Advanced QC Strategies

Risk-Based Design for Medical Laboratories

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Preface, James O. Westgard

Twenty years ago, we published a book on "Basic Planning for Quality" [1] that used Charts of Operating Specifications to selected appropriate control rules and numbers of control measurements based on the quality required for the test and the performance (precision, bias) observed for the methods in the laboratory. Since then, a major advance by Dr. Curtis Parvin's development of a patient risk model [2] has expanded the ability to design QC to provide an objective selection of the frequency of SQC, modeled around the number of patient samples between QC events. This model is especially important for optimizing SQC strategies for the high volume continuous production analyzers that are the workhorses in today's highly automated medical laboratories.

This book focuses on improving SQC practices by better design and planning of risk-based SQC strategies. As you should recall, Deming's PDCA cycle (Plan, Do, Check, Act) is the fundamental underpinning of today's Quality Management Systems (QMS). In the Deming cycle, the Plan step is perhaps the basic function most often overlooked (or under-developed) in medical laboratories. Laboratory scientists tend to be "Do" people who want to get on with doing the work, rather than sitting around thinking about how to do it. Yet we know it is important to have well defined processes and practices for doing the work if we are to provide consistent high-quality testing for our patients.

One area where current processes and practices have questionable quality is Statistical QC itself [3]. Many laboratories have used the "trial and error" approach to establish their control rules, numbers of control measurements, and frequency of QC events. We think laboratories can and should do better by careful design and planning of SQC procedures. Guidance is provided by the CLSI C24-Ed4 document [4] and its "road map" for planning risk-based SQC strategies. The difficulty with this guidance is the mathematical model and related calculations, hence the need for simple and practical SQC planning tools to implement the risk-based model.

Improving SQC practices is our objective with this book. We approach this issue as part of the broader laboratory QMS, recommending adoption of Six Sigma principles and tools, a focus on a Total QC Plan (rather than the Individualized QC Plan recommended for CLIA compliance), adopting the C24-ED4 road map, and implementing the planning process with Sigma SQC planning tools.

In this context, we begin by describing the basic philosophy of Demings' PDCA cycle and then provide a Six Sigma QMS framework for analytical quality management, followed by a detailed SQC planning process that makes use of simple graphical tools and internet and spreadsheet calculators. We discuss how to design/plan SQC for different modes of operation, such as batch, critical control point, and bracketed operation of continuous production processes. We describe a variety of applications based on data in the clinical chemistry literature to demonstrate the planning process and planning tools, but also to address some current SQC problems such as the use of a Repeat:2s sampling strategy, recommendations for patient based real-time QC procedures (PBRTQC), application of clinical control limits, and the use of moving average statistics with stable control materials.

We conclude with a summary of important conclusions, recommendations on how to implement QC planning in your laboratory, and some detailed directions and worksheets to guide and support your applications.

James O. Westgard
Madison Wisconsin

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Preface, Hassan Bayat

The ongoing improvements in science and technology provide more options to treat healthcare issues, including Quality Management. This book is to provide the readers with new achievements and approaches to Statistical Quality Control in laboratory medicine. Adding new techniques and tools to our toolbox, while honing the old ones, leads to a more empowered Quality Management.

As a personal note, over the past 15 years I have learned a lot about QC/QA from Professor Westgard and Sten Westgard. And now it's my great pleasure and pride to collaborate with the Westgards in this book.

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Preface, Sten Westgard

From the vantage point of mid-2022, it is hard to view progress as inevitable, that things always get better, that the "arc of the universe" proceeds toward justice. Indeed, sometimes it feels like there are setbacks.

For laboratories, however, there is objective evidence that things, in fact, have gotten worse. In global surveys on QC Practices conducted in 2017 and 2021, worrying trends were detected:

- The % of labs using manufacturer ranges increased from 43% to 57%.
- The use of 1:2s control rule increased from 55% to 59%.
- The use of manufacturer controls increased from 64% to 67%, while the use of third party controls have declined.
- Running control once a day increased from 49% to 54% of labs.
- The number of labs that never release patient results when there is a control failure declined from 54% to 48%.
- 30% of laboratories release results after control flags on a regular (if rare) basis.

These are not advances, they look like regression into the past.

Sad, to see a resurgence of backward practices, when there are more tools and opportunities than ever to make advances in QC practices. Indeed, the book describes in detail a revolutionary new approach, through the Risk-based MaxE(nuf) model, empowered by Sigma metrics, and enabled by Westgard Sigma Rules and the Sigma QC Frequency Nomogram, that offers a never-before chance for laboratories to design *every* element of their QC: the right rules, the right number of controls, and the right frequency of running QC. It simply has never been possible to answer all these questions before now.

Confounding this opportunity to leap forward are a number of digressions and distractions. The momentum behind measurement uncertainty continues to metastasize – threatening to completely up-end the current practice of quality control. We will discuss what is being proposed by the latest calculations and intended control practices for measurement uncertainty and uncertainty controls.

PBRTQC, the latest wave of enthusiasm for moving averages and other patient-based approaches, has been touted as a replacement for traditional quality control. While there are new capabilities to implement these techniques, as we will discuss, complexities remain and the best approach is to implement PBRTQC selectively, almost sparingly.

Navigating this landscape has been our passion for over 50 years, through this book we hope to provide you the tools to continue moving into a future that has better quality, more efficient operation, and reduced risk.

For more than 25 years, Westgard QC has been publishing books on quality, becoming an essential part of many laboratory shelves. It is the honor of a lifetime to be trusted colleague to so many, and we do not take our responsibility lightly. Here we impart the latest wisdom, and hope you are well equipped for the next part of your quality journey.

About the Authors

James O. Westgard, PhD, **FACB** is an Emeritus Professor in the Department of Pathology and Laboratory Medicine at the University of Wisconsin Medical School. In addition to pioneering the use of validation protocols, he is best known for popularizing the multirule QC procedure, often called the "Westgard Rules."

