, the heightened blood pressure, and the temptation to retire early. But before we can get to the "EXCITING" part of Quality Control, we need to build up the foundation of testing, that involves things like calibrators, standards, linearity kits, etc. These are things that we need to have in place, processes we must run, BEFORE we can even contemplate running QC. In other words, before we try to drive and keep our car within the correct lane, we need to make sure the engine is on and the tires are full of air.

Preparing your method for routine testing: Calibration and Linearity / Reportable Range.

Calibration and Calibrators

Have you ever looked at your watch, or even scarier, your scale? You know they measure quantities, but sometimes they're wrong – very, very wrong. A watch that runs late, a scale that reads too heavy, can ruin your day. So, before you use these items, you'd like them to be set correctly.

The same is true with laboratory instruments. Before we use them, we need to set them up correctly, so they read the "right" numbers. This process of adjusting the set-up of the test is called Calibration.

Here's a more formal definition of Calibration from CLSI and ISO:

> *"operation that, under specified conditions, in a first step, establishes a relation between the quantity values with measurement uncertainties provided by measurement standards and corresponding indications with associated measurement uncertainties and, in a second step, uses this information to establish a relation for obtaining a measurement result from an indication"*

If you find that confusing, congratulations, you're not alone. We'll leave the "measurement uncertainty" to a later portion of this workbook.

Here's a better definition from the US Federal Register (the US regulations that govern medical laboratories):

> *"a process of testing and adjusting an instrument or test system to establish a correlation between the measurement response and the concentration or amount of the substance that is being measured by the test procedure."*

Calibration is the process to provide the best measurement possible for the test, trying to get you as close to the "true answer" as possible.

Calibrators or calibration materials are solutions or devices

> *"of known quantitative/qualitative characteristics (e.g. concentration, activity, intensity, reactivity) used to calibrate, graduate, or adjust a measurement procedure or to compare the response obtained with the response of a test specimen/sample."*
> [ISO definition]

Here's a more down to earth explanation of Calibration: Calibration is the procedure that determines the relationship between the signal generated by an analytical methodology and the test results that are reported. "Multi-point calibration" is used for methods that do not generate a linear response (e.g. immunoassay methods) and usually involves analyzing three to five (or even more) calibrator solutions and utilizing a curve-fitting routine to establish the calibration function. In many commercial automated systems that use multi-point calibration, the "master" calibration of each reagent lot may be performed by the manufacturer using as many as 11 calibrators to establish the curve. This "master" calibration is transferred to the laboratory instrument using a two-point local calibration that adapts the "master" curve to the local instrument.

Linearity

For methods that do have a linear relationship between signal and concentration, "two-point calibration" is commonly used. Typically, one calibrator provides a "zero-point" and the other a "set-point. The assumption is that a linear calibration function can be drawn between the zero-point and the set-point and that the linear range extends beyond the set-point. The manufacturer's claimed analytical or reportable range indicates the full range of concentration over which the assay performance has been documented. Verifying the reportable range, demonstrates that you can achieve that claimed performance.

In addition to the standard, scheduled calibration that the manufacturer recommends, certain accrediting agencies require labs to perform a reportable range study when the method is first installed in the laboratory, and as well as periodically check, update, and verify that calibration every six months or more. That process is called Calibration Verification.

When labs are not performing those regulatory-mandated checks on calibration, they should follow the manufacturer's schedule since they typically define when to use calibrators and how often to perform calibration. Sometimes calibration is once a day, sometimes it's not for many months. When issues arise with performance, a common trouble-shooting step is to perform a new calibration. Whatever the manufacturer recommends, you must follow that calibration frequency. For example, CLIA and US regulations may require that you verify the calibration of the tests semi-annually, if you don't already perform calibration more frequently than that. Each laboratory must review their accreditation organization's unique requirements on this point.

Notice that calibrators are supposed to bring the test close to the truth but not necessarily reach the absolute truth. It's particularly challenging to move a test to the absolute truth.

For some tests where a truth is knowable, the test

gets adjusted to meet a standard or what is often referred to as a reference material.

Here's the official ISO definition of standard:

> *"(measurement) realization of the definition of a given quantity, with stated quantity value and associated measurement uncertainty, used as a reference"*
> [JCGM 200:2012]

Again, measurement uncertainty is rearing its ugly head – ignore it for now. An easier definition of standard can be found here:

> *"(measurement) material measure, measuring instrument, reference material or measuring system intended to define, realize, conserve or reproduce a unit or one or more values of a quantity to serve as a reference"*
> [from CLSI]

The gist here is that if you calibrate your method using standards, you are synchronizing your assay very closely to the truth. If your calibrators are not standards, but just calibrators, you're trying to adjust closely to a truth, but not as close as the scenario in which the standards and calibrators are the same material.

Once we have made that synchronization, we're still not quite ready to run tests yet. We need to make sure the test is linear, that we've established the working range over which the test results are valid. We will discuss linearity a bit later in this workbook

Once calibration is performed, and we've established the appropriate reportable range (or working range, or, in some cases, the linearity), we're one step closer to running QC.

Notes

Self-assessment Quiz

Questions 2-5

2. If your test only produces positive and negative results?
   a. QC is not necessary
   b. Statistical QC is not possible
   c. Testing is not practical

3. When do you NOT use statistical QC?
   a. Quantitative testing.
   b. Semi-quantitative testing
   c. Qualitative testing
   d. Never

4. When should you calibrate your method?
   a. Before you purchase the instrument
   b. Before you turn on the instrument
   c. Before you run controls and patients
   d. Never

5. How often should you calibrate?
   a. As often as your money allows
   b. As often as the manufacturer requires
   c. As often as the manufacturer requires, as often as the regulations require, and whenever an out-of-control situation requires it.

Answer Key: page 42

Control Materials

Finally, now we're ready to discuss controls. So, what's a control? Not to be silly, but do we all agree on what a control is?

Again, the official definition of a control material is rather dry, dull, and overpopulated with commas:

> *"A device, solution, lyophilized preparation, or panel of collected human or animal specimens, or artificially derived materials, intended for use in the quality control process"*
> [CLSI]

Here's a different definition from a different ISO standard:

> *"Substance, material, or article intended by the manufacturer to be used to verify the performance characteristics of an in vitro diagnostic medical device"*
> [ISO 17593]

The key here is that the control material is something we use to verify that the medical device (test) is working correctly. Both definitions note that there are many forms that a control can take.

Types of Control Material

There are some controls that are internal to the workings of the instrument, particularly highlighted at the point of care. If it's a control that essentially doesn't test anything like a patient sample or even a surrogate patient sample, but instead uses some electronic check, this is called **Electronic QC**. These are useful internal checks, much like your "check engine" light on your car. It's important to make sure all these checks are working, but they don't tell you anything about the operator (driver), so they aren't sufficient to provide a full check of the testing process. You can't just rely on Electronic QC to ensure your testing quality.

In just the last few years, some devices have received CMS approval to use what is being called **Embedded QC**. If the control materials

are contained in on-board ampules or cartridges, provided they have similar matrices to patient specimens and follow all steps of the analytical process, those control materials may be used as a substitute for traditional quality control materials (each individual laboratory must develop an **Individualized Quality Control Plan (IQCP)** in order to document this step).

Despite these alternative approaches to Quality Control, the gold standard, "best practice for quality controls", is to use a third party, independent quality control that involves the operator using the control material like a patient sample. This tests the instrument and the operator, covering most of the steps of the total testing process. Even with devices that have Electronic QC or Embedded QC, the traditional steps of running QC should be performed at least periodically.

Formats of Quality Control Material

You can get control materials in a variety of formats:

Lyophilized: this is freeze-dried, perhaps more convenient for transport as it doesn't have to maintain a cold chain (continuous logistical chain of refrigeration), particularly attractive to laboratories operating in remote areas, desert or hot climates, and/or areas where logistics of delivery are not as reliable. In order to use these controls, operators must reconstitute the controls by adding a precise amount of liquid (using a pipette and a well-trained operator).

Liquid: this is easier to understand. These are controls that are ready to go, no reconstitution step required. They must be properly refrigerated during transport and storage. Since a reconstitution step is avoided, this variable in the troubleshooting process is eliminated.

Liquid Frozen: certain controls can be kept frozen for a long period of time. Be aware of the thawing time – you will need to follow those directions carefully to bring these materials to the right temperature before running on your instruments.

It's clear that liquid controls are preferable to lyophilized, but practicalities will dictate what you choose.

Commutability

One last aspect we need to address: commutability, matrix, and matrix effects.

Commutability is when the control material closely mimics a patient sample and is the goal of any type of control. This attribute provides confidence that when the device produces a control value out of range - thus indicating that the test system has a problem, you can be certain that the patient sample results would be incorrect as well.

Commutability also has its own official definition established by the meteorologists of ISO:

> *"ability of a material to yield the same numerical relationships between results of measurements by a given set of measurement procedures, purporting to measure the same quantity, as those between the expectations*

of the relationships obtained when the same procedures are applied to other relevant types of material."

In other words, commutability is good: it's what we want in control materials.

