A Self-instructional Course for
Laboratory Professionals.

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

Advanced Applications in Clinical Laboratory Quality Control

P.A.C.E. Approved Workbook

Skill Level: **Advanced**

Strategies for Appropriate Laboratory QC Design

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TECHNOPATH
CLINICAL DIAGNOSTICS

Dear Reader,

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Introduction

Congratulations! You've advanced to the next level of quality control. Perhaps you didn't realize that there was an advanced level, or even a basic level, but this workbook is going to help you elevate your QC game.

The good news is that using the more advanced quality control techniques will reduce your work, not increase it. You can invest a bit of time assessing your performance, and then customize your QC practice so you aren't running all rules on all tests and running around to troubleshoot every test. Instead, you focus on the right rules and the right number of controls for each test – in support of delivering the right result to the clinician and patient.

If you've been working in the laboratory a long time, this workbook will challenge some of your long-held beliefs about QC. We will, in fact, try to help you "unlearn" your bad habits. If you're new to the laboratory, thank goodness you've joined the profession; we need you and all of your friends.

As you are becoming more acquainted with your professional environment, this advanced practice may actually be easier for you to learn.

If, at any time, the material in this workbook seems too advanced or too overwhelming, remember there is a Basic QC workbook that is also available. You can always refer to that basic workbook whenever a concept or technique seems a little difficult. In this Advanced QC workbook, we won't redefine the key concepts of Quality Control like mean, SD, CV, etc. We will assume you know them and move on with the best way of leveraging those concepts into better QC practices.

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

So, let's begin, shall we?

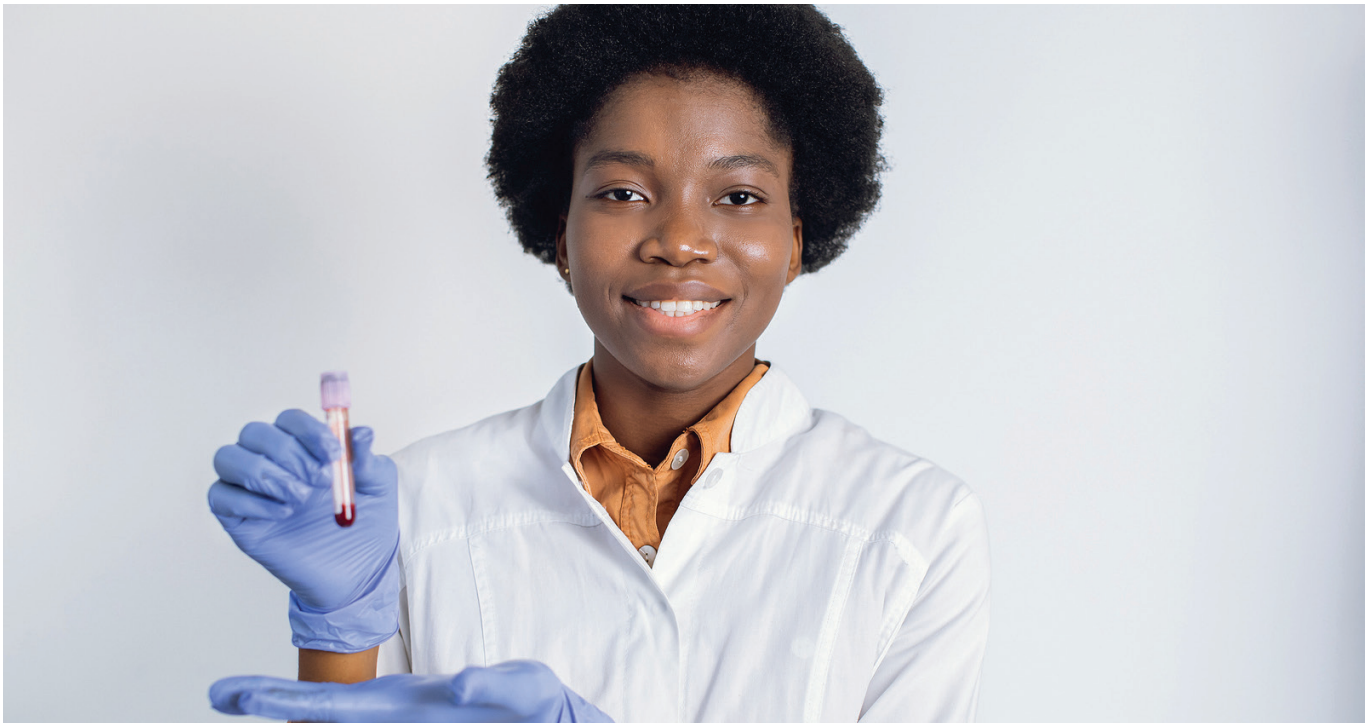
Goals for this workbook

- Setting appropriate QC design strategies (selecting appropriate QC product/levels, QC frequency, QC ranges, rules, etc.)
- Select the right Westgard Rules or Westgard Sigma Rules for your tests
- Assess your QC on a broader scale by calculating the Analytical Sigma-metric of your tests and how to apply to your analytes' QC design

Throughout the book, we provide you with self-assessment quizzes, with answers you can check. 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 are the parts that will be the most difficult to read, since the implicit aim of such documents is to be as scientific, precise, and boring as possible. Along with every official definition, we provide a "real world" definition to preserve your sanity.

Selecting the appropriate control material



While the basic QC workbook discussed some of the elements of good quality control material, there are more aspects we will discuss here. Given all the tests that a modern laboratory must run and monitor, selecting the right control material is trickier – and more critical – than ever. We describe below the various attributes of quality control material of which you must be aware.

Multi-analyte controls

Decades ago, in the early days of quality control, controls were built one analyte at a time. For each test, you had a control dedicated to monitor it. Today's modern laboratories, however, cannot afford to run a single control for every test. We wouldn't have enough room on our instrument to run any patient samples!

It's more efficient in cost and effort to have a single control material that covers as many analytes as possible.

Number of levels of QC

How many levels of QC material are really needed? This is a common question that many laboratorians struggle to answer. Labs are caught between the regulatory mandates and their financial constraints, but there is a third factor they should also consider: the clinical need. Think of the regulations as the minimum: you MUST run at least two levels of controls for most tests, and for some select tests, you must run three levels. But think also about where along the analytical

range the important medical decisions get made is that in only places or are there areas where decisions happen?

Another reason to consider additional levels of control material is when the assay is non-linear. When performing a non-linear test, you want to ensure that key portions of the curve are being monitored for errors. For example, the curve below (Figure 1 is the non-linear curve for phenobarbital.

Let us assume in this case, the lab uses only level one and level three of the control, representing the sub therapeutic level at 5 ug/mL and the toxic level at 60 ug/mL. If the calibration curve drops out in the middle area of the curve between 8 and 58 ug/mL (see Figure 2 below), it is plausible that the level one and level three controls would still be "in" range. Since they are not running a control at the middle therapeutic level, they are missing the aberration in the calibration curve. This could cause the lab to release patient test results falsely representing the test result as a