Hassan Bayat, CLS was born in Tehran, Iran, in 1966. He studied Clinical Laboratory Science, and completed his doctorate in Clinical Laboratory Science in 1994. His professional activity is mainly focused on directing his own private laboratory from Shahid Beheshti University of Medical Sciences. In his research, he has pursued the Total Error model, Sigma-metrics, MaxE(Nuf) QC model, Method Validation/Verification, and Measurement Uncertainty. From 2014 until 2017 he was a member of the EFLM Task and Finish group on Total Error. He has collaborated with the Westgards on several papers; especially papers devoted to providing tools for applying MaxE(Nuf) QC model.

Sten Westgard, MS, is the Director of Client Services and Technology for Westgard QC, Inc. For more than 25 years, he has managed the Westgard media and verification operations, from book publishing, to the web, to training portals and quality assessment programs in Sigma quality. Westgard.com has a membership of over 72,000 laboratory professionals worldwide. It provides over 800 articles, case studies, downloads, and online tools for free to any laboratory. The monthly e-newsletter reaches more than 26,000 laboratory professionals. The Westgard Sigma VP program works with a network of over 80 laboratories worldwide.

There's more online at Westgard Web

Visit **http://www.westgard.com/aqc-extras.html** for access to:

- Spreadsheets, worksheets and other downloads
- Frequently-Asked-Questions (FAQs)
- Glossary of terms
- Complete reference list
- Links to QC Frequency calculators, including some exclusively available to the owners of this book.

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1: Managing Quality

James O. Westgard, PhD

Quality management is often described as a journey without end. In less charitable terms, it could be described as a death march. There's a little truth in both of those perspectives. Quality is never "done" because your success today doesn't guarantee that tomorrow will be successful. It takes continuous effort, week after week, month after month, year after year. You have to succeed *every* day. Ultimately you will need to train the next generation to continue this pursuit.

I know something about that. I have spent more than 50 years of my career devoted to Quality. I didn't "solve" the quality challenges and walk away to retirement and celebration. Each victory lead to another challenge. For 40 years, I also trained the next generation of laboratory scientists, so they can master these challenges, too. It is their journey along the path of Quality that matters next.

In this sense, Quality has a philosophical dimension. But it is equally important to have practical guidance. We might talk about this journey in abstract ways, but we still need a road map and an itinerary to identify the next stop.

Our journey starts with the basic philosophy of Deming: the Plan-Do-Check-Act cycle, or PDCA. To this, we add an error framework which can be applied in medical laboratories. We encapsulate that in a Six Sigma Quality Management System for medical laboratories.

Deming's Plan-Do-Check-Act Cycle

Fundamental to Deming's approach to quality management is the scientific method, which is embodied in the Plan-Do-Check-Act cycle, commonly referred to as PDCA. As scientists, we learned the process of planning an experiment, performing the experiment, checking the experimental data, and acting on that data. In Total Quality Management, this PDCA cycle is applied to planning, implementing, monitoring, and improving production processes.

- PLAN refers to the initial phase where management plans what needs to be done and how to do it.

2. Reviewing Current SQC Practice Guidelines

The state of QC practice in US laboratories is not good! According to a recent survey of 21 large academic laboratories [1], the predominant practice is to use 2 SD control limits and analyze 2 controls once a shift or once a day. That practice represents the minimum requirement for compliance with the CLIA rule [2] *"at least once each day patient specimens are assayed or examined, [laboratories should for] each quantitative procedure include two control materials of different concentrations…"* By comparison, the global standard for accreditation, ISO 15189 [3], requires laboratories to *"design statistical quality control procedures that verify the attainment of the intended quality of results."* The ISO requirement focuses on ensuring quality needed for patient care, whereas CLIA focuses on a minimum frequency of running controls. For regulatory compliance, such a minimum often becomes the maximum standard of practice.

The survey revealed that the frequency of QC varied widely from 1 to 12 QC events a day for chemistry analyzers, with the most common frequency being 3 times per day. For immunoassay analyzers, frequency ranged from 1 to 4 events per day, with 2 or 3 being most common. In addition, the survey found that the most common criterion for judging whether the analytical process is in-control or out-of-control was the 2SD rule, i.e., Target Value ± 2SD. This control rule (1:2s) was used in 95% of these laboratories and common practice was to repeat the control if outside of 2 SD, accept the run if the repeat control was within 2 SD limits, and reject the run if the repeat control was outside 2 SD control limits.

Everyone *knows* that 2 SD control limits cause a problem with false rejections (remember 1 out of 20 outside the limits with N=1 and 1 out of 10 when N=2), but US laboratories have apparently overcome this limitation, possibly by continuously repeating the controls until they are "in", or more likely selecting SDs that are inflated for multiple instruments, multiple laboratories, peer groups, or by using manufacturers' labeled bottle values and assigned values that are expected to encompass the results from a large group of laboratories. In addition, controls are typically analyzed upfront

3. Developing a Total QC Plan

Our purpose in this book is to describe a QC planning methodology that is practical for medical laboratories *today*. However, we first focus on a Total QC Plan (TQCP) to provide an alternative to the Individualized QC Plan (IQCP), the newest option for compliance CLIA regulations.

We recommend development of a Total QC Plan because it keeps you in compliance with CLIA's minimum standards (2 controls per day for most tests), but at the same time it accommodates additional control mechanisms for specific failure-modes throughout the Total Testing Process. This approach does not require a formal Failure Mode and Error Assessment (FMEA). Instead, it fulfills the goal of risk management by developing a risk-based Statistical QC (SQC) strategy, which is easier to execute than formal FMEA.

The advantages of a risk-based SQC strategy are (a) it is a reproducible outcome of quantitative SQC planning process and (b) provides objective specifications for control rules, numbers of control measurements, and the frequency of QC events. In contrast, an IQCP is a subjective process that leads to an arbitrary set of control mechanisms as well as an arbitrary SQC procedure with arbitrary control rules, numbers of control measurements, and frequency of QC events.

