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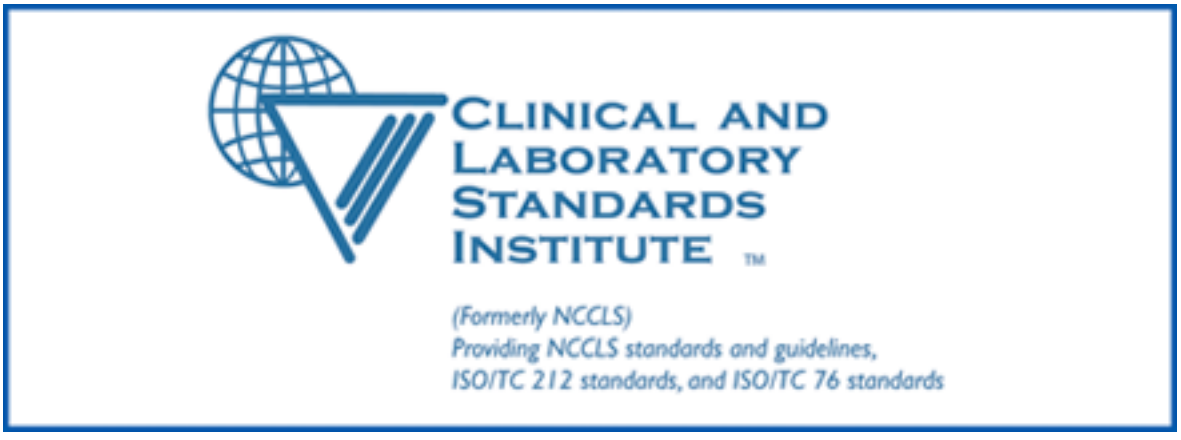
Statistical Quality Control for Quantitative Measurements: Principles and Definitions; Approved Guideline—Second Edition



This guideline provides definitions of analytical intervals, planning of quality control procedures, and guidance for quality control applications.

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Abstract

Statistical Quality Control for Quantitative Measurements: Principles and Definitions; Approved Guideline Second Edition (NCCLS document C24-A2) addresses the principles of statistical quality control (QC), with particular attention to the planning of a QC strategy, the definition of an analytical run, the selection of control materials, and the application of statistical QC in a healthcare laboratory. This guideline is a revision of an earlier guideline. The original definitions are maintained for the manufacturer recommendation run length (MRRL) and the user defined run length (UDRL). Changes include a strong emphasis on defining quality up front to guide the selection of control rules and the number of control measurements, recognition that methodology should be developed to establish run lengths on a scientific basis, and a recommendation that the best response to an out-of-control situation is to identify the sources of the problem and eliminate the cause, rather than routinely repeating control measurements.

(NCCLS. *Statistical Quality Control for Quantitative Measurements: Principles and Definitions; Approved Guideline Second Edition.* NCCLS document C24-A2 [ISBN 1-56238-371-X]. NCCLS, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania, 19087, USA, 1999.)

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Statistical Quality Control for Quantitative Measurements: Principles and Definitions; Approved Guideline—Second Edition

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Foreword

This document is a revision of an earlier document that has been in use by the laboratory community for over ten years. When that earlier document was developed, laboratories were experiencing changes in measurement technology and instrument systems that made many of the conventional quality control practices difficult to apply. In response to those needs, the earlier document clarified the fundamental principles and definitions of quality control that should be considered when managing any laboratory measurement process.

This revision continues that tradition to appraise, clarify, and define concepts, approaches, and practices that should be generally useful in developing a specific quality control strategy for testing with quantitative measurements. It maintains a focus on statistical quality control because of the general capability of this technique for monitoring the effects of many instrument, reagent, environment, and operator variables on the outcome of a testing process.

An example of an important concept is the "analytical run," which in the past often corresponded to the batch of specimens being analyzed. With many modern analytical systems, the definition of a run is not nearly as clear. A run is better understood in terms of the time or number of analyses for which the measurement process is stable.