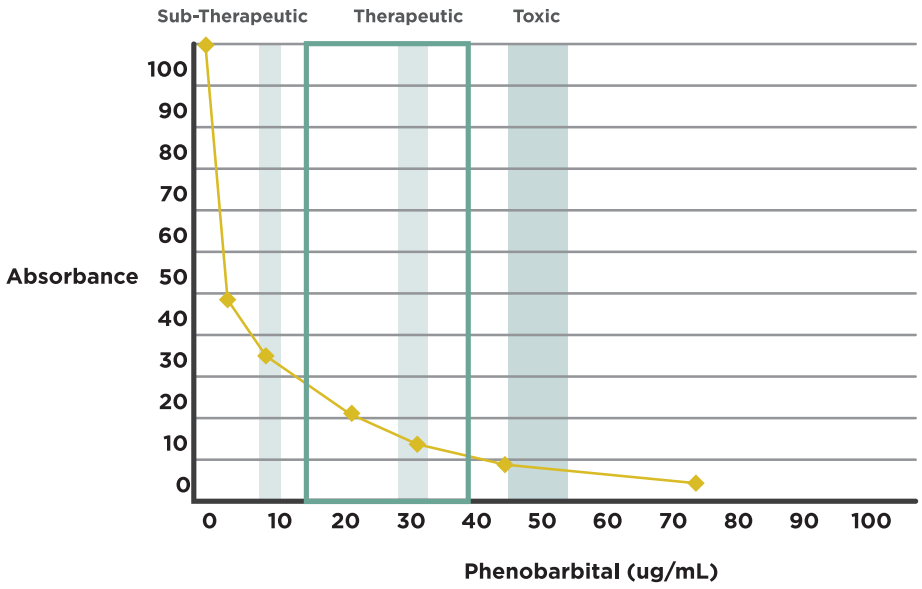


Figure 1

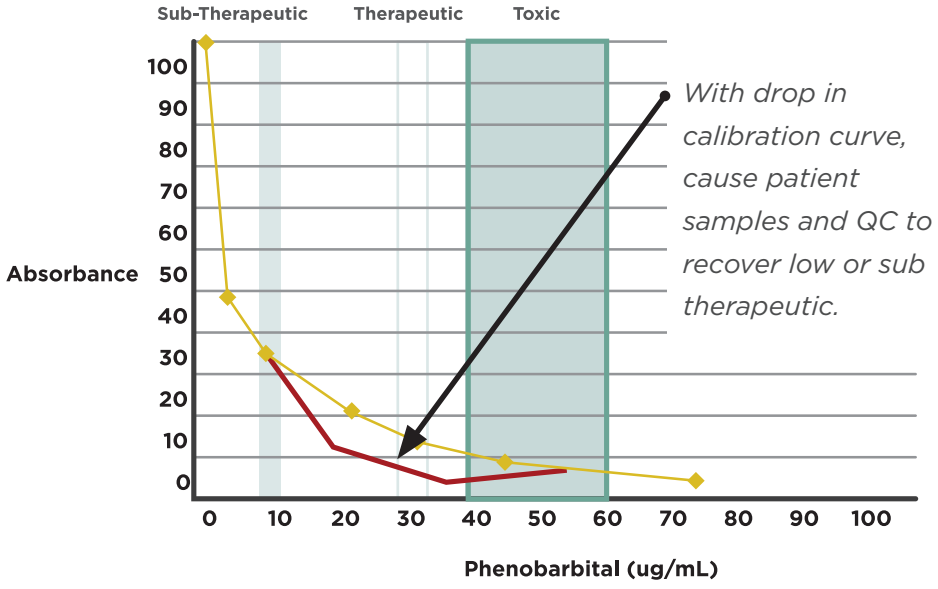


Figure 2

sub therapeutic value when, in actuality, it is therapeutic. The physician in seeing the result as sub therapeutic may increase the dosage which could subsequently move the patient into the toxic range.

Medically-relevant levels

Equally important as the number of analytes in a single control are the analyte values represented in the controls. It's easy enough to manufacture controls with very high and very low values, but those don't necessarily represent medically-relevant values. The utility of this type of control is limited at best. You want the control material values to run near the levels where medical decisions are being made.

Analytical measuring range (AMR) vs. QC levels

You may get confused about covering your working (or reportable) range of each test method with your control levels. Your QC values are more important for covering the medical-decision levels, not the entire reportable range. Your reportable range is established – and when necessary, verified – using patient samples or linearity kits, but you don't use control materials to do that. Target the most important medical decisions, or cutoffs, or diagnosis guidelines, with your control levels. Don't worry if there aren't control levels at extreme levels or edges of your range unless there are critical patient values in those regions.

Shelf life of control materials

One of the best aspects of modern control materials is the long shelf life which allows laboratories to purchase supplies in scale and enjoy efficiencies in storage, logistics, and pricing. For many controls, you can get a shelf life of a year or longer. Now, bear in mind a long shelf life isn't a pure benefit – it's only good if you will consume all the materials within that time period. Make sure the volume you use will allow you to consume all your control material in storage within their expiration dates. There's no benefit of a long shelf life if you end up disposing it because you don't use it all. Make sure to base your QC orders on the expected rate of consumption of the control materials.

Cross-over studies are not only time-consuming, but they are also expensive. The more studies you must perform, the more test reagent you are consuming. The cost of the control plus the test reagents can add up to hundreds, thousands, even tens of thousands of dollars every year. Thus, the longer the shelf life, the fewer cross-over studies are required which ultimately saves a considerable amount of money for the laboratory.

Open vial stability (OVS)

There is a difference in the "shelf life" and the "open vial" life. Both are important. Open vial stability refers to how long after the vial is open the control material is stable and produces optimal results before it deteriorates. Again, a longer open vial life will give you more time to utilize it. You don't want to waste control material because you can't consume the contents in the vial before its open vial expiration.

In other words, with shelf life and open vial stability, the best combination involves not just the control manufacturer, but also the number of tests, volume, and patient decision levels of the laboratory itself. A careful assessment of the decision levels, number of tests, and QC frequency will allow you to optimize your order, so you get maximum value out of your control materials.

QC Frequency – how often should you run controls?

As with the struggle over the number of levels of control to run, there are similar forces at play when it comes to the frequency of running QC. The regulations typically mandate a minimum of running two controls every 24 hours for many tests. For some specific tests, the frequency may be as often as running three controls every eight hours. But when you read the regulations, you quickly notice that there isn't any guidance on the rationale for once a day or three times a day QC. These are simply arbitrary requirements, representing a very bare minimum for compliance.

Should a laboratory running hundreds of tests and a laboratory running tens of thousands of tests have the same once-a-day QC frequency? Any objective assessment of quality would argue for running controls based more on the volume of testing – and the quality of the assays and the needs of the patients – rather than an arbitrary frequency over a 24-hour period.

Westgard sigma rules also aid in determining the frequency of QC runs per day. See page 19 of this workbook for more information.

Commutability, matrix, and matrix effects

Commutability is the ideal goal of any type of control. That is, the control material mimics as closely as possible a real patient sample. Good commutability means you can be confident that a warning result of your control run adequately alerts you that a potential instrument or test reagent malfunction could plague the patient samples too.

Commutability, of course, 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" [1]

Simply put, commutability is good, and it's what we seek in control materials.

The opposite of commutability is often referred to as a Matrix Effect (no, this is not the movie The Matrix with Keanu Reeves, this is the really nerdish, geeky, uncool Matrix). The matrix of a control is all the extra stabilizers, preservatives, and other ingredients present to support the analyte itself but 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 as a patient sample. In the worst case, the matrix of a control material will make the control behave differently than a real patient sample. In the worst-case scenario, this means a control results may be "out", but the analytic performance of patient results 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 need to avoid controls with heavily artificial matrices and need 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.

It is important for the laboratory to seek a control material that uses fresh, human-based materials. While it is impossible to find a QC vendor that produces a control that is 100% fresh human serum or plasma with optimal shelf life and open vial stability, the lab should look for a QC product that mimics the patient samples as much as possible.

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

Notes

Starting your QC: Quality Control Design

How to set ranges

Let's start at the very beginning. You have an absolutely new control – no previous lots, no previous data, nothing cumulative from the past. Today is the first day you're running it. How do you set up your ranges? [By ranges, we are referring to the mean, SD, and the Levey-Jennings chart, by the way. "Range" is a shorthand for a lot of different aspects of the QC chart setup.]

The best practice is to establish your own mean and SD over a period of 20 days for each level of control. Clearly, that means during the first 20 days of your new control, you're waiting for the mean and SD, but what are you going to use in the meantime?

This is where the package insert range is most valuable. If you have an assayed control, there is a data sheet supplied, either in digital format or on old-fashioned paper, providing expected or target means as well as standard deviations. If you have absolutely no other information, start by setting up your mean and SD with the information from this package insert.