This chapter will focus even more narrowly on the Total QC Plan and risk-based SQC Strategy.

Approach for Developing Risk-Based QC Plans

Figure 3-1 outlines the steps for developing QC plans, either a Total QC Plan that includes a risk-based SQC procedure or an Individualized QC Plan based on a risk assessment. As mentioned above, we focus on the Total QC Plan in the methodology presented here.

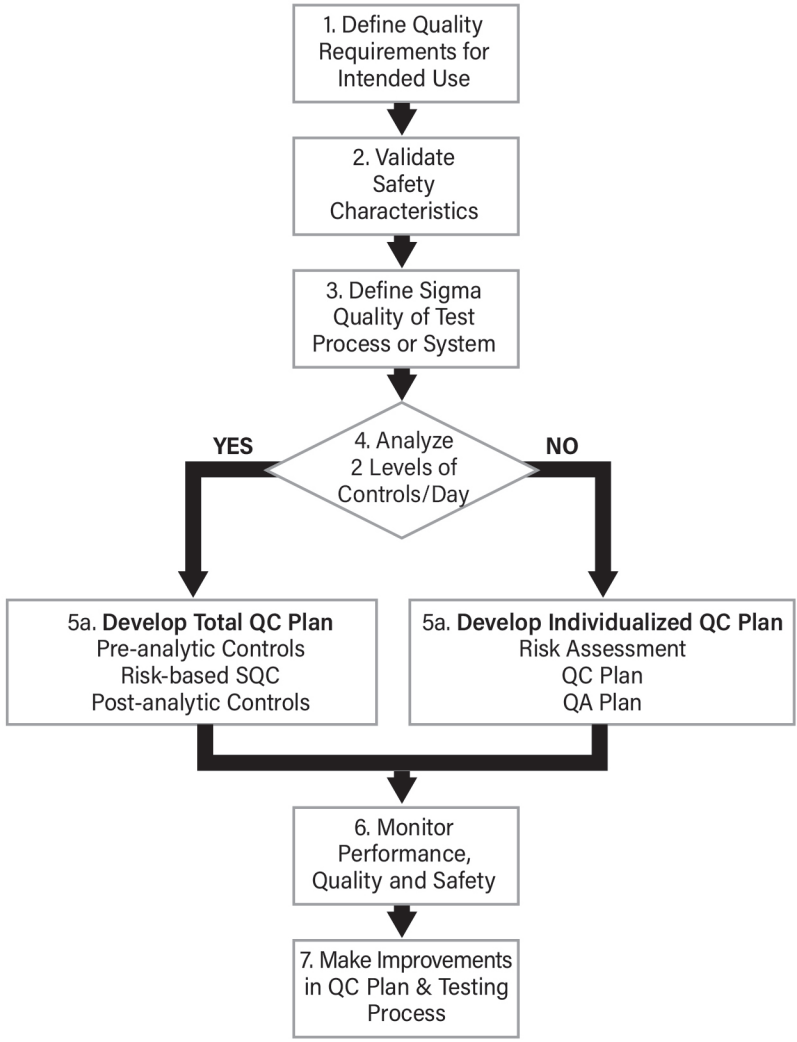

Figure 3-1. Flowchart showing the steps for developing and implementing a QC Plan.

5. Planning SQC Strategies for Bracketed Operation

Our focus here is on risk-based SQC strategies for the bracketed operation of continuous production processes, i.e., the high volume testing processes in use in most medical laboratories. Bracketed operation involves two QC events that are separated by a group of patient samples. Patients' results are not reported unless both the QC events at the beginning and end of the group of patient samples pass QC evaluation. The number of patient samples between consecutive QC events defines the frequency of QC, a critical parameter for continuous production with periodic release of patient test results.

The cost-effectiveness of bracketed operation of continuous production processes may be improved by implementation of multi-stage SQC procedures that involve two or more different designs, switching from one to another when appropriate. For example, a multi-stage control procedure could have a Startup design that is used for initial testing, a Monitor design that is used for routine operation following startup, and even a Retrospective design that is used to review control data over a period longer than a single run.

The design of multi-stage Bracket SQC Strategies can be supported by use of a Sigma SQC Run Size Nomogram (also referred to as Sigma Run Size Nomogram), coupled with a Power Function Graph to ensure that the initial QC event provides the high error detection required for a Critical Control Point Startup design. The Monitor design may be based on the desired reporting interval and may consider single rules with only 1 control measurement. Such candidate SQC procedures have been included in both the Run Size Nomogram and Power Function Graph in the materials provided here. A worksheet is also included to guide and document the process.

These graphical tools have been demonstrated earlier in an article in *Clinical Chemistry* that focused specifically on "*Planning risk-based SQC schedules for bracketed operation of continuous production processes*" [1]. The discussion in that paper is a valuable addition to the material presented here.

6. Optimizing QC Frequency for Patient Risk

We focused on graphical tools in the earlier chapters, but now want to describe some simple calculators available as online tools at the Westgard Website and implementable with spreadsheets. Although the graphical tools are simple to use, they are manual and therefore laborious when considering multiple levels of controls and multi-test analytical systems. To better support more complicated planning activities, we have converted the Sigma Run Size Nomogram into a calculator that also allows the patient risk factor to be a variable for planning SQC strategies. This is particularly useful for applications where there are differences in performance at different levels of controls and differences in performance for individual tests in a multi-test analyzer, which is the ultimate challenge in designing risk-based SQC strategies.

At some point, it became apparent that the Sigma Run Size Nomogram should be converted to a calculator. The relationships between Sigma and the log-base 10 (log10) of run size is essentially linear in the Sigma range from 3 to 6, which is the relevant range of Sigma quality where the design of SQC strategies is important. At 6-Sigma, world class quality is achieved, and QC is easy; below 3.5-Sigma, a laboratory can't do enough QC to ensure the desired quality is achieved; below 3-Sigma, industrial guidance says the process is inadequate for routine production. In between, it is important to implement appropriate SQC strategies to ensure the quality needed for intended medical use.