An example of an important approach is the planning of a quality control procedure. A new section describes how to develop a specific quality control strategy that takes into account the quality required by the test, the performance available from a method, the performance expected from different QC strategies, and the goals set by the laboratory for QC performance.

An example of an important practice is the way a laboratory responds to an out-of-control situation. Following guidelines on statistical quality control proposed by a European working group of the External Quality Assessment Organizers (EQA-Organizers), there is a strong emphasis on trouble-shooting the measurement process. This response is appropriate when the quality control procedure is carefully planned and control rules are selected to minimize false alarms or false rejections.

This document does *not* attempt to define specific quality-control strategies that are appropriate for an individual device or technology, nor does it attempt to describe alternatives to statistical process control. (Currently the NCCLS Subcommittee on Unit Use Testing is dealing with these issues.) It should also be noted that there are other types of errors that may affect individual samples, rather than a whole group of samples, and those errors will not be detected by this type of statistical QC procedure. Such errors may be due to the specific design of an analytical system (e.g., effect of sample viscosity, carryover from previous sample) or possible operator errors that affect individual samples. Special QC procedures are needed to monitor special vulnerabilities that relate to system design.

Nor does this document consider specific legal requirements that may impose different philosophies or procedures on quality control practices; e.g., a specific approach for defining quality requirements, specific values for quality requirements, a specific procedure for determining target values for the means of control materials. NCCLS is interested in feedback from users, worldwide, on how to provide a more global approach for quality control guidelines.

The concepts, approaches, and practices discussed here are interdependent and all must be carefully studied and considered when developing the specifics for any test, system, or laboratory. In an age when the quality of laboratory tests is often taken for granted, this document serves as a reminder that there are technical issues that still require a careful scientific approach if laboratories are to achieve the quality needed by the physicians and patients they serve.

Foreword (Continued)

The committee wishes to thank all who commented on the first-edition guideline. All comments were carefully considered, but not all views could be accommodated. Comments are summarized in the Appendix with responses from the committee.

Standard Precautions

Because it is often impossible to know which might be infectious, all patient blood specimens are to be treated with standard precautions. For specific precautions for preventing the laboratory transmission of blood-borne infection from laboratory instruments and materials; and recommendations for the management of blood-borne exposure, refer to NCCLS document M29—*Protection of Laboratory Workers from Instrument Biohazards and Infectious Disease Transmitted by Blood, Body Fluids, and Tissue*.

Key Words

Quality control, calibration, analytical run, quality control rules.

Statistical Quality Control for Quantitative Measurements: Principles and Definitions; Approved Guideline Second Edition

1 Introduction

There is abundant literature addressing the theoretical and practical bases for initiating and maintaining statistical quality control (QC) procedures in clinical chemistry.[1-6] However, there still are many difficulties in the routine practice of statistical quality control and improvements depend on a better understanding of how to:

(1) Plan QC on the basis of the quality required for a test
(2) Select appropriate control rules and numbers of control samples
(3) Define the analytical run
(4) Select appropriate control materials
(5) Apply QC and respond to out-of-control situations

The emergence of automated clinical chemistry instruments using widely different instrumental principles has complicated the terminology associated with and the procedural steps necessary for statistical control testing. On the other hand, these highly automated systems can often perform specific electronic checks that help identify potential problems and alert the operator to instrument malfunction. The advantage of statistical quality control is to monitor the outcome of the many variables and steps in the whole analytical process.

2 Scope

This guideline addresses the purpose of statistical quality control for quantitative measurements; describes an approach for planning quality control for a specific test and method of measurement; defines various analytical intervals; and addresses the use of quality control material and quality control data, including the use of the data in quality assurance and interpretation. The recommendations are applicable to quantitative laboratory tests in all fields. The document does not contain step-by-step procedures for setting up and maintaining a statistical quality control program, or for other aspects of quality control such as instrument function checks and use of patient data for quality control purposes.

The committee intends this guideline to apply to a broad spectrum of laboratories, from the low test volume to the high test volume. The analytical performance and quality control needed for a testing process must satisfy the medical applications of the particular test, which relate to inherent clinical aspects of the laboratory's patient population and not to the laboratory's size, location, or complexity. In the low-volume environment, special selectivity should be exercised in deciding whether or not to implement specific test procedures. Once implemented, however, quality control is needed to assure that the test results will satisfy the medical needs.

