# Planning Risk-Based SQC Schedules for Bracketed Operation of Continuous Production Analyzers

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James O. Westgard,[1,2*] Hassan Bayat,[3] and Sten A. Westgard[2]

**BACKGROUND:** To minimize patient risk, "bracketed" statistical quality control (SQC) is recommended in the new CLSI guidelines for SQC (C24-Ed4). Bracketed SQC requires that a QC event both precedes and follows (brackets) a group of patient samples. In optimizing a QC schedule, the frequency of QC or run size becomes an important planning consideration to maintain quality and also facilitate responsive reporting of results from continuous operation of high production analytic systems.

**METHODS:** Different plans for optimizing a bracketed SQC schedule were investigated on the basis of Parvin's model for patient risk and CLSI C24-Ed4's recommendations for establishing QC schedules. A Sigma-metric run size nomogram was used to evaluate different QC schedules for processes of different sigma performance.

**RESULTS:** For high Sigma performance, an effective SQC approach is to employ a multistage QC procedure utilizing a "startup" design at the beginning of production and a "monitor" design periodically throughout production. Example QC schedules are illustrated for applications with measurement procedures having 6-$\sigma$, 5-$\sigma$, and 4-$\sigma$ performance.

**CONCLUSIONS:** Continuous production analyzers that demonstrate high $\sigma$ performance can be effectively controlled with multistage SQC designs that employ a startup QC event followed by periodic monitoring or bracketing QC events. Such designs can be optimized to minimize the risk of harm to patients.



Fn4

Risk management principles were recommended by the Clinical and Laboratory Standards Institute (CLSI)[4] for development of quality-control plans in 2011 *(1)* and for the selection/design of risk-based statistical quality-control (SQC) procedures in 2016 *(2)*. For risk-based SQC procedures, "the goal is to use a QC strategy that can detect change in performance reliably before the clinical quality requirement is exceeded while also minimizing the frequency of false rejections. Minimizing the number of potentially affected patient results is achieved by an appropriate frequency for measuring and evaluating QC samples." In this context, C24-Ed4 defines the following terms:

- Quality requirement—specification of the characteristics necessary for a product or service to be fit for its intended use. NOTE: For a laboratory measurement procedure, the quality requirement is usually expressed in terms of an allowable total error (TEa). If the measurement error in a patient's result exceeds the TEa, the result fails to meet its quality requirement.
- QC strategy—the number of QC materials to measure, the number of QC results and the QC rule to use at each QC event, and the frequency of QC events.
- QC event—the occurrence of one or more QC measurements and a QC rule evaluation by use of the QC results.

Traditionally, SQC design has focused on the selection of QC rules and the number of QC results that are necessary to achieve a high probability of error detection ($P_{ed}$) while maintaining a low probability of false rejection ($P_{fr}$) *(3)*. Typically, a goal for $P_{ed}$ has been $\geq$0.90 or a 90% chance or greater of detecting a medically important error, such as the critical systematic error calculated from the TEa and the observed method trueness (Bias) and the observed method imprecision (SD) as $\Delta SE_{crit} = [(TEa - |Bias|)/SD] - 1.65$, in which 1.65 represents the one-sided condition in which 5% of the test results would exceed the allowable error. The goal for $P_{fr}$ has been $\leq$0.05 or a 5% or less chance of false rejection. A variety of SQC planning tools have been developed, such as power function graphs *(4)*, Sigma-metric critical error

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[1] Department of Pathology and Laboratory Medicine, University of Wisconsin School of Public Health, Madison WI; [2] Westgard QC, Inc., Madison WI; [3] Sina Medical Laboratory, Qaem Shahr, Iran.

* Address correspondence to this author at: Westgard QC, Inc., 7614 Gray Fox Trail, Madison, WI 53717. E-mail james@westgard.com.

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[4] Nonstandard abbreviations: CLSI, Clinical and Laboratory Standards Institute; SQC, statistical quality control; TEa, allowable total error; $P_{ed}$, probability for error detection; $P_{fr}$, probability for false rejection; MaxE(Nuf), maximum expected increase in number of unreliable final patient test results; CCP, critical control point; MR, multirule; N, total number of control measurements in a QC event; 1:3s or $1_{3s}$, format for identifying a control rule in terms of the number of control observations (e.g., 1) and the control limit (e.g., mean ±3s).