Matrix Effect

The opposite of commutability is often referred to as a **Matrix Effect** (no, this is not the Matrix that Keanu Reeves found himself inside 20 years ago, this is the really uncool Matrix). The matrix of a control is all the extra stabilizers, preservatives, and other ingredients that are present that are wholly unrelated to a patient sample. These additives may help keep the control material stable, or have a longer shelf life, but they do not make the control behave similarly to a patient sample. In the worst case, the matrix of a control material will make the control behave differently than a real patient sample. This means a control may be "out", but the patients are completely fine and unaffected by whatever is causing the control to be out. This defeats the very purpose of a control – it becomes an unreliable signal of whether patient results are going to be reliable.

As much as possible, labs want to avoid controls with heavily artificial matrices and want to have controls that are as commutable as possible. Inevitably, as labs desire controls with long shelf lives and greater stability, the control materials must be modified with a matrix that will make it less like a real patient sample. Between our financial constraints and our quest for best quality, we must strike a balance.

In summary, commutability is a good thing, matrix effect is a bad thing.

In the Advanced QC workbook, we will discuss even more aspects that are important to selecting control materials.

What are the key attributes to consider with your perfect QC product?

- Stable over a long period: Most labs want a long shelf life to minimize the necessary cost of cross-over testing between lots of QC.
- Appropriate fill size in bottle or box of control: The fill volume (amount of product in the bottle) should be enough that you consume the contents prior to the vial's open-vial stability limit. However, it is also ideal that the volume in each vial is large enough to avoid using a large number of vials. Refrigerator and freezer storage are typically at a premier in any lab. Using more vials will require more boxes of QC material, requiring more storage space or more frequent shipments.
- Matrix of the control must be mimic patient samples.
- Yield results at each test's clinically relevant range.
- The different numerical values of the multi-level QC product should not be too close in range. The lab should monitor the assay's performance along the assay's range.
- Consideration of liquid vs. lyophilized should be assessed. By using a liquid control, it eliminates some troubleshooting steps (water source, proper reconstitution, etc.). However, some labs choose lyophilized due to storage and shipping requirements.
- Try to find a control that is independent from the test system's supplied product, i.e. control material that is different from the calibrators in the test system. By using a control from an independent source, you are truly assessing the test system's performance.
- Verify with the control vendor that they have made great efforts to ensure that their controls are as commutable with the patient samples as possible. This will help your lab minimize the chance of shift in the QC data when new components are implemented into the routine testing process.

Notes

Self-assessment Quiz

Questions 6-8

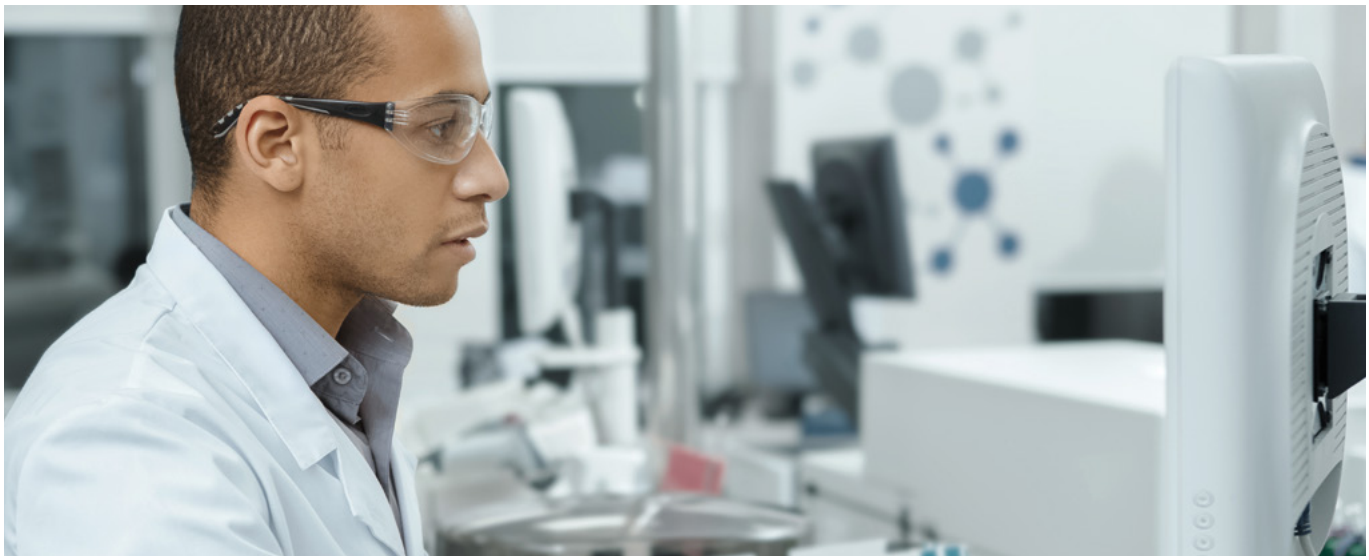
6. Which is better, according to CMS?
   a. Embedded QC
   b. Electronic QC
   c. Simulated QC
   d. Measurement Uncertainty

7. Which type of controls is freeze-dried?
   a. Lyophilized
   b. Liquid
   c. Electronic

8. Which control materials will have results closer to patient values?
   a. Control with high commutability
   b. Control with high matrix effects
   c. Controls placed on high shelves

Answer Key: page 42

Time to do math: The statistics of Quality Control



Do you really have to do math in order to perform QC? Today's laboratorians have it easier than ever: the data is typically handled by the instrument, middleware, Laboratory Information System (LIS) or some other informatics or software, and the math gets done by a computer program with the results displayed on Levey-Jennings charts. So, a lot of the heavy lifting is done for you – what you need to do is understand where the math is coming from and what the results mean when they deviate from expected performance.

Mean

Mean: no, this is not about how your boss treats you, this is the mean that also means Average. This is one of the most fundamental calculations for quality control. It gives you the best estimate of a specific level of the control material.

Simply put, take the sum of all the control values for that level, then divide by the number of measurements.

Calculating the Mean [$\bar{x}$]

$$\sum X_n/n$$

Where:

$\sum$	=	sum
X_n	=	each value in data set
n	=	the number of values in data set

If you have an assayed control, you can compare your calculation to that assayed (the target value or expected value) mean. When you are starting out with a control material, this can be a useful comparison – if your observed mean is wildly

different than the expected mean, that's a sign that something is wrong with the control, your instrument, or your lab.

The good news about the mean is that most software programs will automatically calculate and provide this statistic to you.

Standard Deviation, "the SD", "the s", also known as "imprecision".

Standard deviation is a measurement of how closely the control values cluster around the mean, how tightly packed they are around the mean, or how widely dispersed they are away from the mean. You'd like to see a small standard deviation whenever possible. The smaller the SD, the better the precision. The larger the SD, the worse the imprecision. Simply put, this is the random error of the method.

The implications of random error are clear: it becomes harder to understand the signal of the patient's true health from the noise of the method. Clinicians have reduced confidence in test results where there is more random error present – causing, at worst, misdiagnoses, repeated tests, longer stays, repeated visits, and more expense to the patient, healthcare system and laboratory.

Calculating a Standard Deviation [s] for a set of QC Values

$$s = \sqrt{\frac{\sum(x_n - \bar{x})^2}{n-1}}$$

Where:

s	=	standard deviation
$\bar{x}$	=	mean (average) of QC Values
$\sum(x_n - \bar{x})^2$	=	the sum of the squares of differences between individual QC values and the mean
n	=	the number of values in the data set

The good news about SD is that most software programs will automatically calculate and provide this statistic to you.

Coefficient of Variation, "CV%", "CV"

CV% / CV is simply a percentage perspective on the standard deviation. It simplifies the evaluation of imprecision for you rather than having to look at a blast of raw numbers, all at different levels.

Calculating the Coefficient of Variation [CV]

$$CV = (s \div \bar{x})100$$

Where:

s	=	standard varaiation
$\bar{x}$	=	mean

The CV allows you to look at imprecision across multiple control levels, even compare imprecision between methods and instruments, and compare them against the manufacturer's expectations. Many accrediting organizations have requirements that the CV must be monitored monthly for all quantitative assays. It is imperative that you review and follow your accrediting organizations regulations.

The lower the CV, the lower the test system's imprecision.

The imprecision is also an essential factor in calculating the analytical Sigma-metric and optimizing your QC rules and number of controls. (The analytical Sigma-metric will be discussed much more in the Advanced QC workbook)

Notes

Self-assessment Quiz

Questions 9-11

9. What's the benefit of an assayed control?
   a. Comes with an expected mean
   b. Comes with expected kindness
   c. Comes with an absolute mean and range that you can't deviate from

10. Given a low control with a mean of 105 and an SD of 17, and a high control with a mean of 205 and an SD of 20, which control has the greater CV?
    a. Low control
    b. High control
    c. Both controls have the same CV

11. Given the values in mg/dL 101, 109, 81, 83, 84, 95, 97, 110, 104, 100, 102, 99, 95, 100, what is the mean, SD, and CV?
    a. 97.14 mg/dl mean, 8.93 mg/dl standard deviation, 9.2% CV
    b. 8.93 mg/dl mean, 97.14 mg/dl standard deviation, 9.2% CV
    c. 9.2% mean, 97.14 mg/dl standard deviation, 8.93 mg/dl CV

Answer Key: page 42

Two more common, but not essential, QC statistics

Beyond the internal statistics that a single laboratory can calculate, there are some comparative statistics that can be calculated to give additional perspective and analysis.