3 Definitions[a]

Accepted reference value, *n* - A value that serves as an agreed-upon reference for comparison and which is derived as a theoretical or established value based on scientific principles; an assigned value based on experimental work of some national or international organization; or a consensus value based on collaborative experimental work under the auspices of a scientific or engineering group.

Analyte, *n* - A substance or constituent for which the laboratory conducts testing. **NOTE:** This includes any element, ion, compound, substance, factor, infectious agent, cell, organelle, activity (enzymatic, hormonal, or immunological), or property, the presence or absence, concentration, activity, intensity, or other characteristics of which are to be determined. See also **Measurand**.

Bias, *n* - The systematic, {signed} deviation of the test results from the accepted reference value. **NOTE:** a) Defined in NCCLS document NRSCL8-A as "the difference between the expectation of the test results and an accepted reference value"; b) In general, the deviation/ difference is based on replicate measurement using an accepted (definitive, reference, or

[a]Please see the most currrent edition of NCCLS document NRSCL8—*Terminology and Definitions For Use in NCCLS Documents.*

designated comparison) method and the method being tested, and expressed in the units of the measurement or as a percentage.

Imprecision, *n* - The random dispersion of a set of replicate measurements and/or values expressed quantitatively by a statistic, such as standard deviation or coefficient of variation. **NOTE:** The words "imprecision" and "precision" are often inappropriately interchanged (Cf. EP10).

Matrix, *n* - All components of a material system, except the analyte.

Measurand, *n* - A particular quantity subject to measurement. **NOTE:** This term and definition encompass all quantities, while the commonly used term "analyte" refers to a tangible entity subject to measurement. For example, "substance" concentration is a quantity that may be related to a particular analyte. See also **Analyte.**

Quality control, *n* - The operational techniques and activities that are used to fulfill requirements for quality.

Quality control strategy, *n* - The number of control materials, the number of measurements to be made on those materials, the location of those control materials in an analytical run, and the statistical control rules or decision criteria to be used for interpreting the control data and determining whether or not to accept or reject an analytical run.

Random error, *n* - The result of a measurement minus the mean that would result from an infinite number of measurements of the same measurand carried out under repeatability conditions.

Repeatability conditions, *n* - Conditions where independent test results are obtained with the same method on identical test material in the same laboratory by the same operator using the same equipment within a short interval of time.

Reportable range, *n* - The range of test values over which the relationship between the instrument, kit, or system's measurement response is shown to be valid.

Standard deviation, *n* - The statistical measurement of imprecision among observations or measurement results. A measure of variability/dispersion that is the positive square root of the population variance.

Statistical quality control, *n* - A procedure in which stable samples are measured and the observed results compared with limits that describe the variation expected when the measurement method is working properly. The expected variation is determined by analyzing a stable control material many times, calculating the mean and standard deviation (SD) of those measurements, then calculating control limits as the mean plus and minus certain multiples of the SD. A control chart is prepared to display the observed result on the y-axis versus time on the x-axis. The control limits are drawn on the chart. New control results are plotted and compared with the control limits to assess whether the method is "in-control" (points within control limits) or "out-of-control" (points outside of control limits.)

Systematic error, *n* - The mean that would result from an infinite number of measurements of the same measurand carried out under repeatability conditions, minus a true value of the measurand. **NOTES:** a) Systematic error is equal to error minus random error; b) Like the true value, systematic error and its causes cannot be completely known.

4 Purpose of Statistical Quality Control

Statistical quality control procedures are intended to monitor the analytical performance of a method and alert analysts to problems that might limit the usefulness of a test result for its intended medical purpose. Quality control should assure that the analytical performance characteristics of the test are appropriate for the medical decisions that need to be made.

Quality control is generally performed by analyzing stable specimens (or specimens from patient populations having a stable characteristic) and statistically analyzing the data to describe analytical performance. The statistics are used to make judgements about the quality of analytical results, whether system correction is necessary, whether patient data should be accepted or rejected, and for estimating performance parameters which can be compared to the analytical and medical goals.