One advantage of these calculators is that patient risk itself can be a parameter for optimizing process performance [1,2]. There are situations where performance at one level of control is more critical than at another; cases where one test is more critical for patient care than another in a multitest analytical system. Adjusting the patient risk factor may allow implementation of a simpler SQC strategy.

7. Preparing Simple Excel QC Frequency Calculators

It is important that you have practical tools for your own work. The Sigma Run Size Nomogram is practical [1], but we know many laboratory analysts prefer an automated tool to a manual one. In this case, a simple QC Frequency Calculator can be prepared to calculate appropriate run sizes for different SQC procedures [2]. Given the ready availability of Google Sheets and Microsoft Excel, labs can use the directions here to set up their own run size calculators

The details are shown in Figure 7-1A and B on the following pages. This view of the spreadsheet shows the formulas that are needed in the various cells. Rows 4-12 are for the information that must be entered by the user. Most critical are the rows for the quality requirement, method inaccuracy, and method imprecision. These must all be entered *in the same units*, either concentration units or percentage related to the critical decision level in row 9. We most often work in % units, but concentration units are fine. What matters is that all three parameters are in the same format.

From this information, Sigma will be calculated as ($\%TE_a$ - |%Bias|)/%CV or (TE_a-|Bias|)/SD in row 13, which is labeled "Calculated Sigma-metric" to distinguish it from the "Patient Risk Sigma" in row 14. If the calculated Sigma is greater than 6, it is replaced with value of 6 as the maximum Sigma for use in the calculations. That's the outcome of the equation =+IF(G13>6,6,G13). If G13 is greater than 6, then a value of 6 will be entered. If not the actual calculated value in G13 will be used for the Patient Risk Sigma. Setting a maximum value of 6 for Sigma and a maximum value of 1,000 for run size makes the calculator behave the same as the Sigma Run Size Nomogram, i.e., it limits the calculations to a useful range and eliminates extrapolations that would go far beyond the range of the nomogram (and the reality of the lab).

B	C	D	E	F
			4	Analyst
			5	Date
			6	Analyzer
			7	Test
			8	Units
			9	Critical Decision Level, Xc
			10	Quality Requirement, %TEa
			11	Bias observed, %Bias
			12	Precision observed, %CV
			13	Calculated Sigma-metric
			14	Patient Risk Sigma
			15	Patient Risk Factor
			16	Maximum Run Size
Eq Calc log10 RunSize			17	
Slope	Y-int	log10	18	Candidate SQC Procedures
1.3576	-3.1362	=SUM(B19:C19)	19	1:3s/2:2s/R:4s/4:1s, N=4 (P_{fr}=0.03)
1.2028	-3.0193	=+(G14*B20)+C20	20	1:3s, N=4 (P_{fr}=0.01)
1.2539	-2.8821	=+(G14*B21)+C21	22	1:3s/2of3:2s/3:1s, N=3 (P_{fr}=0.02)
1.1319	-2.9280	=+(G14*B22)+C22	22	1:3s, N=3 (P_{fr}=0.01)
1.0983	-2.8232	=+(G14*B23)+C23	23	1:3s/2:2s/R:4s, N=2 (P_{fr}=0.01)
0.9664	-2.5343	=+(G14*B24)+C24	24	1:3s, N=2 (P_{fr}=0.00)
1.0046	-3.1947	=+(G14*B25)+C25	25	1:3.5s, N=2 (P_{fr}=0.00)
0.8439	-1.6089	=+(G14*B26)+C26	26	1:2s, N=1 (P_{fr}=0.05)
0.8430	-2.0511	=+(G14*B27)+C27	27	1:2.5s, N=1 (P_{fr}=0.01)
0.8372	-2.4638	=+(G14*B28)+C28	28	1:3s, N=1 (P_{fr}=0.00)

Figure 7-1A. Left side of the worksheet shows the regression coefficients for calculating log base 10 (log10) of run size. Middle section shows the entry parameters at the top, calculated parameters in the middle, and candidate SQC procedures for which run size will be calculated . Equations for calculating Sigma (G13) and Patient Risk Sigma (G14) are shown at the top, followed by the parameters for setting Patient Risk Factor of 1 (G15) and Maximum run size of 1000 (G16), and finally the equations for calculating run sizes (G19 to G28).

8. Considering Sigma for Multiple Control Levels

If you haven't already figures it out, the Sigma quality of a test is a predictor of risk and the key parameter for planning risk-based SQC strategies. One issue that must be considered is what is the best estimate of Sigma when 2 or 3 levels of controls are analyzed. Many labs run two levels of controls for chemistry tests. For other tests, e.g., immunoassays, hematology, labs often run three levels.

In an earlier chapter, we illustrated how the online QC Frequency Calculator can accommodate up to 4 tests or up to 4 levels of controls. That allows data from multiple levels of controls to be used to calculate Sigma and compare the run sizes appropriate at different concentrations and different decision levels.

To provide an alternative to use an average Sigma that represents performance over a wide analytical range, 2 other QC calculators are available:

- http://tools.westgard.com/frequency_calculator2.shtml and
- http://tools.westgard.com/frequency_calculator3.shtml.

These are similar in format to the first QC Frequency calculator but include an additional column for the "average" Patient Risk Sigma. This should facilitate selection/design of SQC strategies based on the Sigma performance observed over a concentration range, rather than the Sigma performance at a single concentration. These calculators are intended to support the application of the CLSI C24-Ed4 "road map" [1] for developing risk-based SQC strategies, with calculation of QC Frequency in terms of run size, in accordance with Parvin's patient risk model [2].

These calculators can be used to compare the performance for different levels of controls, compare the SQC strategies appropriate at different levels of controls, and compare the SQC strategies appropriate over the range of concentrations represented by the controls. We know that it is likely to observe different Sigmas at different concentrations. The issue is how to handle those differences

10. Defining Quality Required for Intended Use

Let us admit that what most laboratories actually practice is Arbitrary Control. It doesn't sound as nice as Quality Control, but if you run QC without defining the goal for quality, you have no idea if you are achieving anything.