[Fun fact: The mean and SD in the package insert are commonly determined by running the control on a number of instruments or by sending the control out to a select group of laboratories to run on their variety of instruments. So, the package insert SD is the standard deviation of that group of instruments around the mean of that group. Since it comprises multiple instruments, even multiple labs, the SD will be larger, possibly MUCH larger, than any individual laboratory's SD. Therefore, it is important to switch to your own SD as soon as possible after you have derived it from the data you have captured. The longer you use the package insert SD, the longer you are at risk of having your control limits too wide and missing significant errors. Okay, that's not so fun.]

So, once you have more complete data representing your control material's performance on your method on your instrument in your labs, start using that information. The best practice is to set up each method and each control level with its own mean and its own SD.

What if you want tighter ranges than offered in

the package insert but you, don't have 20 days to collect data?

If you need to establish your mean and SD in a shorter amount of time, you can consider running multiple controls over a shorter number of days: run four control runs per day for five days. Whatever estimates you get from this sprint, should be replaced with updated data as soon as you've been running for a month.

If you have a really short shelf-life control – this often happens with hematology control material – you may need to work with even shorter cross-over intervals.

1. Establish a new mean for the new control with 8-10 values run over a few days. This is statistically sound – you can establish a new mean with as few as eight values.
2. Pair up the new mean with the old CV, and then calculate new mean x old CV = temporary SD
3. As soon as you have enough data (about 20 measurements), calculate the new SD.

You now have the new mean and the new SD for your control charts

Continue to update the SD when you have the next month of data, and the next, until the expiration of the control.

Caution: Many labs believe that if the shelf life of a control is very short, they do not need to perform cross-over studies. Do not fall into that trap! You are required by regulation to establish ranges on all lot numbers prior to use. This is not only a good lab practice, it's essential risk management.

More caution: If control shipments are delayed or sit on the loading dock during excessive hot or cold weather, the only way to prevent that damaged control from going into use is the cross-over study. And from a regulatory perspective, the laboratory must have proper documentation of each new lot number on file for any surveyor request.

Longer term: switching to a new lot of QC

If you are starting a new control lot of a control material you've used recently, and you have experience with and historical data for the previous lot, you can consider using that historical mean and SD as a bridge to the new lot. Assuming these lots are manufactured with the goal of producing nearly identical performance, you can use the historical mean and SD until you have enough data to calculate the new mean and new SD. Again, 20-days-worth of data is preferred.

[Fun fact: different control lots, like different test reagent lots, are never truly identical. They will always be slightly different, but everyone hopes they are different in such minor ways that there is no clinical significance. You get to judge what constitutes a clinically significant difference.]

Multiple instruments: do we need multiple means or a single mean?

In the modern laboratory, it's increasingly common to have several instruments of the same manufacturer. There is a temptation to assume that all these instruments will have the same

mean and same SD, and it certainly could be more convenient to run all the instruments with one set of numbers.

However, we caution your lab to strongly consider the risk to this option. The convenience of having one set of numbers may be outweighed by the risk that you will miss true outliers or that simple instrument differences will present as false outliers.

Further, even if you move to a uniform mean and SD, you will have to constantly monitor that the group of instruments maintain its "uniformity". That means under the convenient unified mean and SD, you must still maintain a log of the individual mean and SDs of each test and instrument. So, you are doing more work than if you would simply maintain the individual mean and SDs of each instrument. Is the superficial similarity worth the additional effort? This is ultimately the decision of the laboratory professional.

Frequent Questions about QC Design

Uncomfortable question: What if your range doesn't match the package insert range?

Remember the range on your package insert is meant to be a guide. Your mean should fall within the package insert range, but the range of values represented by the SD and mean is not required to fall within the package insert range.

If your mean is not within the package insert range, you should examine your method, confirm that you stored and processed the control correctly, etc. If you can eliminate any internal causes, then contact the control manufacturer to ask if there are any other similar reports of the new control lot. If the control lot is found to be the source of the problem, a replacement control lot should be sought.

Uncomfortable question: Should I use my controls to determine the acceptability of new test reagent lots?

Controls are often used to handle the evaluation of new test reagent lots. It's tempting to apply the same protocol for lot-to-lot variations among control lots to the lot-to-lot variations in reagent lots. But the latest advice from CLSI EP26 on handling lot-to-lot variation for reagents emphasizes the use of patient specimens, not control materials. If the patient specimens show there is a significant change from lot-to-lot, that is grounds for concern about the new reagent lot. If the patient specimens show no significant change, but the control mean has changed on the new reagent lot – you should reassign the mean. The patient analysis has shown you that the mean of the control lot has changed, but it's not a clinically significant change.

Therefore, you want to use quality control material that is as commutable as possible. This will prevent the occurrence of a QC shift vs. patient samples recovering the same when comparing data from the old test reagent lot to the new lot, prior to use.

Uncomfortable question: Should I use allowable total error (TEa) to set my ranges?

Allowable total error is a quantity used in assessing external quality assurance, proficiency testing, and analytical Sigma-metrics. It is not directly applied to a Levey-Jennings chart. It is not to be used as an SD or range setting. Do not even use a fraction of the allowable total error as an SD on your Levey-Jennings chart. That is like confusing

the maximum speed listed on your speedometer (the dial) as the recommended actual operating speed (the needle). One is a performance capability; the other is actual performance. You want the QC chart to reflect how your laboratory is actually operating. And you don't want to be running at full speed – consuming every possible component of operating error to the maximum.

Uncomfortable question: What do I do if I notice that it appears that I have significantly different performance in my historical data?

This may occur within the data collection timeframe where there was a change in the test system that caused different results to be generated. This may be due to a shift with a new test reagent lot, implementation of a new component to the test system, operator technique, or some other issue. Remember that whatever you calculate for your current mean, it should only reflect the current performance. If, in the past, there was significantly different performance that does not reflect the current state, that data should not be included in your calculations.

Uncomfortable question: When adjusting our ranges and mean, how much is too much?

How often should you adjust your mean? As often as is necessary, but not more. That's easy to say, but hard to determine when it is truly the right time to make an adjustment. Let's begin by stating that every time a peer group mean changes, that doesn't mean an individual laboratory should change their mean, too. Of course, when you have a QC rule failure, the laboratory will troubleshoot extensively to uncover the root cause of the issue. If the error is significant (and definitely not random, but truly systematic), once it is fixed, the method is now in a new state. If your trouble-shooting uncovers a serious problem, something that needs to be replaced, etc., you're definitely breaking from previous history. Therefore, we will need a new mean, possibly a new SD, to match that new state.

Notes

Self-Pace Exercise # 1:

You have collected the following data in your 20-day cross-over study and recorded the following supporting data.

	Level 1 Instrument A	Level 1 Instrument B	Package Insert Mean	Package insert Range	TEa +/- 3S
Mean	10.48	11.32	11.5	8.4 -14.6	-
SD	0.15	0.12	-	-	-
CV	1.43	1.06	-	-	-
N	20	20	-	-	-

How would you set your ranges using the following information?

1. Do both instrument values fall within the package insert range?

   Yes

   No

2. Previous lot had the following cumulative information:
   - Old lot mean for instrument A = 11.1, Old lot SD = 0.15, old CV = 1.35
   - Old lot mean for instrument B = 12.6, old lot SD = 0.14, old CV = 1.11

   a. What would you choose for instrument A's new control lot mean based upon the table above?

   b. What is instrument A's SD for the new lot using the CV of old lot?

   c. What would you choose for instrument B's new control lot mean based upon the table above?

   d. What is instrument B's SD for the new lot using the CV of old lot?

3. Using the calculated mean and SD, what ranges would you apply to both instruments.

   a. Instrument A: +/- 2 SD range:

   _____

   b. Instrument B: +/- 2 SD range:

   _____

Answer Key: Page 29

Westgard Rules: When to use them and why

[Fun Fact: A majority of labs worldwide still use the 1:2s rule in their QC protocol. Many labs still use the 1:2s as their only QC rule. Despite half a century of experience and all the statistical knowledge that informs us about ruinous false rejection rates (nearly 10% false rejection rate if you run two controls; nearly 15% false rejection rate if you run three levels of control!), this simplistic approach to QC has endured as a tradition at the bench level. Again, this is not-so-fun fact is a practice that creates a lot of extra, unnecessary effort and frustration in the lab.]