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graphs *(5)*, charts of operating specifications *(6)*, as well as simplified tools such as Westgard Sigma Rules *(7)*. However, these tools do not provide a selection or design parameter for the frequency of SQC that is needed to assure the ongoing quality of reported results during the operation of continuous analytical processes.

Parvin's development of a patient risk model for the calculation of a patient risk parameter, termed MaxE(Nuf), is important for optimizing the frequency of SQC *(8)*. The practical implementation of SQC frequency is described in terms of an SQC schedule. C24-Ed4 discusses approaches for establishing SQC schedules for batch operation, continuous operation (also called "bracketed QC"), and critical control point operation. For clarity, C24-Ed4 describes these modes of operation as follows:

- "Batch QC refers to the condition in which a group of patient specimens is measured by a procedure that is characterized by a defined start and stop time with all measurements occurring for all specimens during that time interval.
- "In continuous mode, QC samples are measured periodically along with patient specimens. QC results from the current QC event are interpreted to reflect the current condition of the measurement procedures. If the current QC sample results are acceptable, it is assumed that the measurement procedure has remained stable since the last acceptable QC event, and thus, the results for patient specimens measured during that interval are likely to be acceptable. This type of QC schedule can be called 'bracketed QC' because the results at the beginning and end of a 'bracket' are used to verify that patient results measured within the 'bracket' are acceptable.
- "Critical control point QC [refers to] scheduled events that could alter the performance of a measurement procedure . . . When operating in a continuous mode and a critical control point occurs, it is necessary to verify the performance of the measurement procedure both before and after the event."

For high production continuous processes, both critical control point (CCP) and bracketed SQC should apply. CCP SQC is needed whenever a major change occurs and maybe even for daily occurrences to assess possible sources of variation due to preparation of daily working reagents, changes of reagent lots, preventive maintenance following daily shut down, changes in environmental conditions, and perhaps even changes in operators. Then laboratories should follow with bracketed SQC events for the release and reporting of patient test results. A common approach would be to employ the same control rules and number of control measurements for both QC events in the bracket; however, it may be more cost-effective to consider a multistage SQC design, i.e., "a control procedure involving two or more different designs, switching from one to another when appropriate. For example, a multistage control procedure could have a 'startup' design that is used for initial testing, a 'monitoring' design that is used for routine operation following startup, and a 'retrospective' design that is used to review control data over a period longer than a single run"[3, page 184]. For high production analyzers, the advantages of adopting multistage SQC would be to assure that the quality for intended use is achieved at the beginning of operation (startup design), guarantee quality continues to be acceptable when periodically reporting patient test results (monitor design), enable laboratories to assess when a problem occurs, and identify patient specimens that need to be retested. Our purpose here is to illustrate how such QC schedules can be developed to minimize patient risk.

## Materials and Methods

### ASSESSMENT OF PATIENT RISK AND SQC RUN SIZE

Parvin's risk model focuses on the calculation of the maximum expected increase in number of unreliable final patient test results, termed MaxE(Nuf) *(8)*. A goal of a maximum increase of $\leq 1$ erroneous patient result between QC events is typically set for defining frequency of SQC or run size. While the model and calculations are complex, electronic spreadsheets have been developed by Yago and Alcover for single-rule SQC procedures *(9)* and by Bayat for multirule SQC procedures *(10)*. Both provided nomograms that show the relationships between MaxE(Nuf) and the Sigma metric observed for the analytical process. These nomograms can be further modified to show the run size necessary for MaxE(Nuf) = 1 as a direct function of the Sigma metric *(11)*, and their application has been illustrated in a detailed example for HbA1c *(12)*. The nomogram in reference 11 includes the following SQC procedures:

- MR N4 represents a $1_{3s}/2_{2s}/R_{4s}/4_{1s}$ multirule with 4 control measurements per QC event and a probability of false rejection of 0.03 or 3% ($P_{fr} = 0.03$);
- 1:3s N4 is a $1_{3s}$ single-rule procedure with 4 control measurements per QC event, $P_{fr} = 0.01$;
- MR N2 is a $1_{3s}/2_{2s}/R_{4s}$ multirule procedure with 2 control measurements per QC event, $P_{fr} = 0.01$;
- 1:3s N2 is a $1_{3s}$ single rule with 2 control measurements per QC event, $P_{fr} = 0.00$;

For the purpose of planning multistage SQC procedures, additional single-rule SQC procedures with only one control measurement have been added, as follows:

- 1:2s N1 is a $1_{2s}$ single rule with 1 control per QC event, $P_{fr} = 0.05$.



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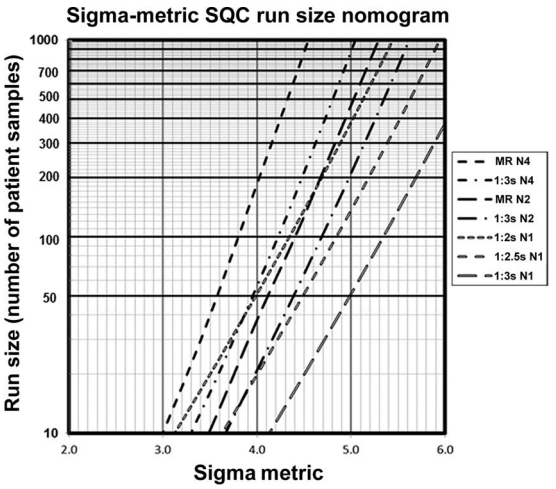


**Fig. 1. A Sigma-metric SQC run size nomogram for estimating the number of patient samples between QC events for bracketed operation of a continuous production analytical testing process.**

Run size is plotted on the *y* axis vs the observed Sigma metric on the *x* axis. The key at the right identifies the control rules and total number of control measurements (N) in a QC event. MR N4 represents the $1_{3s}/2_{2s}/R_{4s}/4_{1s}$ multirule procedure with N = 4 and MR N2 represents the $1_{3s}/2_{2}s/R_{4s}$ control rules with N = 2. Single-rule procedures using the $1_{3s}$ control rule and Ns of 4 and 2, respectively, are represented by 1:3s N4 and 1:3s N2. The double dashed lines represent single-rule procedures, e.g., $1_{3s}$, $1_{2.5s}$, and $1_{2s}$ with Ns of 1. False rejection rates are less than 3% except for the $1_{2s}$ rule with N = 1, which is expected to be 5%.

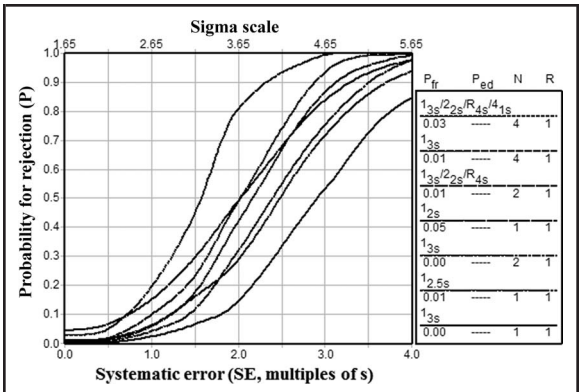


**Fig. 2. Power function graph for SQC procedures included in the Sigma-metric SQC run size nomogram.**

The probability for rejection is plotted on the *y* axis vs the size of a medically important systematic error on the lower *x* axis and vs the Sigma metric on the upper *x* axis. Power curves (top to bottom) correspond to the control rules and total number of control measurements/QC event (N) shown in the key at the right. $P_{fr}$ is the probability for false rejection. R is the number of runs over which the control rules are applied, which is 1 when all the rules can be applied within an individual QC event.

- 1:2.5s N1 is a $1_{2.5s}$ single rule with 1 control per QC event, $P_{fr} = 0.01$; and
- 1:3s N1 is a $1_{3s}$ single rule with 1 control measurement per QC event, $P_{fr} = 0.00$.