Coefficient of Variation Ratio (CVR)

Calculating the Coefficient of Variation Ratio [CVR]

$$CVR = \frac{\text{Within Laboratory CV}}{\text{Peer Group CV}}$$

To understand whether the CV that your laboratory is experiencing is acceptable, you can compare it to the CV that is measure of the entire peer group of laboratories. This is only available if you can access the data of a peer group of similar instruments, similar methods, similar reagent lots, and/or similar control lots [that's a lot of similarities, which is why this is called a peer group – this is a group of laboratories very close in set-up and performance to your lab].

The CVR will tell you whether you are greater than or less than the peer group CV. If you find your CVR is less than 1.0, that means your CV is less than the peer group CV. If your CVR is greater than 1, your individual CV is larger than the CV of the peer group. Given that a large number of labs will have more variation than any single laboratory, it's a bad sign if the CVR is larger than one. That means the laboratory has a higher than expected amount of imprecision.

However, note that having a CVR less than 1.0 is not a guarantee that your imprecision is acceptable.

Most labs will start troubleshooting a CVR result in their monthly peer group program when the result is >1.5. They may monitor the precision of the assay once the result is >1.0 but less than 1.5 by noting "watch" on the report. However, if they see the monthly CVR is >1.0 for more than two or three months, they may choose to troubleshoot the test system.

Standard Deviation Index (SDI)

Calculating the Standard Deviation Index [SDI]

$$SDI = \frac{(\bar{x}_{Lab} - \bar{x}_{Group})}{S_{Group}}$$

This is a measurement of the difference between the laboratory's mean from the peer group mean as measured by the peer group standard deviation. While it's a discussion of accuracy and trueness (bias), it's expressed in units of standard deviation or imprecision (random error). The ideal SDI is 0.0, which means your laboratory mean is the exact same as the peer group mean. If your SDI is 1.0, the difference between your laboratory

mean is and the peer group mean is the size of the peer group SD. Acceptable SDI values are not standardized, but typically SDI of 1.5 to 2.0 or higher indicates that your laboratory mean is significantly biased away from the peer group mean.

Please note that an SDI of less than 1.5 to 0.0 does not necessarily mean that your bias is acceptable. Since the peer group SD may be quite large, an SDI of 1.0 might still indicate a very large bias.

Simply put, SDI and CVR are comparative statistics that can be used with peer group data, that can indicate when there are significant problems with laboratory performance. However, having an acceptable SDI and CVR is not a guarantee that your laboratory is performing well.

Many proficiency testing programs use the SDI for judging the test's bias. If your lab "fails" the SDI for the same test in two of three different PT events, the lab is considered to have failed PT, and the lab is now considered out of compliance. The biggest consequence, the lab could be shut down for that test.

Self-assessment Quiz

Questions 12-14

12. Which is more important to monitor day-to-day?
    a. CV
    b. CVR
    c. SDI

13. If your CVR < 1, and your SDI is 1, does this indicate that you have a perfect method?
    a. Yes
    b. No

14. Given your lab's mean of 4.1, and lab's standard deviation of 0.3, and a peer group mean of 4.3, and a peer group standard deviation of 0.4, what is the CVR?
    a. 1.33
    b. 0.75
    c. 1.0
    d. 0

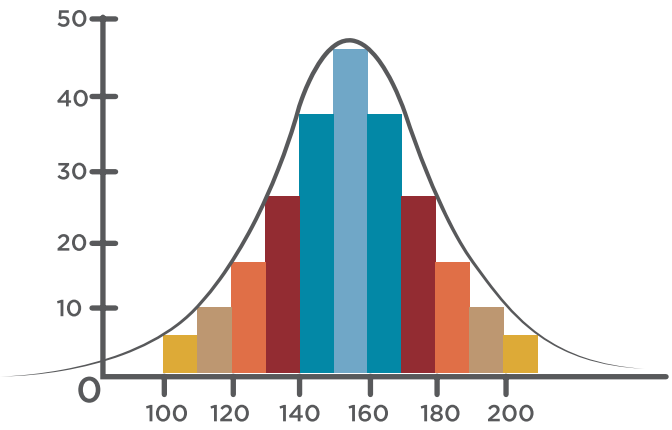
Answer Key: page 42

Notes

The Graphic Tools of QC – learning to grasp QC at a glance

As much as statisticians love to look at numbers all day, perhaps you in the lab would prefer something much simpler and faster to analyze. Luckily, there are tools that can summarize and depict all the important details of QC in a graphic way.

The Histogram



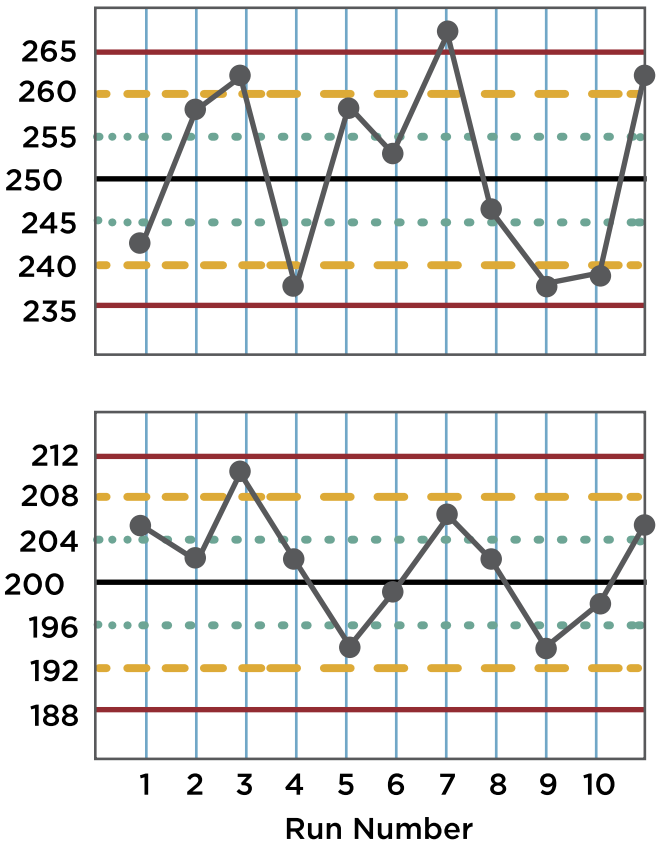
When traditional statistics are analyzed, it is quite common to review the Histogram, which displays the stacked values of a data set. It should ideally form a Normal curve or distribution, taking the Bell shape.

When this shape of a curve is met, the data conforms to a normal distribution, and thus the standard tools of statistics can be applied. Approximate 95% of the values can be expected to fall within 2 SD, approximately 99.7% of the values can be expected to fall within 3 SD. Thus, when values are seen outside 2 or 3 SD, these are uncommon and indicative of a potential problem.

Your lab will not usually look at a histogram, however, as that is only useful when looking at large sets of historical data. When you are running a few controls a day, you need a different visual tool.

The Levey-Jennings Chart

Levey and Jennings introduced statistical process control to medical laboratories in 1950, an adaptation of the original statistical control chart introduced by Walter Shewhart. While Shewhart's original recommendation called for making a group of measurements, calculating the average and range (maximum difference), then plotting the mean and range on two different control charts, Levey and Jennings proposed making duplicate measurements on a patient specimen. Because the actual level of the measured constituent varied from specimen to specimen, this was a challenging application. Henry and Seaglove developed an alternative procedure in which a stable reference sample was analyzed repeatedly, and individual measurements were plotted directly on a control chart. This type of control chart on which individual values or single values are plotted directly is commonly known today as a Levey-Jennings chart.



These charts are typically prepared with horizontal limit lines at each standard deviation: 1, 2, 3, and sometimes even 4 standard deviations. Levey-Jennings charts can be prepared for the specific mean and SD levels, or they can be prepared with z-values that simply show a mean, and +/- 1, 2, 3 SD along the y-axis.

Once you have Levey-Jennings charts, you can begin plotting data, run by run, level by level, and deciding what points constitute acceptable, "in-control" behavior, and what points represent unacceptable, "out-of-control" behavior.

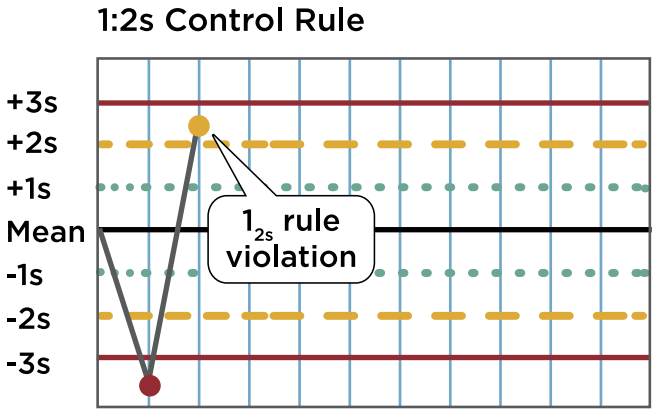
Westgard Rules - The List of Rules

(Single rules, Westgard Rules and otherwise)

1_{2s}

1_{2s} refers to the control rule used with a Levey-Jennings chart with control limits set at the mean ± 2s. In the earlier era of laboratory medicine, this rule was used as a rejection rule. Anything outside 2 SD meant you stopped the run and had to repeat patient samples. However, it was also well known that this single rule generated a large number of false rejections. As the number of tests and test volume increased, the false rejections began to overwhelm the laboratory. This was one of the motivations behind the formulation of a better approach, the multi-rule QC approach that is now commonly called the "Westgard Rules." (More about that later.)