Statistical quality control testing is different from external quality control testing. In the latter, specimens whose values are unknown are submitted to a laboratory from an outside source. External quality control testing measures a laboratory's ability to obtain the correct result on an unknown specimen. The specimens are obtained through quality assurance programs of private, professional, or public organizations or through various governmental agencies responsible for laboratory licensure. External quality control testing is useful both for quality control purposes and for accreditation and licensure.

5 Planning a Statistical Quality Control Procedure

For statistical quality control procedures to be most effective, careful planning is necessary. Quality control planning involves several steps, including the following: (1) Defining the quality requirements for the test; (2) Determining the stable (in control) performance characteristics of the measurement procedure or analytical method; (3) Identifying candidate quality control strategies; (4) Predicting the performance characteristics of the candidate quality control strategies; (5) Specifying desirable goals for the QC performance characteristics; (6) Selecting a quality control strategy whose predicted performance meets or exceeds the quality control performance goals.

5.1 Define the Quality Requirement

A quality requirement may be defined in terms of an allowable total analytical error, such as often provided by proficiency testing criteria for acceptable performance. The allowable total error is the magnitude of analytical error that if exceeded would cause a test result to be of unacceptable quality.[7] It encompasses both random and systematic errors, i.e., both method imprecision and bias. There also are recommendations for medically important changes[8] in test results that similarly include both method imprecision and bias, as well as preanalytical variables such as the within-subject biological variation. Biologic variation itself provides another basis for defining the allowable imprecision and the allowable bias for a test. Clinical treatment models can also be a source of information about the analytical quality required to assure that test results are medically useful. [10]

5.2 Determine Method Performance

The performance characteristics of an analytical process that are critical for the proper planning of QC procedures are imprecision and bias. Estimates of these parameters should represent the stable performance of an analytical process. In addition to imprecision and bias, it would be useful to have information about unstable performance, such as the expected type, magnitude, and frequency of analytical errors, but this information is not generally available.

5.2.1 Imprecision

Imprecision is estimated by repeated measurements on stable control materials. It is generally accepted that a minimum of at least 20 different bottles should be assayed on separate days. NCCLS document EP5 calls for performing two runs a day for at least 20 days.

5.2.2 Bias

Bias should be evaluated in the context of the quality requirement defined in Section 5.1 and the "truth" or accuracy that is being managed by the laboratory. In many cases, the interest is the stable performance since an event, such as a method validation study, a clinical validation study, or a calibration event, in which cases the bias term is often assumed to be zero and the objective in QC is to monitor changes from that baseline period. Other practical approaches for estimating bias include the following:

- Comparison with the certified values by analysis of certified reference materials with the same matrix and demonstrated commutability with test samples.

  Comparison with assigned values on commercial assayed control materials if specific for the method being evaluated.

- Comparison with the peer group mean in proficiency testing surveys. An accuracy based comparative method target value may be used when proficiency testing specimens have demonstrated commuta-bility with patient specimens.

- Comparison of results obtained on patient specimens which are analyzed by the test method and another routine laboratory method (see NCCLS document EP9—*Method Comparison and Bias Estimation Using Patient Samples*).

- Comparison of results obtained on patient specimens which are analyzed by the test method and a reference method (see NCCLS document EP9—*Method Comparison and Bias Estimation Using Patient Samples*).

5.3 Identify Candidate Statistical QC Strategies

A quality control strategy is defined by what control materials are used, how many control samples are analyzed, where these control samples are located, what quality control rules are applied to the control sample measurements, and when the quality control rules are evaluated. The appropriateness of the QC strategy depends on the quality required, as well as the expected instability of the analytical method (e.g., type, magnitude, and frequency of errors). Several QC strategies may be defined and evaluated.