The Westgard Rules were introduced back in 1981 as a solution to the 1:2s rejection rule, and a way to reduce false rejections without compromising error detection. It converted the 1:2s from a rejection rule into a warning rule. Modern versions of Westgard Rules have eliminated even the 1:2s warning rule. The latest advice is, “Don’t wait for a warning to sound. Interpret the rejection rules directly with every control result.”

The table opposite represents 30 runs of a bi-level quality control product. The z-score is another term for Standard Deviation Index (SDI). This z-score or SDI will calculate the positive or negative bias with each level of control as compared to the mean and SD. For example, run # 1 shows that level 1 has a z-score of -0.5. That means if we looked at the Levey-Jennings plot for this level, the data would be plotted at 0.5 SDs below the mean value. The level 2 control shows the same negative bias, but the point is plotted on its Levey-Jennings chart 0.36 below the mean.

In the Basic QC workbook, you can find very detailed discussions of the rationale and evolution of Westgard Rules.

Westgard Rules are a useful tool to maximize error detection while minimizing false rejection. Each of the rules can help you determine whether the error you are experiencing is a random or a systematic error.

The more advanced use of Westgard Rules is to utilize Six Sigma and each assay’s analytical Sigma-metric to determine that appropriate Westgard rule. This advanced usage is known as Westgard Sigma Rule.

Self-Pace Exercise # 2:

Record any rule interpretation based upon the Westgard rule violated and whether you would hold patient results. The following Westgard Rules should be used for this exercise: 1_{2s} (warning), 2_{2s} (reject), 1_{3s} (reject), 10x (warning), and R_{4s} (warning).

Values	Level 1 Z Score	Level 2 Z Score	Rule Interpretation
Run 1	-0.5	-0.36	
Run 2	0.33	-3.21	
Run 3	-1.8	0.4	
Run 4	2.33	-0.2	
Run 5	2.16	1	
Run 6	-0.33	-0.2	
Run 7	-0.1	-0.2	
Run 8	2.33	-2.8	
Run 9	0	0.2	
Run 10	0.67	1.2	
Run 11	-1.83	2.2	
Run 12	0.67	-1.6	
Run 13	-1.1	-1.4	
Run 14	-1	-1	
Run 15	-0.33	1	
Run 16	1.83	-0.4	
Run 17	1.33	-0.6	
Run 18	-0.67	-0.8	
Run 19	0.33	-1	
Run 20	0.67	-0.2	
Run 21	1.33	-0.8	
Run 22	-0.33	-0.2	
Run 23	-1.33	-1	
Run 24	0.67	0.8	
Run 25	-1	-0.8	
Run 26	0.4	0.2	
Run 27	-0.6	-1	
Run 28	0.3	1.2	
Run 29	-1.33	-0.4	
Run 30	-1	0	

Self-Pace Exercise # 3:

Below are two Levey-Jennings charts for two levels of a control product for a certain test. The graph from each day's QC result is plotted based upon the SDI or z-score value. Based upon these two charts, please note what day's QC results failed any of the Westgard Rules:

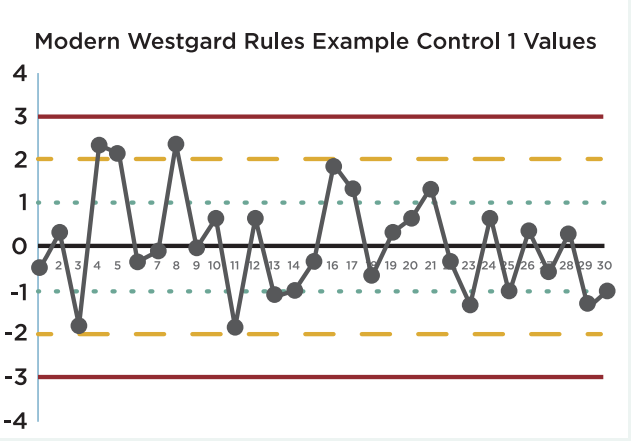
1:2s: _____

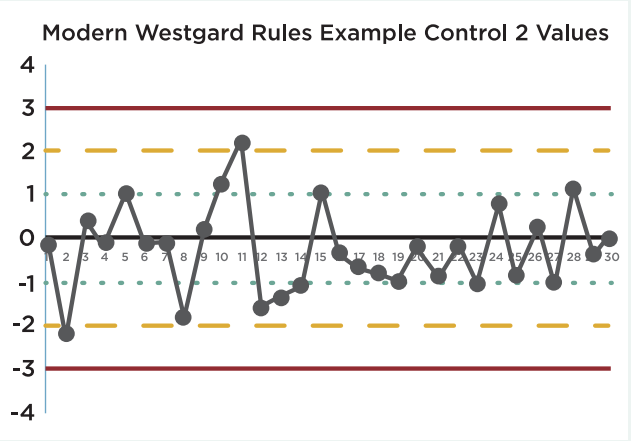
2:2s: _____

1:3s: _____

10x within run: _____

R:4s: _____





Answer Key: Page 29

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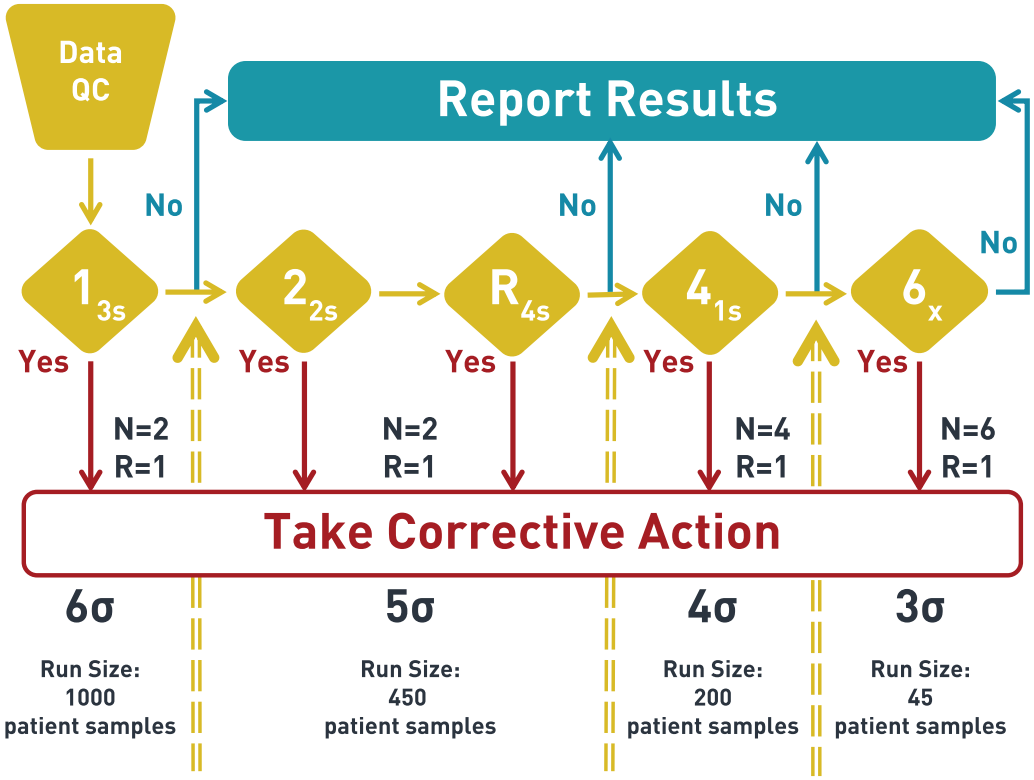


A discussion of how to calculate the analytical Sigma-metric of an analyte is included later in this workbook.

If you can determine the analytical Sigma-metric of your analyte, 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 1:3s rule and two control levels. As your sigma-metric is lower, you need more Westgard Rules, until at Three-Sigma, you need all the Westgard Rules and need to increase the number of control measurements you are making.

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 have to trouble-shoot. This can reduce both test reagent and control costs as well as labor cost.