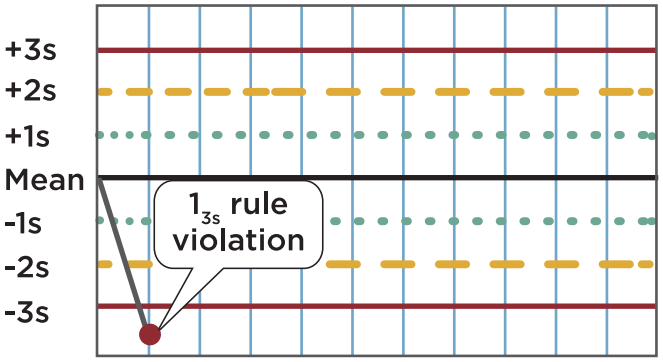
In the original "Westgard Rules", the 1:2s rule is demoted from rejection rule to just a *warning rule*. This means that the "violation" of this warning only triggers careful inspection of the control data by other rejection rules. By making this modification to the 1:2s interpretation, labs can significantly lower their false rejection rates.



1_{3s}

1_{3s} refers to a control rule used with a Levey-Jennings chart with control limits set at the mean +3s and the mean –3s. A run is rejected when a single control measurement exceeds the mean +3s or the mean –3s control limit.

1:3s Control Rule

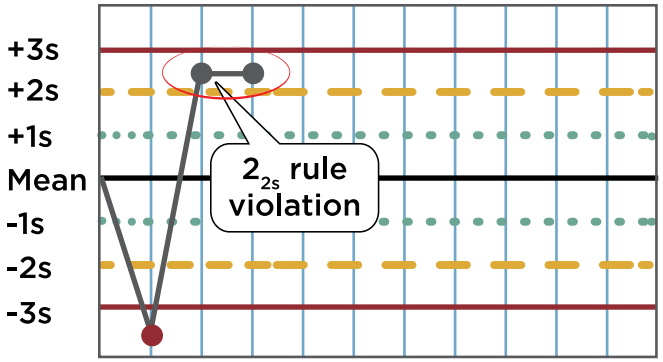


2_{2s}

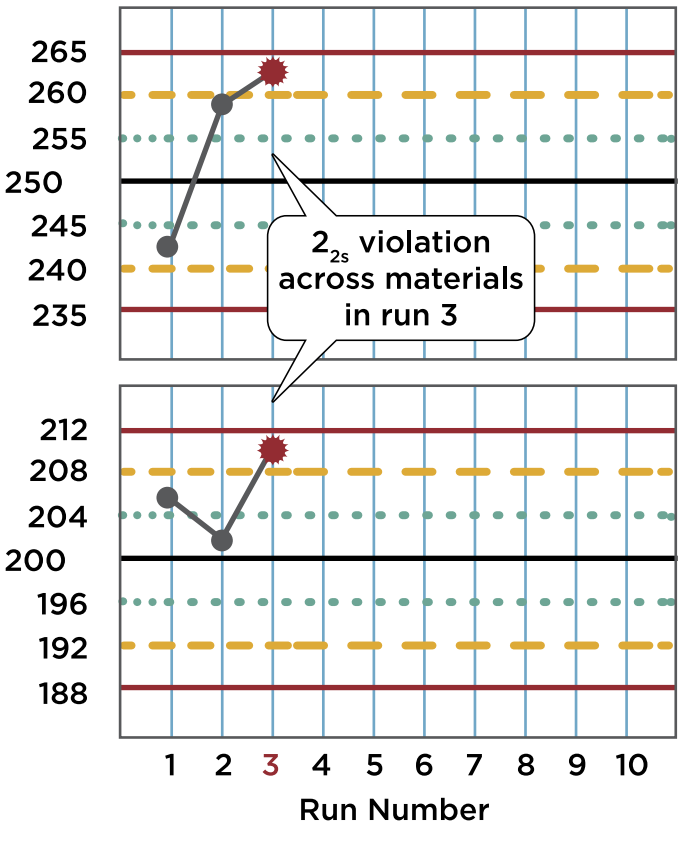
2:2s refers to the control rule used with a Levey-Jennings chart with limits are set at the mean ±2s. In this case, however, the run is rejected when two consecutive control measurements exceed the same mean +2s or the same mean –2s.

Notice that there are two ways to interpret this rule. You can use the same control level, looking at the current run and the previous run (looking across runs), OR, if you are running two levels of control, you can look at both of them within a single run (looking across levels).

2:2s Control Rule

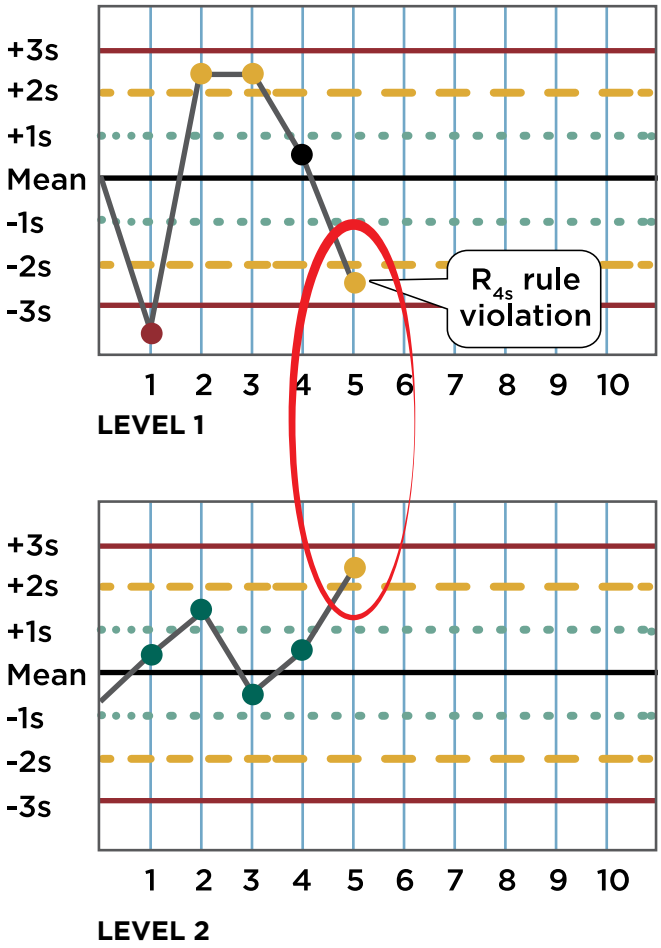


2:2s within level, across run



R_{4s} Control Rule

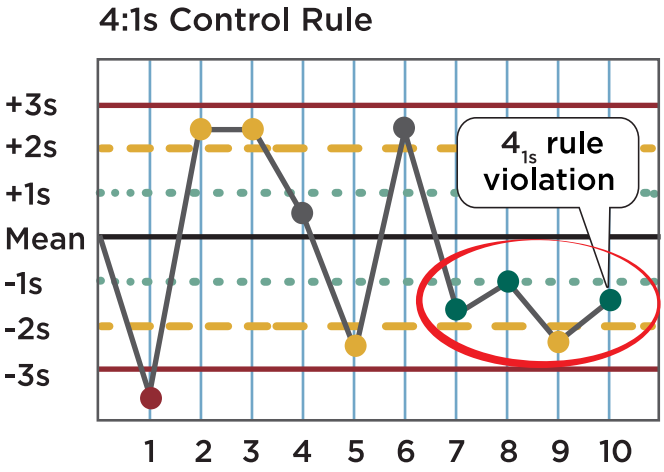
R:4s refers to a control rule where a reject occurs when one control measurement in a group exceeds the mean +2s and another exceeds the mean –2s. Note there is a special, limited application of this rule: it can only be interpreted *within a single* run. Don't look across runs to interpret this rule.



R4s: across level, within 1 run

4_{1s}

4:1s reject occurs when four consecutive control measurements exceed the same mean +1s or the same mean –1s control limit. Again, this rule can be interpreted two ways. Within both control levels, across a single run, OR you can interpret this rule within a single control level, looking at the current run and the previous three runs.