### APPROACH FOR PLANNING AN SQC SCHEDULE

1. Define the quality and workload requirements for the analytical testing process, specifically the quality required for intended use in the form of a TEa, the maximum number of patient samples to be analyzed in a work day or shift, and the desired reporting interval.
2. Determine the precision (SD, CV) and trueness (Bias) of the examination procedure from performance validation data.
3. Calculate the sigma metric as (TEa-|Bias|)/SD for concentration units or (%TEa − %|Bias|)/%CV for percentage units.
4. On the nomogram (Fig. 1), draw a vertical line to represent the observed Sigma metric. F1
5. Estimate the maximum run sizes for the candidate SQC procedure by reading the values on the *y* axis that correspond to the intersections of the vertical line and the lines for the SQC procedures.
6. Identify a startup SQC design whose run size is larger than or equal to the specified test workload by identifying the control rules and Ns from the key on the right of the nomogram. For this CCP QC event, verify that the probability for error detection is high, preferably $P_{ed} \geq 0.90$ or 90% chance of detecting critical systematic error from a power function graph (such as Fig. 2). F2
7. Identify a monitor SQC design whose run size is larger than or equal to the desired reporting interval. From the power function graph, verify that the probability for false rejection is low, preferably a $P_{fr} \leq 0.05$ or 5% chance of false rejection.
8. Prepare an SQC schedule that identifies the test number and the controls to be analyzed for each QC event.

## Results

An example application is shown in Fig. 3, in which the vertical line represents a measurement procedure with an observed performance of 5-Sigma on the *x* axis. The run sizes appropriate for the different SQC procedures are read off the *y* axis for the intersections of the vertical line and the lines representing the different SQC procedures, as identified in the key at the right side of the nomogram. Note that a run size of ≥1000 is assigned to the MR N4 procedure because the intersection is off scale. F3



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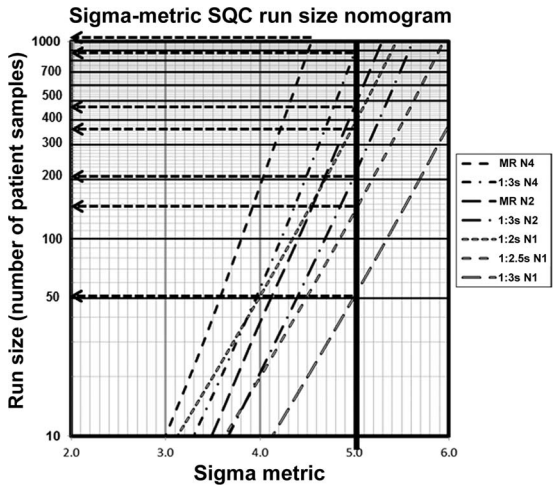


**Fig. 3. Example application for a 5-Sigma quality testing process.**
The intersections of the vertical line at 5-Sigma on the *x* axis and the various SQC lines identify the values for run size, which are found on the *y* axis.

Table 1 identifies the various SQC procedures and their maximum run sizes, which range from 50–1000 patient samples. The table illustrates the planning of SQC schedules for 3 different workload conditions. Option 1 represents a maximum workload of 1000 patient samples and a desired reporting interval of 200 patient samples; option 2 represents 500 and 125, respectively; and option 3 represents 200 and 50, respectively. The startup design should be selected to have a run size as large as the maximum patient workload when possible; the monitor design should always be selected to have a run size as large as the desired reporting interval. The startup design determines the control rules and number of control measurements for the first QC event (a CCP); the monitor design determines the control rules and number of control measurements for the subsequent bracketing QC events that allow the reporting of patient test results.