5.4 Predict QC Performance

The performance of a quality control strategy can be predicted from probability calculations or from computer simulation studies. The most direct indicator of the performance of a quality control procedure is the expected number of unacceptable patient test results that are produced (or reported) when an out-of-control error condition exists.[11] This will depend on the type and magnitude of the out-of-control error condition, when the error condition occurs and how long it lasts, which in turn depends on how frequently quality control testing occurs and the probability that the quality control rules detect the error condition. These predictions generally assume the shape of the error distribution is gaussian, which may not account for some periodic and irregular effects observed with real laboratory systems, therefore, the complexity of the prediction model needs to match the complexity of the potential error sources of the method and system.

5.5 Set Goals for QC Performance

Quality control performance goals set desirable targets for quality control performance. The goal will depend on the chosen quality control performance measure. Thus, one goal could be specified as a maximum allowable number of unacceptable results due to an out-of-control error condition, or a maximum allowable probability of reporting unacceptable results (maximum defect rate), or a minimum acceptable probability of detecting an out-of-control error condition. Another goal could specify a maximum acceptable probability of false rejections.

5.6 Select Appropriate QC

When more than one quality control strategy meets the quality control performance goals, other characteristics such as cost and ease of implementation can be used to select the best approach.

5.7 Example QC Planning Applications

Practical approaches for selecting appropriate QC procedures have been described based on power function graphs, critical-error graphs, and charts of operating specifications.[12] Illustrative applications of QC planning are available in the literature to provide guidance in selecting appropriate QC strategies.[13,14]

6 Analytical Intervals Defined

6.1 Analytical Run

For purposes of quality control, an analytical run is an interval (i.e., a period of time or series of measurements) within which the accuracy and precision of the measuring system is expected to be stable. In laboratory operations, control samples are analyzed during each analytical run to evaluate method performance, therefore the analytical run defines the interval (period of time or number of specimens) between evaluations of control results. Between quality control evaluations, events may occur causing the measurement process to be susceptible to variations that are important to detect.

6.2 Length of Analytical Run

The length of an analytical run must be defined appropriately for the specific analytical system and specific laboratory application. The manufacturer should recommend run length for the analytical system (MRRL) (see Section 6.3) and the user should define run length for the specific application (UDRL) (see Section 6.4).

6.3 Manufacturer's Recommended Run Length (MRRL)

The manufacturer should recommend the period of time or series of measurements within which the accuracy and precision of the measuring system, including instruments and reagents, are expected to be stable. The manufacturer should identify events that may cause the measurement process to be susceptible to variations which are important to detect.

6.4 User's Defined Run Length (UDRL)

The user should define the period of time or series of measurements within which validation of the measurement process is important based on patient sample stability, number of patient samples being analyzed, cost of reanalysis, work flow patterns, operator characteristics, or similar nonanalytic considerations that are in addition to the expected stability of the accuracy and precision of the measuring system. The UDRL should not exceed the MRRL unless the user has sufficient scientific data to document the modifications.[b]

6.5 Periodic Reassessment of Run Length

The UDRL should be reassessed at regular intervals over the lifetime of an analytical method or instrument system to account for possible changes due to instrument wear, reformulated reagents, software upgrades, and other factors that may affect analytical performance.

6.6 Alternative Approaches for Establishing Run Lengths

There currently are no well-accepted methodologies for establishing run lengths in a more scientific manner. It is recognized that long run lengths are advantageous for maintaining low cost and high productivity, but these advantages may be offset by potential failure-costs if quality deteriorates, errors go undetected, and test results are misinterpreted due to these errors. One approach for studying the cost versus quality issue is to apply industrial models for the economic design of control procedures.[15] With further investigation and development of this methodology, or with the development and evaluation of other methodologies, alternative approaches can be expected that will allow run lengths to be established by carefully documented studies.

7 Control Materials

7.1 Application

Control samples must be analyzed for each analyte during the user's defined analytical run length (UDRL).

7.2 Characteristics

The control material should have characteristics which enable it to provide information about what is going on with the testing process. A material whose composition is similar to or identical with the patient sample matrix being analyzed is generally best. Such matrix control materials should be used, when available, and should mimic, insofar as possible, the unknown specimen. A laboratory should obtain enough homogeneous and stable material to last for at least one year. Vial to vial variability should be much less than the variation expected for the system being monitored, and the materials should maintain the analyte being quantified in a stable state.[16,17] If commercial control materials are not available, the laboratory may prepare it's own patient pools. If there is no appropriate QC material available, the analysis cannot be the subject of the type of QC discussed in this document.