Perhaps an analogy will help. You can't tell if you have made a basket (in basketball) if there is no rim, no net, and no backboard. You're just throwing a ball away. Simply put: without defining a goal, you can't tell if you've been successful or if you have failed. When you have defined a goal, you can validate performance in the laboratory, you can determine if the method will achieve the desired quality, and later you can establish *appropriate* SQC procedures for monitoring test performance.

In the absence of a stated requirement for quality, the management of that process can only achieve an arbitrary level of quality that may or may not meet customer needs. Think of the common and widespread use of 2 SD control limits with Ns of 2 or 3 for most of all tests in a laboratory [1]. While many laboratory professionals agree that one size QC does not fit all tests, in practice many apply 2 SD limits across the board for their tests.

The remedy is to implement an objective process for designing SQC procedures based on the quality required for intended use, the imprecision and bias observed in the laboratory, and the rejection characteristics inherent in the control rules and numbers of control measurements applied.

Now we return to the issue of what quality is required for the intended use of a test. We often take up this issue at the beginning of the story, but in the context of the discussion here it fits nicely following the planning process and the "options" available if run size does not satisfy the desired reporting interval, as discussed in the previous chapter and shown in Figure 10-1.

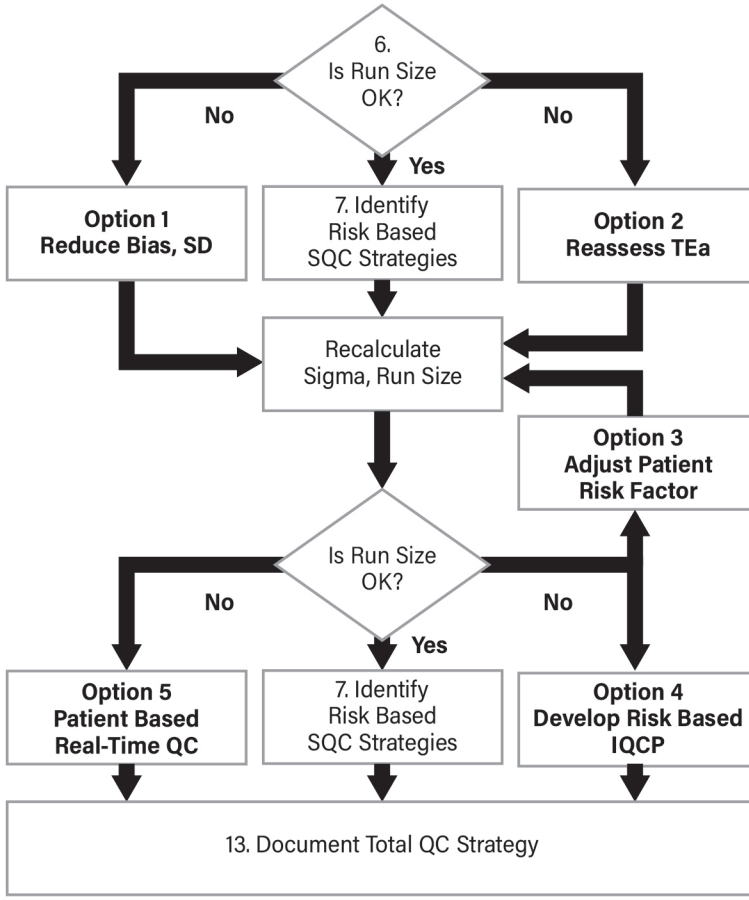

Figure 10-1. Options 1 to 5 for improving QC when run size initially does NOT satisfy the desired reporting interval.

Of course, the first option is to improve performance, if possible, by reducing the bias and/or the SD. The second option is to reassess the quality requirement that was applied. We mentioned earlier that the EFLM is now advising labs using biologic goals is to switch from the "desirable" goal to the "minimum" goal. Changing the goal sounds simple, but it assumes considerable knowledge about analytical performance specifications, so we will undertake a thorough discussion here to review some of the history and current practices.

11. Assessing Potential Usefulness of PBRTQC

One of the options for improving QC is to implement procedures that make use of patient data, rather than depending on a few control measurements using traditional SQC procedures. This approach is becoming popular due to the recommendations and articles coming from an IFCC working group on **Patient Based Real Time Quality Control (PBRTQC)**. *Clinical Chemistry* highlighted the potential usefulness [1]. Presented in an informal Question and Answer format, the IFCC workgroup optimistically promoted PBRTQC applications:

PBRTQC will become the mainstay of QC in laboratories once the profession sees the advantages of this form of process control, and manufacturers and middleware vendors provide the onboard capability.

The power of these techniques is that they offer exquisite customization to provide very sensitive detection of a change in bias.

Hand in hand with the implementation of PBRTQC is a need to change the mindset from human decision making to AI approaches to QC.

There is a need for large analytical systems to not only use the Hospital Information System to identify patient subgroups, but also for the Laboratory Information System to identify a significant drift, interrogate manufacturers databases regarding calibrator and reagent lot quality, and to initiate recalibration.

PBRTQC is a major step to integrating the laboratory into the hospital information system, and to a bigger dataset with the ultimate goal of better patient outcomes.

Dreams of the Future vs Present Reality

While it is exciting to speculate about the future, it's also important to assess what is practical in the present.

12. Upgrading Multirules with Moving Averages

The original multirule paper was never intended to be a "one size fits all" recommendation for IQC. In fact, it recommended different control rules for different numbers of control measurements [1, Table 4]. Certain rules were recommended to inspect within-run results and others were recommended to be used across (consecutive) runs. For example:

- for 2 control measurements, the 1:3s and 2:2s were recommended for use within-run and the 4:1s and 10:x across-runs;
- for 3 control measurements, 1:3s, 2of3:2s, and 3:1s were recommended for within-run and 9:x across-runs;
- for 4 control measurements per run, 1:3s, 2:2s, R:4s, and 4:1s within-run and 8:x across-runs;
- for Ns greater than 4, the recommendation was to use mean and range rules within-run and "trend rules" across-runs.