This example employs 2 levels of controls (C1, C2), as this is a common practice in medical laboratories and widely accepted by regulatory authorities (e.g., US CLIA requirements for minimum SQC) *(13)*. In option 1, in which maximum workload is 1000 patient samples, both

**Table 1. SQC schedules for a 5-Sigma quality testing procedure.[a]**

| | 5.0-Sigma-metric observed | | |
|---|---|---|---|
| **Candidate SQC procedures** | **Max. run size** | **$P_{fr}$** | **$P_{ed}$** |
| MR N4 1:3s/2:2s/R:4s/4:1s | >1000 | 0.03 | 1.00 |
| 1:3s N4 | 900 | 0.01 | 0.98 |
| MR N2 1:3s/2:2s/R:4s | 470 | 0.01 | 0.94 |
| 1:3s N2 | 220 | 0.00 | 0.85 |
| 1:2s N1 | 370 | 0.05 | 0.90 |
| 1:2.5s N1 | 150 | 0.01 | 0.82 |
| 1:3s N1 | 50 | 0.00 | 0.66 |
| **SQC design** | **Option 1** | **Option 2** | **Option 3** |
| Maximum workload | 1000 | 500 | 200 |
| Desired reporting interval | 200 | 125 | 50 |
| Selected CCP startup design | MR N4 | MR N2 | 1:3s N2 |
| Selected bracket monitor design | 1:3s N2 | 1:2.5s N1 | 1:3s N1 |
| **SQC schedule** | | **Test#/Controls** | |
| CCP startup event | 0/C1, C2, C1, C2 | 0/C1, C2 | 0/C1, C2 |
| 1st Bracket event | 200/C1, C2 | 125/C1 | 50/C1 |
| 2nd Bracket event | 400/C1, C2 | 250/C2 | 100/C2 |
| 3rd Bracket event | 600/C1, C2 | 375/C1 | 150/C1 |
| 4th Bracket event | 800/C1, C2 | 500/C2 | 200/C2 |
| 5th Bracket event | 1000/C1, C2 | | |
| **Conformance cost** | | | |
| Number of controls | 14 | 6 | 6 |
| Total number tests | 1000 | 500 | 200 |
| Control consumption | 0.014 | 0.012 | 0.03 |
| % Controls | 1.4% | 1.2% | 3.0% |

[a] Maximum run sizes appropriate for the candidate SQC procedures were determined from the Sigma-metric run size nomogram as shown in Fig. 3. Workload specifications illustrate 3 options for the maximum patient workload and the desired reporting interval, which lead to different startup and monitoring designs and different SQC schedules.



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levels of controls are analyzed twice in the startup QC event ($1_{3s}/2_{2s}/R_{4s}/4_{1s}$ with N = 4) but only once in each subsequent bracketing QC event ($1_{3s}$ with N = 2) every 200 patient samples. In option 2, in which maximum workload is 500 patient samples, the 2 levels are analyzed only once in the startup QC event ($1_{3s}/2_{2s}/R_{4s}$ with N = 2) and only one level is analyzed once in each subsequent bracketing event ($1_{2.5s}$ with N = 1) every 125 patient samples. In option 3, in which the maximum workload is 200 patient samples, the 2 levels of controls are analyzed once in the startup QC event ($1_{3s}$ with N = 2) and only 1 level is analyzed once in each subsequent bracketing event ($1_{3s}$ with N = 1) every 50 patient samples. The $1_{3s}$ N = 2 startup design achieves a $P_{ed}$ of 0.86, slightly less than the desired 0.90 that could be achieved with a $1_{3s}/2_{2s}/R_{4s}$ multirule procedure ($P_{ed}$ = 0.94). Some approximation and judgment is necessary for practical applications, in this case whether to implement a single-rule or multirule design. Finally, Table 1 provides a simple estimate of the cost of conformance, i.e., the cost of SQC when the process is in control. SQC consumes 1.4%, 1.2%, and 3.0% of the production capacity, respectively, for the 3 options considered.

F4 Fig. 4 shows applications for both 4-Sigma and 6-Sigma quality processes. For 6-Sigma performance, the appropriate run sizes are all ≥1000 patient samples, except for the $1_{3s}$ N = 1 procedure in which run size is about 370 patient samples. In short, a startup QC event can make use of a $1_{3s}$ rule and N = 2 (one result for each of 2 levels of controls to be compliant with US CLIA regulations), and subsequent bracketing QC events can use the same rule with N = 1. Reporting intervals of any size up to 370 may be chosen to provide timely reports. QC costs of conformance may be as low as 5 controls per 1000 analyses, or 0.5% of output.