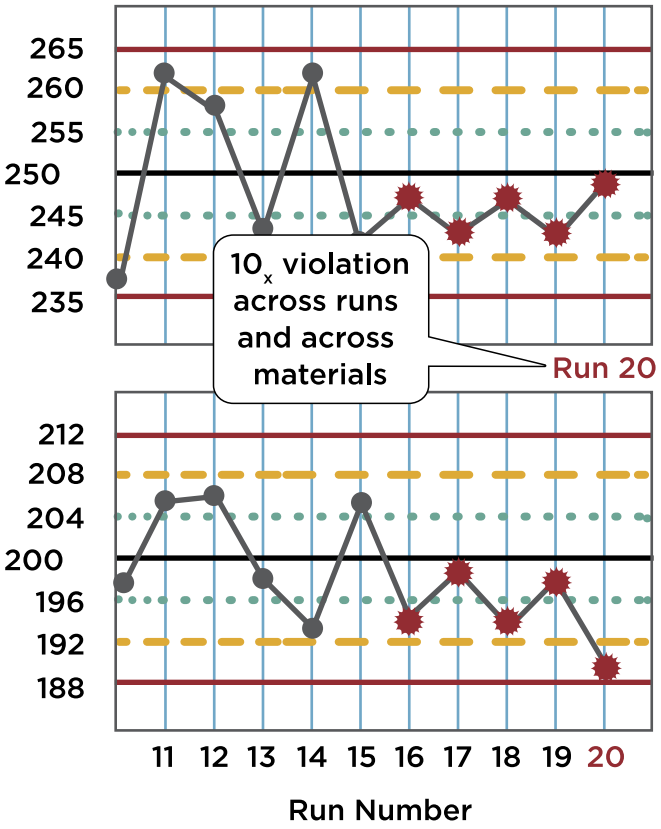
4:1s within a single level, across 3 runs

10_x

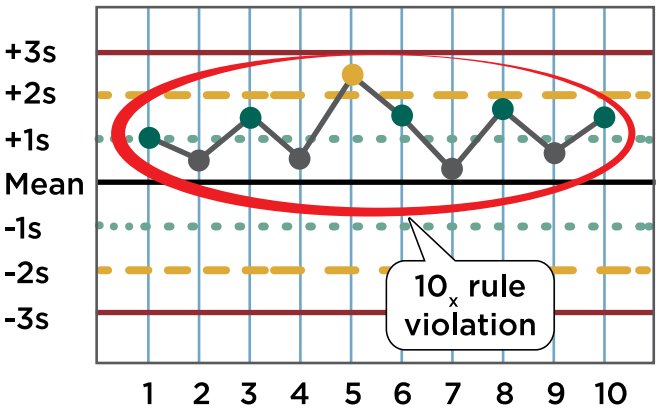
10:x reject occurs when 10 consecutive control measurements fall on one side of the mean. Again, this rule can be interpreted two ways. Within both control levels, across a total of five runs, OR you can interpret this rule within a single control level, looking at the current run and the previous nine runs.

There are versions of this "mean rule" that work for 6:x, 8:x, 9:x, and 12:x.

You may have noticed that most of these rules are good for situations when you are running two levels of control. What do you do when you have three levels of control, which is true for some tests? Three levels of control are frequently used to gain more coverage of decision levels.



10:x across level, across five runs

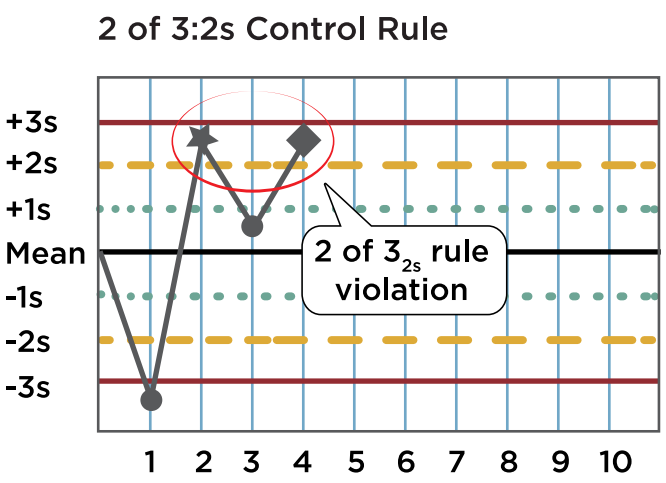


10:x within a single level, across 10 runs

2 of 3_{2s}

2 of 3:2s reject occurs when two out of three control measurements exceed the same mean +2s or mean –2s control limit.

This is best interpreted across three levels of control, within a single run. This replaces the 2:2s rule.

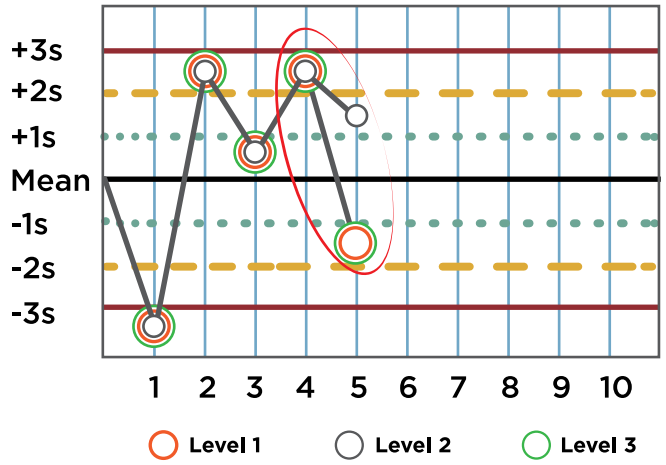


3_{1s}

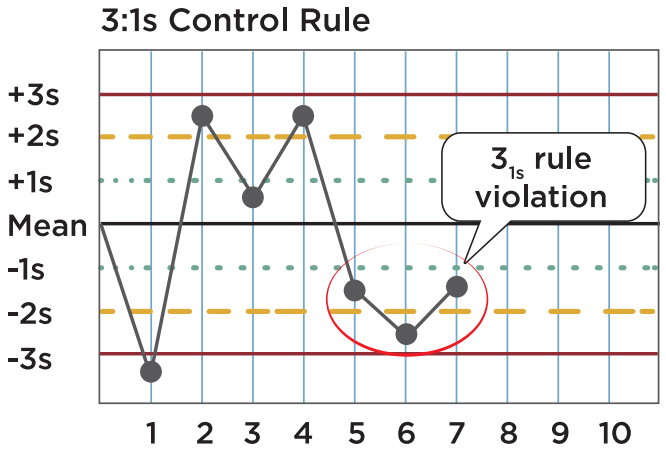
3_{1s} reject occurs when three consecutive control measurements exceed the same mean +1s or mean –1s control limit.

This can be interpreted within a single run, across all three control levels, OR it can be interpreted in a single control level, looking at the current run and two previous runs.

At this point, you may feel a bit overwhelmed by all the possible rules you could implement. Do you have to use all of these? The good news is no. In fact, there's even better news for labs today – a technique that allows you to reduce the number of rules and controls you need.



3:1s, across levels, within single run



3:1s, within single run, across three runs

Self-assessment Quiz

Questions 15-21

15. Why don't we typically look at histograms to assess day-to-day QC status and instead we examine Levey-Jennings charts?
    a. Histograms make us hysterical.
    b. Levey-Jennings charts give us better run to run analysis
    c. Histograms require a short term, smaller set of data
    d. Levey-Jennings charts require a longer term, larger set of data.

16. If the mean is 10 and the standard deviation is 1.5, where are the 2 and 3 SD limits set?
    a. 10 and 20; 30 and 40
    b. 7 and 13; 5.5 and 14.5
    c. 7 and 13; 4 and 16
    d. 8.5 and 11.5; 7 and 13

17. The notation for 1:3s as a control rule means...
    a. 3 controls of +/- 1 standard deviation, on either side
    b. 3 controls of +/- 1 standard deviation, all must be on one side
    c. 1 control of +/- 3 standard deviations, on either side
    d. 3 controls of +/- 3 standard deviations, on either side

18. The notation for R:4s as a control rule means...
    a. Random error rule
    b. 1 control of +/- 4 standard deviations
    c. Within-run rule
    d. 2 controls with one control + 2 standard deviations and one control – 2 standard deviations