Checking on your QC: Beyond the dot-to-dot

While your bench-level specialists and technologists are in charge of reviewing each new control point and thus, each new dot on the Levey-Jennings chart, there is a higher-level review which you or someone you designate should conduct periodically. Typically, there is a monthly QC review, where additional actions are evaluated.

- Review the observed mean, observed SD and CV of the entire month.
  - » How does it compare to the package insert mean and SD? (Hint: Your mean should still be within the package insert range)
  - » How does it compare to peer group mean

and peer group SD? (Hint: your individual SD should be smaller than the peer group SD)

- Review Levey-Jennings charts to evaluate outliers, shifts, trends.
  - » Did your staff miss any random or systematic errors?
  - » Are there some errors occurring more frequently this month?
  - » Review the bench-level actions.
  - » Is everyone running QC when they are supposed to?
  - » Are some technologists repeating and repeating controls to get them in range?
  - » Are all troubleshooting actions being logged?
  - » Are the technologists interpreting rule violations correctly?
  - » Are the technologists troubleshooting correctly?
- Are multiple instruments of the same manufacturer still performing similarly?
  - » Have you run split patient specimens this month to check this performance?
    - Split patient samples are aliquots of a single patient specimen run on all the similar instruments.
  - » Are individual means, SDs and CVs still similar?
- Review the instrument history.
  - » Has maintenance been performed in the last month?
  - » Have any calibrators, reagents, or parts been changed?
  - » Are there any alerts from the manufacturer?
  - » Has the peer group report shown any changes in performance?
  - » Has the EQA/PT report shown any changes in performance?

These are just some of the things a QC Review should consider. For problematic tests that generate an outlier more than once a week, you shouldn't wait a whole month before conducting this kind of review.

The main thing you are doing with this review is trying to look at the bigger picture, trying to connect other events in the laboratory with any changes you've seen in QC, and to identify patterns over a longer time-frame than just the run-to-run, dot-to-dot perspective.

While this review can be conducted by section heads or QC specialists, the summary should at least be reviewed by the Director and signed each month.

Self-Pace Exercise # 4:

Using data from example one above, review the actions taken by the bench technologist for troubleshooting as noted below.

Remember, the following Westgard Rules were used for this exercise: 1_{2s} (warning), 2_{2s} (reject), 1_{3s} (reject), 10x (warning), and R_{4s} (warning). Are these actions correct?

Values	Level 1 Z Score	Level 2 Z Score	Technologist Action	Action Correct?
Run 1	-0.5	-0.36	Accepted	
Run 2	0.33	-3.21	Repeat L2	
Run 3	-1.8	0.4	Accepted	
Run 4	2.33	-0.2	Repeat L1	
Run 5	2.16	1	Accept	
Run 6	-0.33	-0.2	Accept	
Run 7	-0.1	-0.2	Accept	
Run 8	2.33	-2.8	Accept	
Run 9	0	0.2	Accept	
Run 10	0.67	1.2	Accept	
Run 11	-1.83	2.2	Accept	
Run 12	0.67	-1.6	Repeat L2	
Run 13	-1.1	-1.4	Accept	
Run 14	-1	-1	Accept	
Run 15	-0.33	1	Accept	
Run 16	1.83	-0.4	Accept	
Run 17	1.33	-0.6	Accept	
Run 18	-0.67	-0.8	Accept	
Run 19	0.33	-1	Accept	
Run 20	0.67	-0.2	Accept	
Run 21	1.33	-0.8	Accept	
Run 22	-0.33	-0.2	Accept	
Run 23	-1.33	-1	Accept	
Run 24	0.67	0.8	Accept	
Run 25	-1	-0.8	Accept	
Run 26	0.4	0.2	Accept	
Run 27	-0.6	-1	Accept	
Run 28	0.3	1.2	Accept	
Run 29	-1.33	-0.4	Accept	
Run 30	-1	0	Accept	

Answer Key: Page 29

Notes

Even more advanced statistics

(Oh no, do we really need to know these things?)

Analytical Sigma-metric

This concept has been mentioned before in both the Basic QC workbook and in this Advanced QC workbook. This is an application of the Six Sigma theory which has been used successfully in industry, business, and healthcare for decades. But we're going to skip all the traditional Six Sigma theory – we don't have space to describe it here, and you don't have the time to learn about 40 years of quality management evolution – so don't worry about learning about green belts, black belts, and master black belts. We're skipping the belts and some of the more colorful (read: extraneous) elements of Six Sigma. We're going to focus on the core idea: quantifying, identifying, and eliminating defects in your processes.

Six Sigma is really just a scale for benchmarking. If you have a Six Sigma process, you're getting just under four defects-per-million outcomes of a process – or less than four false positives, false negatives, or errors-per-million reportable results.

That's really good. When the creators of Six Sigma reached it in their processes, they found they had very happy customers, a very reliable product, and a very efficient profitable operation. Labs implementing Sigma-metrics have found the same thing: reduced effort, reduced errors, reduced expenses, all while delivering better, more effective, more accurate, and more timely results to patients.

Analytical Sigma-metric Equation

$$\text{Sigma-metric} = \frac{(TE_a - \text{Bias})}{CV}$$

Where:

TE_a = Total Allowable Error

Bias = inaccuracy

all variables expressed in %

For the laboratory, the analytical Sigma-metric is built on three variables:

- Allowable Total Error (TEa): this is a performance specification, or, if you prefer other words – a quality goal. This is how good your test should be, and when it isn't, it means you are in danger of producing false positives and false negatives.
- CV: We've gone over this before. It's your observed imprecision.
- Bias: We've also gone over this before. It's your trueness, or if you like older terms, your inaccuracy.

You may quickly notice that two of the three variables are already routinely collected by your lab. You run controls at least daily, so you're already determining your imprecision (your CV). You are participating in an external quality assurance/proficiency testing (EQA/PT) program, or in a peer group, or you're comparing your observed mean against the control package insert mean, so you have a way to determine your bias. Sigma-metrics simply leverages your data on the observed performance of your method and places it into the context of a universal scale.

Allowable Total Error (TEa)

The TEa is the trickier part, but it's really not that hard. For labs in the US, CLIA has directly specified the allowable total error for more than 80 analytes in the PT criteria. The same goals that you are using to judge whether you are going to pass or fail your EQA/PT are TEa goals. So, there are goals for analytes in the CAP survey, in EQA/PT programs all over the world. All you have to do is look them up – and most of them can be found easily online.

When you have a choice of TEa goal – not all EQA/PT programs agree about the performance specifications they set – you want to evaluate the needs of your patients to choose the most appropriate goal. Don't automatically choose the biggest or the smallest – that may not be right for your patients. Industry leaders have tried to sort through the different resources to find challenging, but not impossible goals.

You may be familiar with a set of allowable total errors derived from biological variation. These were informally known as the "Ricos goals" in honor of Dr. Carmen Ricos of Spain who originally organized the group of scientists who compiled a global database of biological variation. Dr. Ricos led the group until about 2014. The theory behind this database is that by assimilating all the information we know about within-subject and within-group biological variation for any analyte, we can scientifically determine how good any measurement of that analyte should be (simply put, our analytical methods should have only a fraction of the biological variation for each analyte, otherwise we're adding more noise rather than generating a signal). The good news is that the Ricos 2014 database is available for free online and covers more than 350 analytes. A new database organized by the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) is also available, which covers, at the time of this booklet printing, about 80 analytes. The bad news about all the biological variation data, regardless of the source, is that for some analytes, the performance specifications are impossible to achieve. No method on the market currently can hit the electrolyte goals for performance as derived from EFLM or Ricos databases. The EFLM has recognized that even

as they update and expand their biological variation database, that may only reveal that there are analytes where the biologically derived performance specifications are impossible to hit by any of today's diagnostic manufacturers. So, don't simply choose all biological goals to set for your analytical performance.

The other good news hidden in there is that labs do not have to conduct their own biologic variation studies to set their performance goals. Evaluate the current biologic goals, see if they are appropriate, and if they aren't, look to other sources of performance specifications.