The term "trend rules" referenced a paper by Cembrowski *et al* [2] that described the use of a Moving Average Algorithm (MAA) in the form of an exponentially smoothed moving average. Thus, it was expected that when the number of control measurements increased above 4 per run, simple traditional control rules would be replaced by control techniques related to mean and range rules (and associated moving estimates).

Power curves for mean and range QC procedures with Ns of 6 and 8 are shown in Figure 12-1, along with the power curve for an N=6 multirule. The mean and range procedures have been selected to maintain low false rejections from 0.02 to 0.00, whereas the N=6 multirule procedure has a P_{fr} of 0.07. You can most easily identify the multirule procedure by looking at the y-axis and identifying the curve with the highest intercept. The family of mean/range rules demonstrate their appropriateness for maintaining low false rejections and high error detection as Sigma quality approaches 3.0. Thus, the recommendations from the original multirule paper

anticipated the use of mean and range types of procedures for higher numbers of control measurements due to the higher false rejections for multirule procedures.

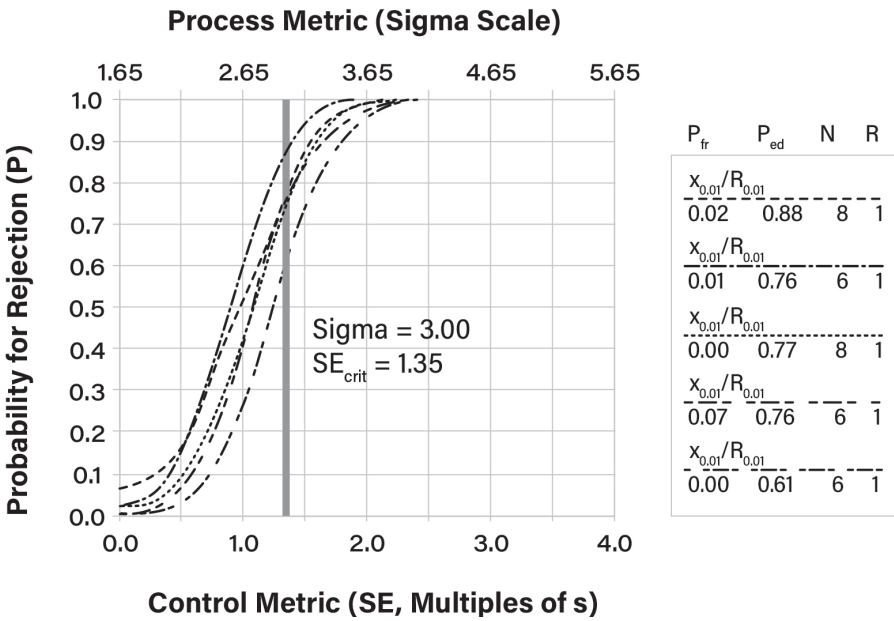

Figure 12-1. Power curves for mean and range rules with Ns of 6 and 8 compared with a multirule procedure with N of 6.

Performance of Moving Average Algorithms

More recently, a paper by Po *et al* [3] recommended replacing Westgard multirules by moving average algorithms (MAA). One of these authors has been involved with the IFCC group that is promoting PBRTQC procedures, thus their work with MAAs for patient-based QC might be expected to carry over to applications for stable control materials used in IQC. The authors studied the performance of Westgard multirules with Ns of 2 and 4 and MAA with block sizes of 5, 10, and 20. The larger block sizes for MAAs should provide better error detection, however, there is a subtle issue with the speed of response after a systematic error occurs that

13. Re-designing QC Wrongly for the Traceability Era

According to published recommendations from a 2019 conference on metrological traceability and IQC [1], the structure of Internal Quality Control (IQC) should be *fundamentally* changed. IQC should be divided into **two** parts.

- **IQC Component I** applies to control materials that are used to monitor analytic performance and make decisions to accept or reject analytical runs.
- **IQC Component II** requires a commutable control that is analyzed once per day over a period of 6 months solely for the purpose of estimating measurement uncertainty (MU).

While there will be an obvious objection to doubling the amount of QC being run in laboratories, that's not what we want to address in this chapter. Instead' we will focus on the Component II's recommended decision-making for acceptance or rejection of analytical runs.

The specific recommendation is to calculate the control limits for a control chart as Target Value ± 2***APS**$_u$, which represents a 95% "acceptability range" for the Analytical Performance Specification (APS) for standard Measurement Uncertainty (u, expressed as SD, s, or CV). One of the fundamental principles of SQC is that each laboratory should characterize its own imprecision and use that SD in calculation of control limits. Instead, the authors argue:

> *"What is lacking is the link with the new scientific background [for metrological traceability] … To obtain this, the acceptability range for QC component I should correspond to APS for MU derived according to the appropriate Milan model and it should be set based on unbiased target value of the material obtained by the manufacturer as the mean of replicate measurement on the same measuring system optimally calibrated to the selected reference."*

Fixed control limits still have statistical performance characteristics

The direct use of an "acceptability range" for control limits has the same problems as earlier practices using "clinical limits" and "fixed limits". We discussed the fallacy of using such limits when the CLIA rules were being finalized in the mid-1990s [2]. The mechanics of applying today's "acceptability limits" are the same. The idea is , just draw the limits that represent the performance specification *directly* on the control charts, in this case ± 2*APS_u. This advice does not consider measurement uncertainty in the interpretation of individual control measurements. If the purpose of MU is to aid the interpretation of test results, that should apply to control results as well as patient results.

Regardless of the rationale, those lines for fixed control limits still have the properties of statistical control limits because of the measurement uncertainty associated with each individual control result. The particular statistical control rule can be identified by dividing the clinical control limit by the SD observed for the particular laboratory method. Then the power curve for that control rule can be determined to characterize the probabilities for rejection for various error conditions. Given that individual laboratory methods in different laboratories will have different amounts of imprecision, the performance of such fixed control limits will differ from one laboratory to another. Measurement uncertainty itself is the reason that fixed clinical control limits won't provide appropriate QC.