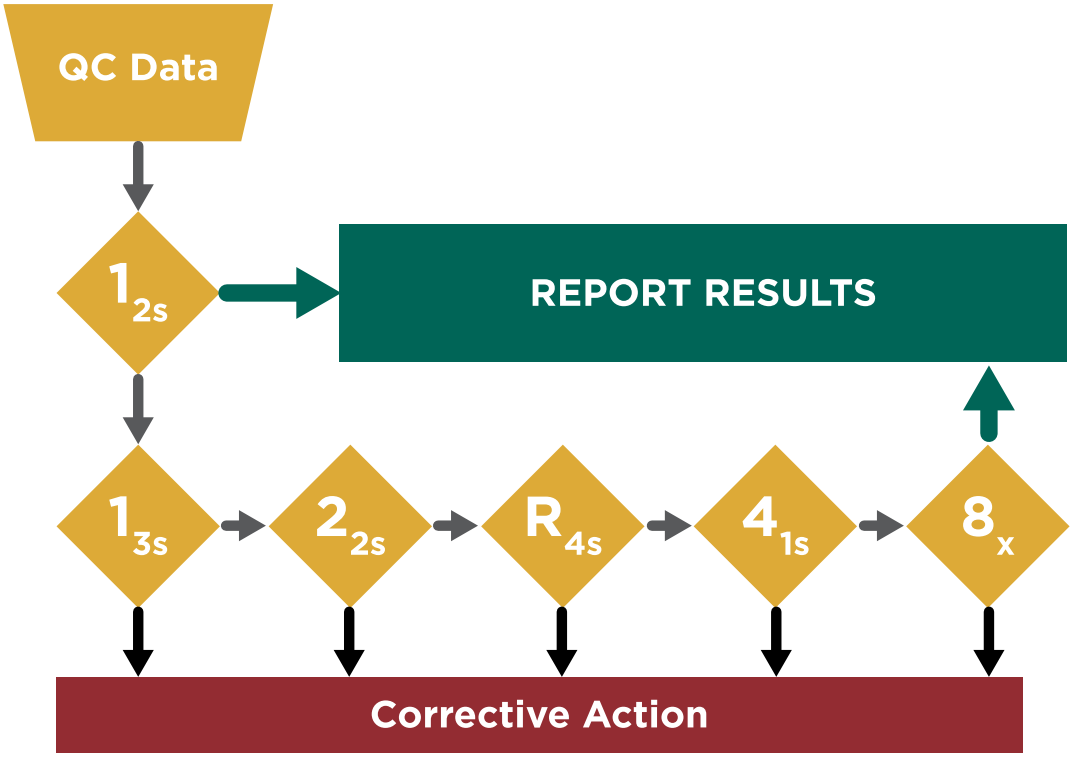
19. The notation of 10:x as a control rule means...
    a. X controls that are 10 standard deviations from the mean
    b. 10 controls that are on both sides of the mean
    c. 10 values that are x standard deviations from the mean
    d. 10 controls that are all on the same side of the mean

20. Given 2 controls, implementing a 10:x rule, if 3 values on the high control are above the mean, while 7 values on the low control are above the mean, this violates the 10:x rule? Yes or No?
    a. Yes
    b. No
    c. Not clear

21. In what order should you interpret the "Westgard Rules" or any multi-rule QC procedure?
    a. All at once
    b. Interpret the biggest rules (i.e. 10:x) first
    c. In sequence as the flowchart shows
    d. In reverse order

Answer Key: page 42

How many rules should I use? Implementing your approach to Westgard Rules



Multi-rule QC

Multi-rule QC – the name that was first applied to what is now commonly called "Westgard Rules" - uses a combination of decision criteria, or control rules, to decide whether an analytical run is in-control or out-of-control. The well-known Westgard multi-rule QC procedure uses 6 different control rules to judge the acceptability of an analytical run.

The real story of how "Westgard Rules" were developed is born of the urgent need for a better alternative to the 1:2s rule. Labs of that era were getting overwhelmed by the false rejection problems caused by the 1:2s, but there wasn't a good rule that had the same high error detection. Other control rules, like the 1:3s, had low false rejection rates, but they weren't as effective at detecting errors. Using one of the first applications of computer simulation (remember this is in the 1970s, way before personal computers), Dr. James O. Westgard determined that when a series of statistical control rules were combined, they could provide high error detection, without generating high false rejection rates. Thus, the multi-rule QC procedure was born. It was quickly adopted by the manufacturers of newly introduced autoanalyzers for multiple tests. [Westgard JO, Barry PL, Hunt MR, Groth T. A multi-rule Shewhart chart for quality control in clinical chemistry. Clin Chem 1981;27:493-501]

Now, a non-technical description. When Dr. Westgard's daughter Kristin was young and still living at home, she liked to party. One day when she said she was again intending to be out late; Dr. Westgard felt the need to exert parental control

over her hours. So, Dr. Westgard told her that if she was out once after three, twice after two, or four times after one, she was in big trouble. That's the essence of multi-rule control.

Dr. Westgard's daughter hates this version of the story, and while it isn't entirely true, it's still a good story and makes multi-rule QC understandable to everyone. (By the way, she turned out fine; she graduated first in her class at law school and has reached the pinnacle of her corporate law practice.)

One thing to realize is that there are additional benefits to using the Westgard Rules. Not only do they reduce the false rejection, but they aid in the troubleshooting of the error by noting which rule has been violated.

Error Condition	High P_{fr}	High P_{ed}
No Errors	1_{2s}	
Random Error		1_{3S}, R_{4S}
Systematic Error		2_{2S}, 4_{1S}, $2of3_{2S}$, 3_{1S} 6_{X}, 8_{X}, 9_{X}, 10_{X}, 12_{X}
Error Condition	**High P_{fr}**	**High P_{ed}**

When 1:3s and R:4s rules are violated, this points toward random error as being the likely source of the error.

When 2:2s, 3:1s, 4:1s, and 6:x or 8:x or 10:x, etc. are violated, that points toward systematic error as the likely source of the error.

What to do when you're out-of-control

After all the controls are run, the points are plotted, the rules are interpreted, what do you do once an alarm actually goes off?

The best practice is to stop testing. Investigate and find the source of the error, fix it, and then resume testing. Any patient samples that were impacted during the out-of-control period should be retested.

Troubleshooting is the name we give to the hunt for the source of the error. Troubleshooting is a very individual activity – it's impossible to create a universal prescription on how to troubleshoot all methods, all instruments, and all labs. Your lab has a unique set of environmental factors, instrument factors, even operator factors. You will need to use all your professional judgment to create the best troubleshooting protocol for each of your tests.

There are, however, some general sources of errors that all labs will face in one form or another.

Systematic Error Troubleshooting

Systematic errors are most worrisome because when they occur, they impact larger numbers of patients. They generally fall into two categories: shifts and trends

Trends are gradual changes in the QC values due to slow degradation of the test system or test system components. In the worst-case scenario, the errors are so slow in accumulating, you don't notice them. A few common examples of gradual changes in a system include the following:

- Deterioration of a photometric light source, lamp or bulb
- Deterioration of reagent
- Deterioration of control materials
- Deterioration of temperature sensitive components
- Deterioration of electrodes
- Deterioration of filters
- Debris accumulation

You can see the general fashion in how trends manifest themselves – components wear out, corrode, etc.

Shifts are more abrupt and are caused by a distinct and, in some cases, dramatic change in a component of the test system.

If the components listed above don't degrade or deteriorate, but suddenly fail outright, this could be the source of the shift. Typical examples include the following:

- Changes in reagents, calibrators, controls
- Instrument maintenance
- Changes in temperature or humidity in the laboratory
- Failed calibrations
- Inadequate storage of reagents or calibrators, and, thus, degradation of the materials
- Change in sample or reagent volumes due to pipettor maladjustments or misalignment,
- Change in temperature of incubators and reaction blocks,
- Change in procedure from one operator to another

This list is not meant to be exhaustive but is merely meant to stimulate your thinking about what could go wrong in your methods and instruments.

Random Error Troubleshooting

Problems resulting in increased random error are much more difficult to identify and resolve, mostly due to the nature of the error which cannot be predicted or quantified as can systematic error.

Here are a few of the possible sources of random error:

- bubbles in reagents and reagent lines,
- inadequately mixed reagents,
- unstable temperature and incubation,
- unstable electrical supply
- individual operator variation in pipetting, timing, etc.
- occasional air bubbles in sample cups or syringes
- defective unit-test devices (if you are testing with POC devices, or cartridges, etc.)

Here's another list that can be helpful to make sure that everything is correctly set up in your system:

Quality Control

- Correct material, lot number, level?
- Correctly prepared?
- Levels interchanged?
- Within stated expiration date?
- Analyzed within known stability period after preparation?
- Correctly stored?

Reagents

- Correct material, lot number?
- Correctly prepared?
- Correctly loaded and used?
- Within stated expiration date?
- Correctly stored?

Calibrator

- Correct materials, lot number?
- Correctly prepared and used?
- Correct number and order?
- Correct calculations and settings?
- Within stated expiration date?

Analyzer

- Adequate periodic maintenance?
- Any recent changes?
- Materials within stated on-board stability?
- Visual inspection for problems?

Environment

- Proper water system?
- Waste disposable functioning properly?
- Temperature and humidity at proper levels?

Documenting Your Flags and Corrective Actions

Every laboratory should have a log for QC, electronic or paper, but something where all events and actions are recorded. This is particularly important for errors that are observed and troubleshot. If the same error can be fixed with a particular corrective action, this log will help you speed through the troubleshooting process. Also, if multiple errors of the same type are occurring, this log is helpful in identifying the long-term trends and issues with performance. Finally, of course, it is both a regulatory mandate and best practice to maintain a history of the instrument behavior.