Stepping back a bit, you may also be familiar with the term Total Error, which is related to but not the same as Allowable total error (TEa). Total Error was one of the first estimates of combined imprecision and inaccuracy, first published in the 1970s. Approximately, Bias + 2 * SD, it represents a worst case scenario of test results. Decades ago, you compared your Total Error against your Allowable Total Error, and as long as the former was smaller than the latter, you were fine. However, since the turn of the century, the Six Sigma approach is more appropriate for today's laboratories and their quality management. Given today's higher volume and greater accuracy needs of patient care, using the analytical Sigma-metric is a better way to manage your QC.

Crunch the numbers! An actual analytical Sigma-metric example.

Let's take the following ALT data.

Analyte: Alanine Aminotransferase (ALT), U/L											
	Monthly Lab Stats						Peer Stats				
	Level	Mean	SD	%CV	N	Peers	Mean	SD	%CV	N	Peers
Test System Peer	Level 1	28.40	1.199	4.22	335	64	28.23	1.364	4.83	2432	77

The laboratory's control at level 1 has a monthly mean of 28.4, compared to a peer group monthly mean of 28.23. That control is showing a difference of

(28.4-28.23)/28.23 = 0.17 / 28.23 = 0.006 or 0.6% bias.

[**Note** if the bias had been negative, we would still have converted it into an absolute value. Sigma-metrics always plan for the worst-case and does not assume that in some situations a bias will cancel out some of the imprecision or vice versa.]

The laboratory's monthly imprecision of that control is 4.22%.

The TEa for this analyte is 25%.

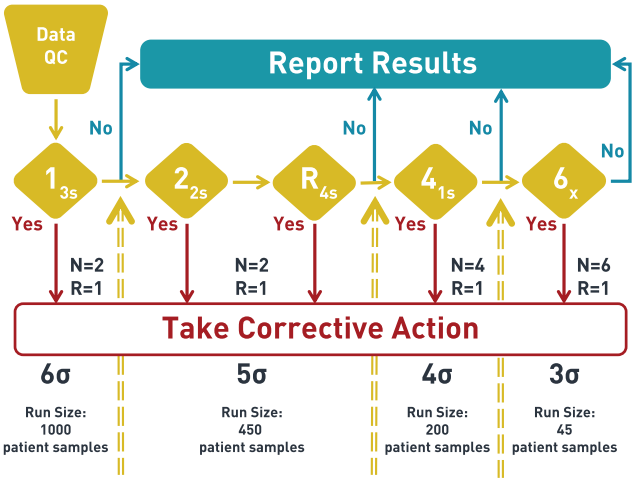
Now we have all the elements necessary to calculate an analytical Sigma-metric.

Sigma-metric = (TEa – bias%) / CV
= (25 - 0.6) / 4.22
= 24.4 / 4.22
= 5.78

ALT, at this decision level and at this time, is performing at an excellent level on the Six Sigma scale since the calculated sigma is 5.78 and therefore rounded to 6.0. A six sigma result is considered world-class.

Now that you have your Sigma-metric, what next?

The Sigma-metric allows you to make design choices for your QC rules and frequency. The Westgard Sigma Rules are the easiest tools to convert a Sigma-metric into actions you can take in your laboratory.



Self-Pace Exercise # 5:

QC rules: 1_{2s} warning, 2_{2s} run rejection, 2_{2s} run rejection, 1_{3s} run rejection, 10x run rejection.

Situation # 1:

Sigma score is 7.2. Based upon the action above, which Westgard rule(s) could you implement?

_____

Situation #2:

Now, let's assume that the sigma score is 4.1. Which Westgard rule(s) could you implement?

_____

Sigma scores can be used when comparing like instruments and tests.

Analyte	Instrument	Level 1								Level 3							
		Mean	SD	% CV	Peer Avg mean	% bias	% TEa	Sigma Calc	Sigma Score	Mean	SD	% CV	Peer Avg mean	% bias	% TEa	Sigma Calc	Sigma Score
ALT	1	28.40	1.20	4.22	28.23	0.6	25	5.78	5	249.8	3.2	1.28	240.92	3.69	10	4.92	4
ALT	2	28.38	1.17	4.12	28.23	0.52	25	5.98	5	249.7	3.3	1.32	240.92	3.64	10	4.81	4

When we compare the performance of Aspartate Aminotransferase (AST) for both instruments, we see the following data:

Analyte	Instrument	Level 1								Level 3							
		Mean	SD	% CV	Peer Avg mean	% bias	% TEa	Sigma Calc	Sigma Score	Mean	SD	% CV	Peer Avg mean	% bias	% TEa	Sigma Calc	Sigma Score
AST	1	36.83	0.75	2.04	36.4	1.2	20	9.2	6	273	0.89	0.33	267.46	2.07	20	54.72	6
AST	2	36.23	0.44	1.21	36.4	0.45	20	16.15	6	266	1.41	0.53	267.46	0.54	20	36.59	6

Notice how the two instrument's ALT results generate similar calculated sigma scores for both levels of QC. Also, notice, that you can apply different TEa limits for different levels of QC.

Answer Key: Page 29

How often should you calculate the Sigma-metric?

Once you know the (relatively) easy way of calculating the Sigma-metric, you may be tempted to calculate it every day. Your software may even be able to update the Sigma-metric with every new control data point. But don't chase the metric every day. It's most useful to re-visit the Sigma-metric about once a month, or even quarterly. Particularly when you have high Sigma-metric performance, you will see steady performance and you won't be changing your QC rules every day, week, or month. You may not even need to change your QC rules for years at a time if you are so fortunate to have a world -class assay or instrument.

That said, if some major event happens – a replacement of the internal mechanics, a new lot of reagent, a serious error condition, etc. – common-sense dictates that we should re-establish our mean, our SD, and our Sigma-metric.

Reference Change Value (RCV)

This is a statistic that is useful not in the management of QC, but in the interpretation of patient results. It is sometimes called the Critical Difference. It represents the smallest change between two serial patient results that is nevertheless a clinically important difference. This formula can be seen immediately below.

When comparing two results on the same patient, if the difference between them is less than the RCV, there is no reason to believe anything has changed clinically with the patient. If the difference between the two results is greater than the RCV, then the clinician can have confidence that something clinical has changed in the patient. The RCV is useful for helping clinicians focus on the most important test results.

But again, this is a reporting and interpretation tool, not a tool to determine the acceptability of the method or to monitor the analytical state. It is listed here mainly because many use this as a quality assurance check on the test system.

Reference Change Value

$$RCV = \sqrt{2} * Z * \sqrt{CV_a^2 * CV_i^2}$$

Where:

Z value of 1.65 to represent 95% probability

CV_a = analytical imprecision

CV_i = within-subject biological variation

RCV may also be used when monitoring delta checks in your laboratory as a quality assurance monitor. Delta checks are useful for detecting pre-analytical (specimen identification or specimen integrity errors), analytical errors, and post-analytical errors. For example,

A delta check flag occurred for ALT when comparing the first patient result 12 hours ago as 19 IU/L to their most recent value of 25 IU/L. Is this a true medically-relevant change in the patient or just the noise of day to day measurement? Given the within-subject

biological variation of ALT, according to the Ricos 2014 database, is 19.4%, and also given that the ALT method has an 8% imprecision, the following calculation for RCV can be performed:

RCV = ($\sqrt{}$ 2) x 1.65 x ($\sqrt{}$ $CV_{imprecision}^2$ + $CV_{individualbiologicalvariation}^2$)

= 1.41 x 1.65 x $\sqrt{}$ (82 + 19.42)

= 1.41 x 1.65 x $\sqrt{}$ (64 +376.36)

= 1.41 x 1.65 x $\sqrt{}$ (440.36)

= 1.41 x 1.65 x 20.98

= 48.82 %

Interpretation of RCV:

Percent change of ALT result from

19 to 25 = (25-19)/19 = 6/19 = 31.57%

With the test change of 31.57% and because 31.57% is less than the RCV of 48.82%, the change in values may simply be a result of analytical imprecision and within-subject biological variation.