T2 For 4-Sigma performance, the run sizes are summarized in Table 2. For the $1_{3s}/2_{2s}/R_{4s}/4_{1s}$ multirule procedure and 4 control results, the maximum run size is nearly 200 patient samples (about 190 graphically, but again some approximation and rounding is useful for practical applications). For a workload of 1000 samples and a reporting interval of 200 samples, this multirule procedure with N = 4 should be used for the startup QC event as well as subsequent brackets every 200 samples. For a maximum workload of 500 samples and a reporting interval of 125 samples, the same multirule procedure is needed for both startup and bracketing QC events.

For a workload of 200 samples, the same multirule procedure is again needed for the startup QC event, but a $1_{2s}$ N = 1 procedure may be used for monitoring every 50 samples. Whereas a $1_{2s}$ control rule is seldom recommended due to the high false rejection rate, this is an application in which the rule is limited to an N of 1 where the false rejection rate is a tolerable maximum of 5%. When the rule is satisfied, test quality is acceptable and patient results can be reported. If the rule is violated, then patient results should be held until the next control measurement is obtained. That QC event should then be evaluated and the run should be rejected if a second violation occurs ($2_{2s}$ or $R_{4s}$ rules); if not, the run can be accepted and patient test results reported. It would also be appropriate here to employ the multirule procedure as a "retrospective" design to review all 4 control results collected in the 200-patient interval. This option 3 approach could also be applied for each 200-patient interval in option 1 to provide more rapid reporting of patient test results.

For measurement procedures with Sigma metrics <4.0, the SQC strategies and schedules become more difficult and costly. For example, from inspection of the nomogram, a 3.5-sigma process would have a maximum run size of 50 patient samples when using a $1_{3s}/2_{2s}/R_{4s}/4_{1s}$ multirule procedure with N = 4. For bracketed operation, the cost of conformance would be 84 controls per 1000 patient samples, or 8.4% of production. For methods with <3.5-sigma quality, even higher N multirule procedures, and shorter run sizes or more frequent SQC may be needed. A better remedy would be to select better measurement procedures that achieve higher Sigma quality and can be more easily controlled.

## Discussion

In a recent survey of nearly 1000 laboratories *(14)*, about 50% of laboratories indicated they analyze controls only once a day at the beginning of an analytical run; in other words, they implement one SQC event and practice one-stage SQC. The other 50% employ some form of bracketing or periodic analysis of controls throughout the day or at regular intervals based on the number of patient samples analyzed, though their practices for test reporting are varied and lack conformity in principle and design. That means it will take considerable effort to establish more objective and better optimized practices for bracketed SQC. The 2016 CLSI C24-Ed4 document provides guidance in this direction by its emphasis on risk-based SQC, its implicit recommendation for bracketed operation of continuous production processes, and its emphasis on an SQC schedule as a detailed plan for implementation.

The SQC schedule provides the laboratory with an "operational definition" of its QC strategy. Deming discussed the need for operational definitions that describe what to do and include a measure for ensuring that the desired quality is achieved *(15)*, e.g., answer the telephone within 3 rings. For laboratory application, it may also be as simple as "provide test results within 60 min," in which the measure of time permits an assessment of acceptable service. Or, it may be more complex, such as "provide test results that are correct within 10%," which



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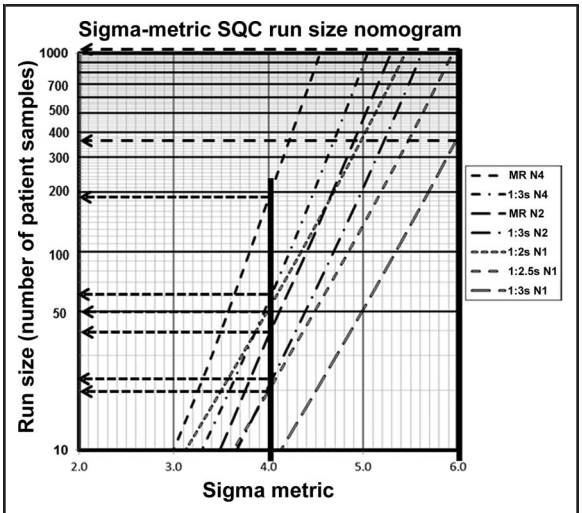