[b] For U.S. laboratories, federal and state regulations set the maximum UDRL as 24 hours.

7.3 Relation to Calibrators

Control materials need to be different from the calibrator materials to ensure that the QC procedure provides an independent assessment of system performance.

7.4 Concentrations of Analytes in Control Materials

The number and concentration of matrix quality control materials should be sufficient to determine proper operation over the range of interest.

7.4.1 Clinical Decision Levels

For most analyte-method combinations, a minimum of two levels (concentrations) of control materials is recommended. Where possible, analyte concentrations should be at clinically relevant levels to reflect values encountered in patient specimens.[5,18] Concurrently using matrix control samples at different levels allows application of additional quality control rules which improve interpretation of analytical error (i.e., proportional vs. constant, random vs. systematic).

To ascertain the acceptability of patient data, additional control materials may be added at clinical decision levels appropriate for the test and analytical system. Laboratories should plan their quality control strategies to include these important decision levels unless performance can be monitored with fewer levels (e.g., two materials have levels that bracket a third clinical decision level, the 2nd and 3rd clinical decision levels are close enough to be adequately monitored by one control material at mid-concentration of these decision levels).

7.4.2 Confirmation of Reportable Range

Control materials may be selected to cover the reportable range. Routine testing of these control materials may also be helpful for confirming the expected reportable range.

8 QC Applications

8.1 Statement of QC Strategy

The laboratory should define the control materials that are to be analyzed, the number of measurements to be made on each material, the location of each material in the analytical sequence, the decision criteria or control rules that are to be applied to decide whether or not analytical performance is acceptable, and the actions to be followed in response to the decision on acceptability.

8.2 Frequency of Control Measurements

Quality control samples must be analyzed at least once during each user-defined analytical run length (UDRL). Manufacturers of analytical systems or reagents should recommend the number of quality control specimens and their location within the run. However, manufacturer recommendations should be used as guidelines. The frequency and location of control samples should reflect actual test system performance at the site of testing. The user may need additional control specimens and a different location in order to meet different laboratory circumstances.

8.3 Location of Control Samples

The user should determine the location of control samples within a run, keeping in mind the principle that quality control results should be evaluated before reporting patient results from the run. The location of control samples should consider the type of analytical process, the kinds of errors that might occur, and the protocol for reporting patient results. For example, if the UDRL corresponds to a discrete batch of samples, the controls might be located at the end of the run to detect shifts, might be spaced evenly throughout the batch to monitor drift, or distributed randomly among the patient samples to detect random errors. In any case, the QC results would be evaluated before patient results were reported. For a high-volume analyzer that continuously produces test results, an appropriate UDRL might be defined as a certain interval of time, then QC samples would be analyzed and evaluated at the beginning of a run and if the system is determined to be in-control, patient results could be reported for the remainder of

the UDRL. If a quality control fault is detected, results reported since the previous quality control event need to be reviewed. Note that routine placement immediately after calibration materials may give falsely low estimates of analytical imprecision and will not provide any estimate of shift or drift during the run.

8.4 Decision Criteria or Control Rules

Control data must be evaluated before reporting patient data. Decisions are made by inspecting a written or graphic record of control results or by computer review of results. Many different decision criteria or control rules have been used, most of them assuming a Gaussian distribution of the random errors of the measurement system and setting control limits from the mean and standard deviation calculated for the error distribution observed in each individual laboratory. Control limits are customarily based on multiples of the observed standard deviation on both sides of the observed mean value, e.g., the observed mean plus and minus 3 times the observed standard deviations. Control limits are usually based on the total standard deviation that includes all the sources of variation in the stable measurement system.