Measurement Uncertainty (MU)

This is a much-debated statistic, and paradoxically, it is basically unknown within the US, while outside the US it is a mandated requirement. ISO 15189 and all derivative accreditation guidelines, requirements, and regulations mandate that every method should determine MU, and report it to clinicians. In practice, labs often comply by calculating MU, showing it to the inspector, and possibly never doing another thing. It's a statistic more honored in the breach than in the observance. Labs generate it, as they are required to, but mostly ignore it. A few labs enjoy the additional rigor of calculating and using measurement uncertainty. There are many ways to calculate measurement uncertainty, and it seems more methods to calculate are published every day.

At its simplest, MU is your intermediate imprecision, and your expanded uncertainty is 2*CV.

There are more texts and publications that take MU very seriously, but these are beyond the scope of this workbook. If you are governed by an ISO 15189 standard, you need to calculate MU, but you only have to satisfy the inspector. If you find the statistic mystifying or unhelpful, don't use it any further than compliance.

Moving Averages and Exponentially Weighed Moving Average (EWMA)

There are still more patient-based techniques that are useful to employ in concert with traditional QC. Moving Averages, Average of Normals, Patient-based QC, these are all terms that apply to a set of "normal" patient specimens that are averaged continuously to monitor the stability of the method. The trickier part is filtering out all the abnormal patient values and determine how many patient specimens need to be combined to generate the average. The EWMA uses a weighting that values the more recent values more than the older ones. The technical details are beyond the scope of this workbook, but these techniques, if you have the informatics architecture to support the calculations, are a useful complement to traditional QC. Moving Averages are often described as "real-time" QC, since the results are far more immediate than the periodic traditional controls that are run.

Think of Moving Averages as a light on the dashboard of your car. Once you see this light, you take the car to the mechanic to get more sophisticated tests run on the car and usually obtain a better assessment of the problem. Moving Averages are the dashboard lights whereas the QC analysis will usually be a better assessment of the problem. Labs using Moving Averages can track instrument performance between QC events. But, if the Moving Average indicates a true change in normal patient results, it is highly recommended that the lab run the quality control material to better ascertain what kind of problem is impacting the test result.

Wrapping up

Advanced QC means more planning before the actual QC material is run and the data captured, and more planning to utilize additional techniques after the QC is run, with the goal of reducing how much effort you expend on all of these processes.

So how do you take your QC to the next level of laboratory operations?

Make sure the basics of quality control are known and faithfully and correctly implemented. But invest time before you run QC – in the selection of the control material and training of the staff, in the construction and set up of the Levey-Jennings charts. The act of quality control is compromised if we start out with inferior controls, or the wrong ranges and limits, or the wrong rules.

Make sure you also invest in what you do beyond QC, such as Sigma-metrics, RCV, Moving Averages, EWMA, etc. You can maximize the usefulness of your outputs with these additional, complementary statistics. Remember, however, that while RCV and Moving Averages can add value to basic quality control, they can't replace it.

The ultimate goal of this workbook is to make sure you get maximum benefit from your QC processes, with no wasted effort. Through the Sigma-metric approach, you can optimize and customize your rules, controls, and frequency, so you aren't "over-controlling" methods that are highly reliable, and you aren't "under-controlling" methods that are more unstable.

There are more resources available to you on all of these subjects online.

Thanks for spending time with this workbook and course materials.

Self-assessment Quiz - Answer Key

Exercise 1:

Q1: Do both instrument values fall within the package insert range?

Answer: Yes.

Q2a: What would you choose for instrument A's new control lot mean based upon the table above?

Answer: 0.48.

Q2b: What is instrument A's SD for the new lot using the CV of old lot?

Answer: 0.14.

Q2c: What would you choose for instrument B's new control lot mean based upon the table above?

Answer: 11.32.

Q2d: What is instrument B's SD for the new lot using the CV of old lot?

Answer: 0.13.

Q3 Using the calculated mean and SD, what ranges would you apply to both instruments.

Answer 3a: Instrument A: +/- 2 SD range: 10.20 to 10.76.

Answer 3b: Instrument B: +/- 2 SD range: 11.06 to 11.58

Exercise 2:

Record any rule interpretation based upon the Westgard rule violated and whether you would hold patient results. The following Westgard Rules should be used for this exercise: 1_{2s} (warning), 2_{2s} (reject), 1_{3s} (reject), 10x (warning), and R_{4s} (warning).

Answer:

Run 2: 1_{3s} Reject
Run 4: 1_{2s} Warning
Run 5: 2_{2s} Reject
Run 8: 2_{2s} Reject
Run 11: 1_{2s} Warning

Exercise 3:

Below are two Levey-Jennings charts for two levels of a control product for a certain test. The graph from each day's QC result is plotted based upon the SDI or z-score value. Based upon these two charts, please note what day's QC results failed any of the Westgard Rules:

Answer:

1_{2s}: 4, 11
2_{2s}: 5, 8
1_{3s}: 2
10x within run: R_{4s}: 4, 12

Exercise 4:

Using data in example one above, review the actions taken by the bench technologist for troubleshooting. Remember, the following Westgard Rules were used for this exercise: 1_{2s} (warning), 2_{2s} (reject), 1_{3s} (reject), 10x (warning), and R_{4s} (warning). Are these actions correct?

Answer:

Run 1	Yes
Run 2	Yes
Run 3	Yes
Run 4	Yes
Run 5	No- repeat level one
Run 6	Yes
Run 7	Yes
Run 8	No- repeat both levels
Run 9	Yes
Run 10	Yes
Run 11	Yes
Run 12	No- no need to repeat
Run 13	Yes
Run 14	Yes
Run 15	Yes
Run 16	Yes
Run 17	Yes
Run 18	Yes
Run 19	Yes
Run 20	Yes
Run 21	Yes
Run 22	Yes
Run 23	Yes
Run 24	Yes
Run 25	Yes
Run 26	Yes
Run 27	Yes
Run 28	Yes
Run 29	Yes
Run 30	Yes

Exercise 5:

QC rules: 1_{2s} warning, 2_{2s} run rejection, 2_{2s} run rejection, 1_{3s} run rejection, 10x run rejection.

Situation # 1: Sigma score is 7.2. Based upon the action above, which Westgard rule(s) could you implement?

Answer: 1_{3s}

Situation #2: Now, let's assume that the sigma score is 4.1. Which Westgard rule(s) could you implement?

Answer: 1_{3s}, 2_{2s}, R_{4s}, 4_{1s}

Glossary

Allowable Total Error (TEa) encompasses the imprecision and bias of a single test measurement. It is a quantity used in assessing external quality assurance, proficiency testing, and analytical Sigma-metrics.

Analytical measuring range (AMR): this is the same as your working or reportable range for each assay in your laboratory. This is the range of values the method is able to report patient and quality control samples. Your controls should recover close to key medical decision levels or cutoff levels.

Analytical Sigma-metric: leverages the observed performance of your method and places it into the context of a universal scale. This is frequently referred to as Six Sigma or Sigma-metric.

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.

Exponentially Weighed Moving Average (EWMA) or sometimes called **Moving Averages,** Average of Normals, Patient-based QC; these are all terms that apply to a set of "normal" patient specimens that are averaged continuously to monitor the stability of the method.

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.

Measurement Uncertainty (MU): is your intermediate imprecision, and your expanded uncertainty is 2*CV. ISO 15189 and all derivative accreditation guidelines, requirements, and regulations mandate that every method should determine MU, and report it to clinicians.

Multi-analyte controls: These are control products with more than one analyte. The goal of the laboratory is to utilize control materials that cover as many analytes as possible. This will allow for the reduction of the single analyte controls and therefore saving the lab time in processing many vials of controls, managing all the lot numbers and expiration dates, and performing multiple cross-over studies throughout the year.

Open vial stability: Refers to how long the control material, once opened, is stable and produces optimal results before it deteriorates. A longer open vial life will give you more time to utilize it.

QC design: This is planning and designing QC procedures for maximum error detection, minimum false rejection, and optimum efficiency. The design should take into effect the appropriate mean, ranges, appropriate rules, frequency of control testing, consideration on patient testing volume, quality of the assay itself, etc.