For example, APS_u for HbA1c is 3.0%, according to recommendations published by these same authors [3], so the acceptability range of ± 2*APS_u would be TV ± 6.0%. If Method A has stable imprecision of 1.0% and bias of 0.0%, the method demonstrates 6-Sigma performance [(6.0%-0.0%)/1.0%] and the MU acceptability range provides a 6s control range (6.0%/1.0%). If out-of-control is defined as 1 control result exceeding a control limit, then for Method A the control rule is 1:6s N=1, where N represents the total number of control measurements in a QC event. If another method has stable imprecision of 1.5% and bias of 0.0%, it demonstrates 4-Sigma performance and will require more intensive QC. A method with a CV of 2.0% and bias of 0.0% would provide 3-Sigma performance, which

14. Determining MU from QC Data

As discussed in the previous chapter, metrologists have proposed that measurement uncertainty be estimated from QC data. While they would prefer a commutable control material be used, current practices for estimating MU do in fact rely on QC data. However, there are issues about the proper way to estimate MU from that data. Having already opened the metrology can of worms, it seems necessary to address the issue of how to calculate MU from QC data.

According to ISO 15189 [1], section 5.5.1.4, *"the laboratory shall determine measurement uncertainty for each measurement procedure in the examination phases used to report measured quantity values on patients' samples."* Although this requirement has been in place for years, there are continuing arguments about *how* to calculate measurement uncertainty. A new ISO document 20914:2019 [2] specifically addresses the issue, but there still is vigorous debate in the literature about how to properly calculate measurement uncertainty [3-4], particularly how to incorporate the effects of uncorrected clinically significant bias.

Originally, the debate was about proper application of the **bottom-up** methodology recommended by GUM – Guide to the expression of uncertainty in measurement [5]. The bottom-up approach depended on identifying individual components of variation, estimating their size, then summing the variances and extracting the overall standard deviation, or standard uncertainty. After many attempts at implementation, it was concluded that the bottom-up approach was too complicated for medical laboratories. The alternative was to employ a **top-down** methodology that made use of available data on measurement precision, specifically, internal quality control data obtained over a period of a few months, commonly referred to as intermediate precision data. By 2012 when the CLSI published guidance C51-A on "*Expression of Measurement Uncertainty in Laboratory Medicine*", both bottom-up and top-down methodologies were included [6]. Given the more complicated mathematical calculations behind the bottom-up model, a large portion of that document is devoted to explaining that model.

15. Evaluating Repeat:2s QC Practices

If at first you don't succeed, try, try again

– Thomas H. Palmer

Those who do not remember the past are condemned to repeat it.

– George Santayana

History repeats itself, first as tragedy, second as farce.

– Karl Marx

There are many aphorisms that can provide us wisdom and guidance on how to work in the laboratory. But while the proverbs listed above are catchy, *they are not QC rules.*

In Chapter 2, we observed that common QC practices don't always conform to good laboratory practices. The issue of using Repeat:2s control rules provides a good example of the problem. As surveys of QC practices show[1], the most common QC practices is using 2SD control limits. Everyone knows about the false rejection problem with 2SD limits, so how have laboratories rationalized the use of this practice? The existence of a scientific paper that recommends a repeat:2s sampling strategy is the answer [2]. It may be questionable whether laboratories actually comply with the protocols for using Repeat:2s rules, but they still rationalize their applications based on the theory of repeat QC sampling.

We first became aware of the Repeat:2s sampling strategy from a poster presentation at the 2011 National AACC Meeting. In response, we discussed this recommendation on the Westgard website in October of 2011 [3].

16. Applying Individual vs Pooled Means and SDs for Multiple Analyzers

One of the biggest challenges of laboratories today is to grapple with the sheer scale of testing. At the dawn of the laboratory age, a laboratory had a single instrument for each test, and it operated in isolation from all other tests. One of the first major breakthroughs was the multitest instrument, but even then, the laboratory had a single chemistry instrument that might run a score of tests.

Today's laboratories can run dozens of instruments – reference laboratories exist that run *hundreds* of instruments – and they no longer operate in a vacuum. Your laboratory is probably part of a healthcare system, and patients will migrate from outpatient clinics to smaller clinical centers to large hospitals (and then back). They will be tested by multiple instruments located across multiple laboratories. And of course there is great pressure to make sure those results are comparable across all instruments and all laboratories.

There is relatively little discussion in the literature of how to sustain such an effort. It's clear there are a wide range of approaches. The most popular choice seems to be common means and common SDs. While this may be the easiest and most convenient choice, there's no evidence that this is the appropriate solution to a scientific problem. And while everyone seems to agree that the discussion is restricted to a set of the same instruments, same lot of reagents, same lot of control materials, etc., the reality is that this approach is also being implemented across heterogeneous systems – where different instruments, different reagent lots, are nevertheless being assigned the same mean and SD.

Selecting SQC strategies for multiple instruments is a sufficiently difficult problem that the most recent CLSI C24-Ed4 guidance document [1] did not address this issue, stating that *"although significant advances in QC thinking have occurred, there are still important areas that could benefit from additional developments, such as QC strategy design and implementation for laboratories with multiple instruments of the same type performing the same measurement procedures."* The C24-Ed4 guideline deliberately

17. Controlling Differences between Reagent Lots

Reagent lots have differences. This is widely known and despite all the advances in engineering and technology, remains distressingly common. Across decades of encounters with laboratories, we have seen a wide array of practices for approving / validating / verifying new reagent lots. Some of the old habits include a simple of check of the QC ("Controls in? all right then…"), to a flat goal of 10% allowable difference between lots, to the use of the entire total allowable error budget as the acceptability criteria.

Let's be honest: in many cases, these practices are wrong.