8.4.1 Representation of Quality Control Rules

Quality control rules can be represented by abbreviations of the form A_L, where "A" represents the number of control observations and "L" is a control limit derived from Gaussian statistics. [6,19] For example, 1_{3s} refers to a control rule wherein action is taken when a single control result is beyond three standard deviations from the mean. The 2_{2s} rule refers to a control rule wherein results from two concurrent control samples on the same run are beyond two standard deviations from the mean in the same direction, or results from control samples across runs are beyond two standard deviations from the mean in the same direction. Commonly used rejection rules are $1_{3,4s}$ and the 2_{2s}, but many others are described.

Quality control rules for ranges can be represented in the form R_L, where "R" is the absolute difference between two control results in the same run and "L" is a limit derived from Gaussian statistics. For example, R_{4s} refers to a control rule where action is taken when the difference between the high and low measurements is greater than four times the standard deviation. Quality control rules should be designed to detect both random and systematic error. Generally random error will be detected by using 1_{3s} and R_{4s}; whereas systematic error will be detected by the 2_{2s} rule, or procedures noting four consecutive observations exceeding the mean plus 1s, or the mean minus 1s, or seven to twelve consecutive observations on the same side of the mean. Very large systematic error is detectable by the 1_{3s} rule. Specific rules chosen should be based on the analytical and clinical goals of the particular assay and this clearly may be different for different analytes and clinical needs.

8.4.2 Error Detection

Quality control procedures should be capable of detecting analytical errors at an appropriately high rate accompanied by an appropriately low false rejection rate, based on the characteristics of the particular analytical procedure being monitored, and the relevant medical requirements for assay quality.[20] Using multiple control rules improves error detection with a low probability of false rejection.[6] The performance of control rules can be assessed by determining the probabilities for rejecting analytical runs with differing patterns of analytical errors. Graphic presentations of the probability of rejection versus size of errors are available.[21]

8.4.3 False Rejection

Using the 1_{2s} rule can warn that the system may be approaching an out-of-control situation. However, using the rule as a rejection signal may cause an inappropriately high incidence of false run rejections and is not generally recommended when the number of control measurements is greater than 1.

8.5 Control Charts

The graphic display of control results on control charts is often helpful in interpreting the control data. The Levey-Jennings type of chart is most commonly used.[22] Charts that make use of cumulative summation techniques or trend analysis techniques may provide better displays of systematic shifts and

drifts.[23,24] When a high number of control measurements is needed (6 or greater) to provide the necessary control for a process, mean and range charts may be more appropriate [25]

8.6 Setting Control Limits

Control limits should be calculated from the mean and standard deviation that describe the variation expected when a control material is analyzed by the methods in use in a laboratory. For example, a 1_{3s} control rule would have control limits calculated as the mean plus and minus 3 standard deviations.

8.6.1 Values for the Mean and Standard Deviation

The mean and standard deviation of a control material should be established on the basis of repeated measurements on those materials by the methods in use in the laboratory. Control limits can then be calculated from the means and standard deviations observed in the laboratory.

8.6.2 Assayed Control Materials

If assayed materials are used, the values stated on the assay sheets should be used only as guides. Actual values for the mean and standard deviation must be established by replicate testing in the laboratory.

8.6.3 Establishing the Value of the Mean on a New Lot

New lots of control material should be analyzed for each analyte in parallel with the control material in current use. Ideally, a minimum of at least 20 bottles should be assayed on separate days. If the desired 20 data points from 20 days are not available, provisional values may have to be set from fewer than 20 days. Possible approaches include making no more than four control measurements per day for at least five different days.

8.6.4 Establishing the Value of the Standard Deviation on a New Lot

If there is a history of quality control data from an extended period of stable operation, the established estimate of the standard deviation should be used with the new lot. The estimate of standard deviation should be reevaluated periodically.

If there is no history of quality control data, the standard deviation should be estimated, preferably with a minimum of 20 data points from 20 separate days. This value should be replaced with a better estimate when data from a longer period of stable operation becomes available.