**Fig. 4. Example applications for 4-Sigma and 6-Sigma quality testing processes.**

The intersections of each vertical line on the *x* axis and the various SQC lines identify the values for run size, which are found on the *y* axis.

depends on the precision and bias of the analytical procedure, as well as the QC that is necessary to assess whether performance is acceptable. In laboratory practice, the SQC schedule brings together the theory and principles of SQC; the quality required for intended use; the observed performance of the measurement procedure; the expected performance of the SQC procedure; and now, in the age of risk management, the expected risk of harm to patients from poor quality results.

The C24-Ed4 document *(2)* addresses this complex issue and provides a "roadmap" for developing an SQC strategy based on principles of quality management and risk management *(16)*. The outcome should be an SQC schedule that describes the number of levels of control materials to be analyzed, the number of times each material is analyzed, the control rules to be used for evaluating the control results, and the frequency of QC events or run size. The difficulty for laboratories is to translate the 60-some pages of guidance into a practical procedure for planning SQC schedules. A more detailed methodology and planning tools are needed to facilitate the development of such SQC schedules.

The complexity of this task becomes apparent with recognition of the many factors that are involved. These

**Table 2. SQC schedules for a 4-Sigma quality testing procedure.[a]**

| | 4.0-Sigma-metric observed | | |
|---|---|---|---|
| **Candidate SQC procedures** | **Max. run size** | **$P_{fr}$** | **$P_{ed}$** |
| MR N4 1:3s/2:2s/R:4s/4:1s | 200 | 0.03 | 0.92 |
| 1:3s N4 | 60 | 0.01 | 0.68 |
| MR N2 1:3s/2:2s/R:4s | 40 | 0.01 | 0.64 |
| 1:3s N2 | 25 | 0.00 | 0.50 |
| 1:2s N1 | 50 | 0.05 | 0.62 |
| 1:2.5s N1 | 20 | 0.01 | 0.46 |
| 1:3s N1 | 10 | 0.00 | 0.28 |
| **SQC design** | **Option 1** | **Option 2** | **Option 3** |
| Maximum workload | 1000 | 500 | 200 |
| Desired reporting interval | 200 | 125 | 50 |
| Selected CCP startup design | MR N4 | MR N4 | MR N4 |
| Selected bracket monitor design | MR N4 | MR N4 | 1:2s N1 |
| **SQC schedule** | | **Test#/Controls** | |
| CCP startup event | 0/C1, C2, C1, C2 | 0/C1, C2, C1, C2 | 0/C1, C2, C1, C2 |
| 1st Bracket event | 200/C1, C2, C1, C2 | 125/C1, C2, C1, C2 | 50/C1 |
| 2nd Bracket event | 400/C1, C2, C1, C2 | 250/C1, C2, C1, C2 | 100/C2 |
| 3rd Bracket event | 600/C1, C2, C1, C2 | 375/C1, C2, C1, C2 | 150/C1 |
| 4th Bracket event | 800/C1, C2, C1, C2 | 500/C1, C2, C1, C2 | 200/C2 |
| 5th Bracket event | 1000/C1, C2, C3, C4 | | |
| Retrospective review | | | 200/MR N4 |
| **Conformance cost** | | | |
| Number of controls | 24 | 20 | 8 |
| Total number tests | 1000 | 500 | 200 |
| Control consumption | 0.024 | 0.04 | 0.04 |
| % Controls | 2.4% | 4.0% | 4.0% |

[a] Maximum run sizes appropriate for the candidate SQC procedures were determined from the sigma-metric run size nomogram in Fig. 4. Workload specifications illustrate 3 options for the maximum patient workload and the desired reporting interval, which lead to different startup and monitoring designs and different SQC schedules.