The better approach to judging lot-to-lot reagent acceptability is to use real patient samples and determine an analyte-specific criterion for allowable difference. We'll explain in more detail. But first, let's explain why the practices above are less than ideal.

1. The problem with just checking some controls is that there is always the issue of commutability and matrix effects. If the controls aren't fully commutable (and most aren't), the acceptability of controls does not guarantee that the patients won't be affected by a difference in reagent lots.

2. The problem with using a single goal for lot acceptability for all analytes is that we all know there are individual performance specifications for individual analytes. Reagent lot criteria also need to be individualized.

3. Finally, given an allowable error specification that needs to encompass all sources of random and systematic error, you can't use it all up at once. You can't blow the whole budget just on the bias between reagent lots.

20. Preparing for Practical Applications

This chapter provides materials that you can copy – or download – for use in your own applications. You also can used them as a starting point for developing your own QC design procedures. The materials include step-by-step directions for use of the various graphical tools, worksheets to guide the calculation of the Sigma quality of a testing process, forms for documenting planning applications, and a template for the Sigma Run Size Nomogram (likely the most useful tool).

D-1. Directions for Calculation of Sigma for a Testing Process

WS-1. Calculation of Sigma from Manufacturer's Claims

WS-2. Calculation of Sigma from Method Validation Data

WS-3. Calculation of Sigma from SQC and PT(EQA) Data

D-2. Directions for Comparing Current QC Procedures with Westgard Sigma Rules with Run Size.

WS-4. Initial Assessment of Current QC Procedures

D-3. Directions for Planning Batch and CCP SQC Events using Power Function Graphs

WS-5. Planning a Batch/CCP SQC Event (2 control levels)

WS-6. Planning a Batch/CCP SQC Event (3 control levels)

D-4. Directions for Assessing Batch and CCP SQC Procedures for a Group of Tests using Normalized OPSpecs Charts

WS-7. Assessing Batch/CCP SQC using NOPSpecs Chart for 2 levels

WS-8. Assessing Batch/CCP SQC using NOPSpecs Chart for 3 levels

D-5. Directions for Assessing Performance of Bracketed SQC using a Sigma Run Size Matrix

WS-9. Assessing Bracketed SQC using a Sigma Run Size Matrix

WS-10. Planning a Risk-Based Bracket SQC Strategy

Analyst/Date			
Laboratory/Location			
Test/Units/Device			
Quality Requirement (TEa, ATE)			
Critical Decision Conc. (Xc)			
|Bias| observed			
Precision observed			
Calculated Sigma-Metric			
Sigma-Metric for SQC Design			
Candidate SQC Procedures	**Run Size**	**Pfr**	**Ped**
1:3s/2:2s/R:4s/4:1s N4		0.03	
1:3s N4		0.01	
1:3s/2:2s/R:4s N2		0.01	
1:2s N1		0.05	
1:3s N2		0.00	
1:2.5s N1		0.01	
1:3s N1		0.00	
Maximum Workload			
Desired Reporting Interval			
Selected Startup CCP Design			
Selected Monitor Design			
C1 Control Material			
C2 Control Material			
C3 Control Material			
SQC Schedule	**Test#/Controls**		
Conformance Cost			
Number of Controls			
Total Number Tests			
Control Consumption			
% Controls			

WS-11. Comparing Risk-Based Bracket SQC Strategies

Analyst/Date			
Laboratory/Location			
Test/Units/Device			
Quality Requirement (TEa, ATE)			
Critical Decision Conc. (Xc)			
|Bias| observed			
Precision observed			
Calculated Sigma-Metric			
Sigma-Metric for SQC Design			
Candidate SQC Procedures	**Run Size**	**Pfr**	**Ped**
1:3s/2:2s/R:4s/4:1s N4		0.03	
1:3s N4		0.01	
1:3s/2:2s/R:4s N2		0.01	
1:2s N1		0.05	
1:3s N2		0.00	
1:2.5s N1		0.01	
1:3s N1		0.00	
Comparison of SQC Strategies	**Option 1**	**Option 2**	**Option 3**
Maximum Workload			
Desired Reporting Interval			
Selected Startup CCP Design			
Selected Monitor Design			
C1 Control Material			
C2 Control Material			
C3 Control Material			
SQC Schedule	**Test#/Controls**		
Conformance Cost			
Number of Controls			
Total Number Tests			
Control Consumption			
% Controls			

21. A Final Word

We cannot end this book without commenting on the impact of COVID19 on the laboratory community, and how it reflects a longer-term struggle for the future.

In the past 2 years, there has been ample dissection of what went wrong in the US pandemic response, from initial CDC testing method failures to the vacuum of political leadership. At the same time, there's been a similar media narrative praising all the hard-won accomplishments, the heroic achievements, the sacrifices of our healthcare heroes.

If these last few years represent a triumph for laboratory testing, it is a strange victory. It's not the win we were hoping for, nor is it the win we needed.

By any measure, the response of the laboratory to the COVID19 has been amazing. From PCR to antibody to antigen, the testing methods available now are ample to the need. But testing lagged so far behind, it was the vaccinations that truly saved the patients, not the laboratories. In the public mind, the laboratory was not where the war was won. In the thick of this crisis, laboratory professionals worked punishing hours, 6-7 days a week, grappling with constant supply shortages, allocations, and a roller coaster of regulatory recommendations. Even as vaccinations have risen, and some COVID19 testing volumes have diminished, for many hospital labs, there is now a new normal – COVID19 testing on everyone, on top of the typical routine testing workload. So the "post"-pandemic workload is greater than the pre-pandemic, which was already crushing.

As the news from medical technology programs comes in, we have not seen larger incoming classes, expanded programs, or new programs being established. Apparently, the pandemic has had no impact at all on the number of people entering the profession.

So, instead of a triumph, we have the same crisis that we were facing before: too much work, not enough staff, not enough respect or resources given to us. Except now it is worse than ever. Particularly in the US, there is a critical shortage of staff at the bench level – we have gone from Lean to skeletal.

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