Self-assessment Quiz

Questions 22-25

22. If a 2:2s control rule is violated, what type of error is likely to have occurred?
    a. Random error
    b. Systematic error
    c. Total error
    d. Measurement uncertainty

23. If trouble-shooting a suspected systematic error, what should you check?
    a. Deterioration of reagent
    b. Deterioration of control materials
    c. Deterioration of filters
    d. All of the above and more

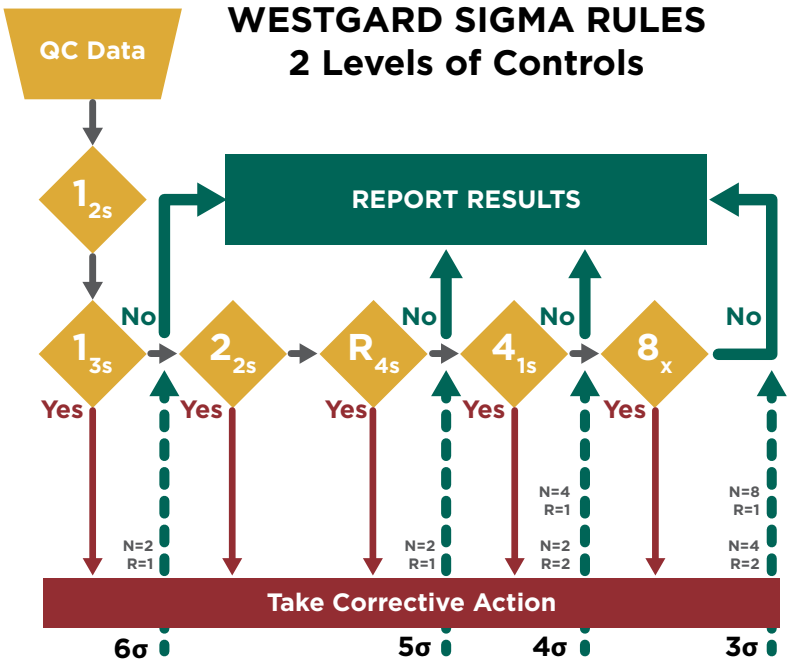
24. If trouble-shooting a suspected random error, what should you check?
    a. Bubbles in reagents or reagent lines
    b. Unstable electrical supply
    c. Individual operator variation in pipetting, timing, etc.
    d. All of the above and more

25. What possible events could cause a shift in control values?
    a. Instrument maintenance
    b. Inadequate storage of reagent or calibrators
    c. Change in the temperature of the laboratory
    d. All of the above and more

Answer Key: page 42

Notes

A teaser for the sequel, the Advanced QC Workbook: What if you could utilize fewer rules?



Westgard Sigma Rules for 2 levels of controls. Note Sigma-scale at the bottom of the diagram. To apply, determine Sigma-metric, locate on the Sigma Scale, identify rules above and to the left, find N and R above the Sigma Value.

While it's beyond the scope of this lesson, there is an even better way to run QC: a technique that adjusts the frequency of QC measurements to the quality required by the observed performance of the method. This technique is called analytical Sigma-metrics, it's a specific application of the widely known Six Sigma management approach. There's a specific adaption of Six Sigma for laboratory testing, and the simplest embodiment of this is called the "Westgard Sigma Rules"

If you can determine the Sigma-metric of your test, you can also determine how many "Westgard Rules" are necessary to properly monitor the test. For a Six-Sigma test, you don't truly need multiple rules. You can sufficiently monitor your test with just the 1:3s rule and two controls. As your Sigma-metric is decreased, you need more Westgard Rules, until at 3 Sigma, you need all the Westgard Rules and need to increase the frequency of control runs.

What does this mean? Labs with excellent performance can reduce the number of rules and controls they use, which will reduce the number of out-of-control events they must troubleshoot. This can reduce both outright expense and staff time spent.

Glossary

Calibrators or Calibration Materials: solutions or devices of known quantitative/qualitative characteristics (e.g. concentration, activity, intensity, reactivity) used to calibrate, graduate, or adjust a measurement procedure or to compare the response obtained with the response of a test specimen/sample.

Coefficient of Variation (CV): a calculation that allows you to monitor the imprecision across multiple control levels, even compare imprecision between methods and instruments, and compare them against the manufacturer's expectations. The lower the CV, the lower the test system's imprecision.

Coefficient of Variation Ratio (CVR): This calculation will allow you to assess if the CV of your test system is comparable to other systems exactly like yours. This is usually provided with QC and QA peer group programs.

Commutability is the goal of any type of control – that the control material is as close as possible to a real patient sample. This attribute provides confidence that when the device produces a control value out of range - thus indicating that the test system has a problem, you can be certain that the patient sample results would be incorrect as well.

Embedded Quality Control: control materials contained in on-board ampules or cartridges, provided they have similar matrices to patient specimens and follow all steps of the analytical process, those control materials.

Frozen: certain controls can be kept frozen for a long period of time

Liquid: These are controls that are ready to go, no reconstitution step required.

Lyophilized: this is freeze-dried

Matrix Effect: The matrix of a control is all the extra stabilizers, preservatives, and other ingredients that are present that are wholly unrelated to a patient sample. These additives may help keep the control material stable, or have a longer shelf life, but they do not make the control behave similarly to a patient sample

Mean: Also referred to as the average.

Qualitative Tests: tests that give results that are descriptive, not numerical. For example, "positive" or "negative", "present" or "absent", etc.

Quality Control material: a substance, material, or article intended by the manufacturer to be used to verify the performance characteristics of an in vitro diagnostic medical device (ISO 17593).

Quantitative Tests: these are tests that give results expressing a numerical amount or level (concentration) of an analyte in a specimen.

Random Errors: these errors are much more difficult to identify and resolve, mostly due to the nature of the error which cannot be predicted or quantified as can systematic error. Some describe these as "flukes".

Semi-Quantitative tests: these are tests that have "a dose-response gradient that may be included in the reported result, but for which no authoritative calibration scale exists to determine inaccuracy and imprecision; tests that yield results in an approximate range of values (e.g., trace, moderate)" [ISO and CLSI].

Shift: This is an abrupt change in the QC results and are caused by a distinct and, in some cases, dramatic change in a component of the test system. This is a systematic error.

Standard: measurement material measure, measuring instrument, reference material or measuring system intended to define, realize, conserve or reproduce a unit or one or more values of a quantity to serve as a reference.

Standard Deviation: a measurement of how closely the control values cluster around the mean, how tightly packed they are around the mean, or how widely dispersed they are away from the mean.

Standard Deviation Index (SDI): This is a measurement of the difference between the laboratory's mean from the peer group mean as measured by the peer group standard deviation. While it's a discussion of accuracy and trueness (bias), it's expressed in units of standard deviation or imprecision (random error).

Systematic Errors: See trends and shift definitions.

Trend: This is usually observed with the QC values gradually increase or decrease over time on the Levey-Jennings chart. This is indicative of a systematic error.

Self-assessment Quiz - Answer Key

1. What is Quality Control? **[Correct Response: d]**
2. If your test only produces positive and negative results? **[Correct Response: b]**
3. When do you NOT use statistical QC? **[Correct Response: c]**
4. When should you calibrate your method? **[Correct Response: c]**
5. How often should you calibrate? **[Correct Response: c]**
6. Which is better, according to CMS? **[Correct Response: a]**
7. Which type of controls is freeze-dried? **[Correct Response: a]**
8. Which control materials will have results closer to patient values? **[Correct Response: a]**
9. What's the benefit of an assayed control? **[Correct Response: a]**
10. Given a low control with a mean of 105 and an SD of 17, and a high control with a mean of 205 and an SD of 20, which control has the greater CV? **[Correct Response: a]**
11. Given the values in mg/dL 101, 109, 81, 83, 84, 95, 97, 110, 104, 100, 102, 99, 95, 100, what is the mean, SD, and CV? **[Correct Response: a]**
12. Which is more important to monitor day-to-day? **[Correct Response: a]**
13. If your CVR < 1, and your SDI is 1, does this indicate that you have a perfect method? **[Correct Response: b]**
14. Given your lab's mean of 4.1, and lab's standard deviation of 0.3, and a peer group mean of 4.3, and a peer group standard deviation of 0.4, what is the CVR? **[Correct Response: b]**
15. Why don't we typically look at histograms to assess day-to-day QC status and instead we examine Levey-Jennings charts? [**Correct Response: b]**
16. If the mean is 10 and the standard deviation is 1.5, where are the 2 and 3 SD limits set? **[Correct Response: b]**
17. The notation for 1:3s as a control rule means... **[Correct Response: c]**
18. The notation for R:4s as a control rule means... **[Correct Response: d]**
19. The notation of 10:x as a control rule means... **[Correct Response: d]**
20. Given 2 controls, implementing a 10:x rule, if 3 values on the high control are above the mean, while 7 values on the low control are above the mean, this violates the 10:x rule? Yes or No? **[Correct Response: b]**
21. In what order should you interpret the "Westgard Rules" or any multi-rule QC procedure? **[Correct Response: c]**
22. If a 2:2s control rule is violated, what type of error is likely to have occurred? **[Correct Response: b]**
23. If trouble-shooting a suspected systematic error, what should you check? **[Correct Response: d]**
24. If trouble-shooting a suspected random error, what should you check? **[Correct Response: d]**
25. What possible events could cause a shift in control values? **[Correct Response: d]**

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Basic QC Workbook PACE Continuing Education Test

1. The term "quality control" can refer to any of the following, except:

a. Performing calibrations in order to report patient samples.

b. Testing normal and abnormal control material, charting the results, analyzing them to identify sources of error, and evaluating and documenting any action taken as a result of this analysis.

c. Operational techniques and activities that are used to fulfill requirements for quality.

d. Procedures intended to monitor the performance of a test system to ensure reliable results.