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factors include the quality required for intended use (TEa); the precision and trueness observed for the measurement procedure (CV, bias); the SQC strategy (control rules, number of control results, frequency of SQC or run size); the performance characteristics of the SQC procedure ($P_{ed}$, $P_{fr}$); and the risk of harm to the patient due to increased erroneous test results, as described by Parvin's risk model and MaxE(Nuf) risk parameter *(8)*. Furthermore, applications must consider the maximum workload conditions and desired reporting intervals in individual laboratories. The difficulty becomes even more evident with recognition that the C24-Ed4 document is focused on principles and consequently does not provide any detailed example applications or specific tool to support laboratory applications *(11)*. Additional guidance is needed, in particular, simple graphical tools to help laboratories apply the concepts, principles, and recommendations *(9–12)*. The Sigma-metric SQC run size nomogram described here demonstrates the practical utility of one such tool for planning SQC schedules for bracketed operation.

An important principle in the design of bracketed SQC is to consider the initial SQC event to be a critical control point (CCP) that requires high error detection. Many regulations require daily SQC, therefore there is some point at which analytical performance must be verified each day, likely after maintenance, changes of reagents, changes in environmental conditions, changes in operators, and a new calibration. Once analytic performance is verified by the startup CCP QC event, ongoing monitoring may employ simpler rules and lower Ns. In principle, the monitor SQC procedure should be selected to have a very low false rejection rate to establish a long time between false rejections, even at the expense of some loss in error detection. If the conditions are such that an SQC procedure cannot have both high error detection and low false rejection, then the multistage approach permits one design for high error detection and another for low false rejection. The application of the designs then depends on whether a high prevalence of errors is expected (use the startup CCP design) or a low prevalence is expected (use the monitor design).

In the approach described here, we recommend that the monitoring QC event be designed to minimize patient risk for the desired reporting interval. In principle, Parvin's model assumes the same SQC design for all QC events in bracketed operation. Given that run size depends primarily on the error detection capability of the SQC procedure and given the error detection of the CCP event will always be more than or equal to the error detection for subsequent bracket events, the recommended run size will be safe and appropriate for the first bracket event and strictly correct by Parvin's model for subsequent bracket events. The value of defining a desired reporting interval is recognized as an important operating parameter in many laboratories, both for responsive service and for cost-effective operation when patient samples need to be reanalyzed. The reporting interval, of course, depends on the speed of the analyzer as well as the clinical service needed for intended use, thus it will vary with individual laboratory applications.

The cost-effectiveness of a multistage design depends on the Sigma quality of the testing process. Processes with Sigma metrics of 5.0 and greater can employ simple SQC designs, accommodate large workloads, provide responsive patient reporting, and maintain low costs of conformance. Greater effort is needed with 4-Sigma processes: SQC procedures require more control results, multiple rules will be needed, and run sizes will be shorter. For processes in which Sigma $\leq$3.5, even more complex and costly SQC strategies will be needed. One approach may be to add a third SQC design for retrospective review of individual control measurements that accumulate to provide a bracketed QC event. Alternatively, it may be possible to implement a moving average type of SQC procedure that would effectively evaluate a specified number of control results, or a moving window of control results, that provide the desired error detection and run size. Such a procedure could also be built on patient data, although assessment and optimization of performance is more difficult and would require more advanced tools, particularly to consider patient risk in a quantitative manner.

Implementation of multistage bracketed SQC designs may require improvements in SQC software. Feasibility was demonstrated many years ago *(17)*, but it will take customer demand to get suppliers to make such improvements widely available. Meanwhile, implementation for high Sigma quality methods is possible with use of a simple single-rule design with N varying from 2 for the startup design and 1 for the monitor design. Multi-rule designs may also be readily implemented by scheduling multiple controls consecutively for the startup design then spacing out the subsequent monitor controls for appropriate reporting intervals. Multitest systems will require additional strategies to systemize the design to provide appropriate performance for the different tests. Practical applications will require reasonable approximations, judicious choices, and logical adaptations. In spite of such difficulties, laboratories will benefit from having a more objective methodology for planning bracketed SQC operation and will reduce patient risk by their efforts to implement bracketed SQC.

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