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”.

Reference Change Value (RCV): smallest change between two serial patient results that is nevertheless a clinically important difference

Shelf life: This is the length of time that the product remains stable. The product should not remain in use in the laboratory past the expiration date unless approved by the manufacturer. Labs must maintain a copy of the manufacturer’s extension letter for future inspection needs.

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

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.

Total Error (TE) is related to but not the same as Allowable total error (TEa). Total Error was one of the first estimates of combined imprecision and inaccuracy, first published in the 1970s. The net or combined effect of random and systematic errors.

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.

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P.A.C.E Continuing Education Assessment

Each person may receive three (3) P.A.C.E. contact hours of continuing education credit by studying this workbook, performing the study questions, and returning the completed final assessment to:

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Advanced QC Workbook PACE Continuing Education Test Contact Hours: 3

1. **What's the downside of having controls at extreme levels but not at medically relevant decision levels?**
   a. Controls might be out, but patient samples might be perfectly fine
   b. Controls might be fine, but patient samples are experiencing a significant error
   c. All of the above

2. **Do you need controls running at the very lowest and highest levels of the range of the test?**
   a. Only if those levels are medically relevant
   b. Only if those levels are medically irrelevant
   c. Only if those levels are measurement uncertainty
   d. Only if those levels are moderate complexity

3. **When aligning your control material usage to your shelf life, you want to your use of controls to**
   a. Exceed the shelf life of the controls
   b. Match the shelf life of the controls
   c. Fall short of the shelf life of the controls.
   d. All of the above

4. **What aspect of the control material characterizes how long you can use the material once you have opened it?**
   a. Open Source
   b. Open Book
   c. Open Vial
   d. Open Sesame

5. **Commutability means...**
   a. Technologists can easily commute to work
   b. Technologists gain a superpower that allows them to change controls into patient samples
   c. Controls mimic patient samples
   d. Technologists gain the power to commute prison sentences

6. The Matrix of a control is...

a. Stabilizers, preservatives, and other additives that make the control Less similar to a patient sample.

b. Aspects of artificial reality that make it Less likely people will wake up and fight their robot overlords

c. Aspects of a control material that make the control More similar to patient samples

7. When is the best time to use the package insert range of a control?

a. When the control has expired

b. When you have accumulated 3 to 6 months of performance data

c. When you have accumulated 20 days of performance data

d. When you have no other information

8. Once you have calculated the mean and SD over the first 20 days, when should you update or change the mean and SD?

a. As soon as the control lot expires

b. As soon as you have a new control lot

c. As soon as you have peer group means and SDs to use instead

d. As soon as you have more data, an additional month, or an additional 2 months, etc.

9. What is the danger of having one common mean and a common SD for a group of instruments?

a. Small SD may generate more outliers

b. Large SD may miss errors

c. Mean too high may generate more outliers

d. Mean too low may generate more outliers

e. All of the Above (and possibly more)

10. If your control material has a matrix issue, what is the problem that could emerge during a reagent lot change?

a. Control will indicate a shift, but patients will not change.

b. Control will not change even when patient values are shifted

c. Either of the above

11. When the control material has a short shelf life, you should not perform:

a. Eliminate the practices of performing cross over study.

b. Notate the date when the control vial when put in use

c. Track performance in the control in the QC Data Management program/record.

12. After completing the new lot's crossover study, you notice that your calculated mean is not within QC vendor's package insert range. What are appropriate action(s)?

a. Review is the control was stored properly in the laboratory

b. Review performance of the current QC data for any issues

c. Verify the QC vendor's units and method compared to the package insert data

d. All of the above

13. How often should I adjust my test's mean?

a. Every time I get my peer group reports

b. When it is a significant change in the test system that has caused a truly systematic change resulting in the test's new state.

c. With every reagent lot change

d. Just prior to the inspection so the surveyor knows I am paying attention

14. What should you use to set your range?

a. Allowable Total Error (TEa)

b. Peer group SD

c. PT/EQA peer group SD

d. Your individual laboratory SD, ideally

15. Why use "Westgard Rules"?

a. They balance high error detection with low false rejection

b. They balance high cost with low quality

c. They balance high complexity with low comprehension

d. They balance high uncertainty with low measurement

16. What is the difference between "Westgard Rules" and Westgard Sigma Rules?

a. Westgard Sigma Rules is just 6 times more Westgard Rules

b. Westgard Sigma Rules is one sixth of the Westgard Rules

c. Westgard Sigma Rules is just a way to optimize Westgard Rules

d. Westgard Sigma Rules is just a way to maximize Westgard Rules

17. During monthly QC review you should NOT...

a. Review bench level actions

b. Review instrument history

c. Review observed mean, SD, CV of the method

d. Rerun all control outliers including any warnings or errors.

18. What 3 variables do you use to calculate the analytical Sigma-metric?

a. Measurement uncertainty, expanded measurement uncertainty, and permissible measurement uncertainty

b. TAT, throughput, and calibration time

c. TEa, CV, Bias

d. insert mean, peer group mean, reference mean

19. Where can you find TEa performance specifications?

a. CLIA

b. EQA PT

c. EFLM biological database

d. All of the above

20. If you use TE and compared to TEa, what should you monitor?

a. You should ensure TE < TEa

b. You should ensure TE > TEa

c. You should ensure TE < 1/6 TEa

d. You should ensure TE < 6* TEa

21. Where can you find TEa goals?

a. CLIA PT criteria

b. CAP PT criteria

c. Ricos and colleagues from Spain

d. All of the above and more

22. When given a choice between possible TEa goals, you should always choose

a. The smallest goal

b. The largest goal

c. The average of the goals

d. The goal that best matches patient needs

23. What is the difference between TE and TEa?

a. One is allowable and the other is actual

b. One is uncertain and the other is unknown

c. One is compliant and the other is complacent

d. One is total and the other is terrifying

24. Given a 5 Sigma method, what would the Westgard Sigma Rules recommendation be?

a. $1:_{3s}$

b. $1:_{3s}/\ 2:_{2s}/\ R:_{4s}$

c. $1:_{3s}/\ 2:_{2s}/\ R:_{4s}/\ 4:_{1s}$

d. $1:_{3s}/\ 2:_{2s}/\ R:_{4s}/\ 4:_{1s}/\ 8:_{x}$

25. Given a TEa of 15%, Bias of 3%, CV of 2%, what is the analytical Sigma-metric?

a. 3 Sigma

b. 4 Sigma

c. 5 Sigma

d. 6 Sigma

26. Given a TEa of 13%, Bias of 3%, CV of 2.5%, what is the analytical Sigma-metric?

a. 3 Sigma

b. 4 Sigma

c. 5 Sigma

d. 18.5 Sigma

27. Given a 4 Sigma method, how many Westgard Rules are recommended?

a. $1:_{3s}$

b. $1:_{3s}/\ 2:_{2s}/\ R:_{4s}$

c. $1:_{3s}/\ 2:_{2s}/\ R:_{4s}/\ 4:_{1s}$

d. $1:_{3s}/\ 2:_{2s}/\ R:_{4s}/\ 4:_{1s}/\ 8:_{x}$

28. If the difference between 2 serial patient results is greater than RCV, that means...

a. The run is out of control.

b. The run is uncertain.

c. You can't be sure there is anything changed in the patient's status.

d. A clinically significant change is likely to have occurred in patient replicates

29. Within the US, measurement uncertainty is...

a. Basically unknown

b. Completely uncertain

c. Mandated by CLIA.

d. Cornerstone of compliance

30. Moving Averages and EWMA are a

a. Replacement for QC

b. Complement to QC

c. Complication of QC

d. Reduction of QC

Please record your laboratory details below to receive P.A.C.E. continuing education contact hours:	
Laboratory Name:	
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Evaluation of Advanced 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 advanced 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 Advanced QC Workbook. . .

1. ...helped me with understanding advanced QC practices and applications.. .
2. ...was user friendly and well formatted. . . . . .
3. ...is not a reference source for future use . . . . . .

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.

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