2. Qualitative tests:

a. Expressed in a numerical value or concentration of an analyte.

b. Provide a signal to cutoff result. However, for patient samples, is reported as positive or negative.

c. Do not provide a numerical value or concentration of an analyte in a specimen.

d. Are no longer performed in the laboratory.

3. Calibration is:

a. A necessary step to perform once at the time of the assay start-up.

b. When laboratorians use the quality control material to test and adjust an instrument or test system to establish the correlation between the measurement response and the concentration or amount of the substance that is being measured by the test procedure.

c. A lab task required to be performed once a year to test the linearity of the assay.

d. When laboratorians use the traceable material to a known concentration of the analyte that will test and adjust an instrument or test system to establish the correlation between the measurement response and the concentration or amount of the substance that is being measured by the test procedure.

4. Liquid controls are:

a. Controls that must be reconstituted before use.

b. Preferable to lyophilized because there is one less variable to troubleshoot when QC issues arise.

c. Are more desirable since they do not require refrigeration during transportation and storage.

d. All the above.

5. Commutability is important to consider since:

a. It closely mimics the patient samples you are testing.

b. It provides confidence when the device produces a control value out of range.

c. It is a bad thing.

d. A and B

6. What is Matrix Effect?

a. The opposite of commutability

b. When a control shifts in concentration, but patient samples do not show the same shift.

c. When added components to the quality control (stabilizers, spiking analyte levels, etc.) cause the control to t perform differently than a patient sample.

d. All the above

7. Calculate the mean for the following points that were collected during the new lot's cross-over study: 5.1, 5.5, 5.3, 5.6, 5.1, 5.3, 5.4, 5.7, 5.2, 5.5, 5.3, 5.3, 5.7, 5.3, 5.7, 5.1, 5.4, 5.6, 5.3, 5.5.

a. 5.40

b. 5.43

c. 5.45

d. 5.50

8. The calculated mean value:

a. Should be compared with the QC vendor's range provided in the assayed controls package insert to determine validity of the data collection.

b. Should be used regardless of values provided in the QC vendor's package insert.

c. Is difficult for most software programs to calculate, therefore manual calculation is required.

d. A and C only

9. Calculate the standard deviation of the following points that were collected during the new lot's cross-over study: 5.1, 5.5, 5.3, 5.6, 5.1, 5.3, 5.4, 5.7, 5.2, 5.5, 5.3, 5.3, 5.7, 5.3, 5.7, 5.1, 5.4, 5.6, 5.3, 5.5.

a. 0.18

b. 0.20

c. 0.23

d. 0.26

10. What is the coefficient of variation of the following points that were collected during the new lot's cross-over study: 5.1, 5.5, 5.3, 5.6, 5.1, 5.3, 5.4, 5.7, 5.2, 5.5, 5.3, 5.3, 5.7, 5.3, 5.7, 5.1, 5.4, 5.6, 5.3, 5.5?

a. 3.45

b. 3.54

c. 3.68

d. 3.86

11. Coefficient of variation (CV) is:

a. Always expressed in percentage.
b. Always a qualitative result and used to measure precision as "Good Precision" or "Bad Precision."
c. Calculated by dividing the mean by the standard deviation.
d. Calculated by multiplying the standard deviation by 100.

12. The Standard Deviation Index (SDI):

a. Is used to measure the lab's standard deviation compared with the peer group's standard deviation.
b. Is used to monitor the precision of the test.
c. Is used to measure that lab's mean value against the peer group mean.
d. Ideally should be close to 2.0.

13. The Coefficient of Variation Ratio (CVR):

a. Measures the lab's CV to the peer group's CV.
b. Monitors the bias or accuracy of the test.
c. Measures that lab's mean value against the peer group mean.
d. Ideally should be close to 2.0.

14. Levey-Jennings charts are:

a. Always prepared horizontally with limits at 1, 2, and 3 standard deviations.
b. Charts used for each test to monitor run-to-run QC to track whether data points are "in control" or "out of control".
c. Typically prepared with horizontal limits for 1,2, and 3 standard deviations.
d. B and C

15. The Westgard 12s rule is:

a. One data point that exceeds three standard deviations.
b. Known to generate many false rejections.
c. Used when 2 levels of quality control in a run exceed two standard deviations.
d. One that should only be used as a run rejection rule.

16. The Westgard rule 13s rule is:

a. When one data point exceeds plus or minus three standard deviations
b. When three data points exceed plus or minus one standard deviation
c. A rule that should always generate a run warning.
d. One that can be ignored.

17. The Westgard rule 22s rule is:

a. A rule that is rarely seen and is always a random source of error.

b. When two levels in the same run or across run with the same level of control that is greater than plus or minus two standard deviations of the mean.

c. When one point is greater than plus or minus two standard deviations.

d. A and C

18. The Westgard rule R4s:

a. Occurs when the four QC values are on one side of the mean.

b. Is always a warning since it does not indicate a serious problem.

c. Occurs when one control exceeds 4 standard deviations from another QC level.

d. Should only be evaluated across QC runs, not within QC runs.

19. The Westgard rule 41s:

a. Indicates a random source of error.

b. Occurs when four consecutive controls values exceed plus or minus 2 standard deviations.

c. Occurs when four consecutive control values exceed plus or minus 1 standard deviation.

d. Is only applicable to a single QC run.

20. The Westgard rule 10x:

a. Indicates a random source of error.

b. Occurs when ten consecutive controls values are on one side of the mean value.

c. Occurs when one value exceeds plus or minus 10 standard deviations.

d. Is only applicable to a single QC run.

21. The Westgard rule 2 of 32s is:

a. Usually a rejection rule.

b. When two values of a tri-level control exceed plus or minus two standard deviations.

c. When two levels of a tri-level control exceed plus or minus three standard deviations.

d. A and B

22. Westgard Multi-rule strategy:

a. Uses a combination of Westgard rules to determine if the test system is performing within control or out of control.

b. Confirms the validity of using only the 12s rule for all tests.

c. Generates a low level of both run rejection and false rejection rates.

d. Generates a high level of both run rejection and false rejection rates.

23. Systematic errors are:

a. The least worrisome type of error.

b. Linked only to QC trends in the test system.

c. Are usually linked to problem with the test system. Patient testing should be suspended.

d. Linked only to QC shifts in the test system.

24. Random errors are:

a. Much easier to troubleshoot than systematic errors.

b. Very predictable and quantified.

c. More difficult to troubleshoot than systematic errors.

d. A and B

25. Documentation of laboratory flags and corrective actions:

a. Should be retained via an electronic or paper log where all QC runs, and actions can be recorded.

b. Are not very helpful when troubleshooting.

c. A way to determine whether multiple errors of the same type of rule violation are occurring and to identify long term trends and issues with performance.

d. A and C

Evaluation of Basic QC Workbook

This section must be completed with the answer key in order to process your quiz for P.A.C.E. content hour credits.

How well did this book meet the objectives/goals of this basic workbook?

Objective	Did not meet	Met	Exceeded
Illustrate the purpose and practice of statistical QC			
Outline the setup, implementation and interpretation of single statistical rules as well as "Westgard Rules"			
Reveal useful troubleshooting techniques			

Grade the following statements:

1 = Disagree Completely

2 = Somewhat Disagree

3 = Agree

4 = Completely Agree

The Basic QC Workbook. . .

1. ...helped me with understanding basic QC practices and applications. 1 2 3 4

2. ...was user friendly and well formatted. 1 2 3 4

3. ...is not a reference source for future use 1 2 3 4

About the Author

Sten Westgard MS

Sten Westgard, MS, is the Director of Client Services and Technology for Westgard Quality Control.

For nearly 25 years, Sten has managed the Westgard website, course portal, and blog, creating and administering online training, as well as editing and writing hundreds of reports, essays, and applications on quality control, method validation, Six Sigma, Risk Management and other laboratory management topics.

He has edited and contributed to numerous books on quality, including Basic QC Practices, Basic Method Validation, Basic Quality Management Systems, Six Sigma QC Design and Control, Six Sigma Risk Analysis, CLIA Final Rules, Assuring the Right Quality Right, The Poor Lab's Guide to the Regulations and Nothing but the Truth about Quality. He has co-edited two special issues of Clinics in Laboratory Medicine (2015 and 2017), as well as a special issue of Biochemica Medica (2018)

Sten is also an adjunct faculty member of the Mayo Clinic School of Health Sciences in Rochester, Minnesota; an adjunct faculty member of the University of Alexandria, Egypt; an adjunct visiting faculty member of Manipal University in Mangalore, India; and an honorary visiting professor in 2017 at Jiao Tong University, Shanghai.

www.westgard.com

www.westgard.org

james.westgard.com

www.linkedin.com/in/sten-westgard-683770/

TECHNOPATH
CLINICAL DIAGNOSTICS

www.**technopathcd**.com

info@technopathcd.com | Tel: +353 61 525700
Technopath Life Sciences Park, Fort Henry, Ballina, Co. Tipperary, V94 FF1P, Ireland.

USA
info@technopathusa.com | Tel: 1.888.235.3597
99 Lafayette Drive, Suite 179, Syosset, NY 11791