8.6.5 Cumulative Values

Estimates of the standard deviation (and to a lesser extent the mean) from monthly control data are often subject to considerable variation from month to month due to inherent difficulty of estimating a standard deviation from the available number of measurements (e.g., with 20 measurements, the estimate of the standard deviation might vary up to 30% from the true value; even with 100 measurements, the estimate may vary by as much as 10%).[26] More representative estimates can be obtained by cumulating the control data from shorter periods of time, e.g., combining control data from six consecutive one-month periods to provide six month cumulatives. Care should be taken to ensure that the mean is not changing consistently lower or consistently higher for the monthly periods being combined.

8.7 Out-of-Control Situations

Laboratories need to establish guidelines for responding to out-of-control situations. Responses such as repeating control measurements or reanalyzing new control materials are not productive when QC strategies have been carefully planned and control rules selected to minimize the false rejection of analytical runs, as described in guidelines for statistical quality control proposed by a European working group.[27]

8.7.1 Eliminate Causes of Problems

When QC has been carefully planned and properly implemented (which requires reliable estimates of the mean and standard deviation be used in calculating control limits), false rejections are minimized from the outset. The best response to an out-of-control signal is to

identify the cause of the problem, find fail-safe solutions that eliminate that cause, and prevent that problem from occurring in the future. [27]

8.7.2 Clinical Significance of Analytical Errors

It is better to define the clinical quality that is necessary in the beginning to guide the planning of QC strategies rather than be faced with having to make a judgment on the clinical importance of errors during the pressure of daily service.[27] Guidelines for planning quality-control strategies to detect medically important changes in test results have been published by Linnet.[28] Guidelines for planning QC procedures to satisfy biologic goals have been provided by the European working group. [27]

8.7.3 Verifying Patient Results

The laboratory should establish a policy that defines the appropriate action for verifying patient results that may have been affected by a QC fault. This is particularly important when using long UDRLs and provides a caution to consider clinical validation needs as well as stability for defining practical run lengths.

8.7.4 Limitations

This recommended practice for dealing with out-of-control situations depends on following the other recommendations in this document and shows the interdependence of all the concepts, approaches, and practices described in this document. Implementation of this recommendation in isolation from the rest of the recommendations in this document will not result in any improvement in laboratory QC. The laboratory must begin by:

- defining the quality required for each test
- establishing a process for planning QC procedures
- selecting appropriate control rules and numbers of control measurements
- establishing appropriate UDRLs
- obtaining reliable estimates of the means and standard deviations to calculate appropriate control limits
- implementing a proper action for responding to out-of-control situations.

9 Interlaboratory QC Programs

When laboratories share a common pool (lot number) of control materials and report the results to an interlaboratory program, a database is created. This data base yields statistical information, which may be used to describe or define:

(1) Intralaboratory and interlaboratory imprecision
(2) Laboratory bias relative to a peer group
(3) Relationship of analytical and statistical parameters of imprecision and relative bias to medical requirements.

For laboratory self-evaluation, peer-related bias and relative imprecision are useful parameters. Participation in an interlaboratory program provides an effective mechanism to complement external quality control (proficiency survey) programs. Consequently, laboratories are encouraged to actively participate in interlaboratory QC programs when such programs are available.

References

1. Westgard JO, Klee GG. Quality Management. In: Burtis CA and Ashwood ER, eds. *Tietz Textbook of Clinical Chemistry*. 2nd ed. Philadelphia: W.B. Saunders Company; 1994:548-592.

2. Woo J, Henry JB. Quality management. In: Henry JB, ed. *Clinical Diagnosis and Management by Laboratory Methods*. Philadelphia: W.B. Saunders Company; 1996:125-136.

3. Cembrowski GS, Carey RN. *Laboratory Quality Management*. Chicago: ASCP Press; 1989:264.

4. Westgard JO, Barry PL. Cost-Effective Quality Control: Managing the Quality and Productivity of Analytical Processes. Washington, DC: AACC Press;1986:230.

5. Haven GT, Lawson NS, and Ross JW. Quality control outline. *Pathologist.* 1980;34: 619-621.

6. Westgard JO, Barry PL, Hunt MR. A multirule Shewart chart for quality control in clinical chemistry. *Clin. Chem.* 1981;27:493-501.

7. Burnett RW, Westgard JO. Selection of measurement and control procedures to satisfy HCFA requirements and provide cost-effective operation. *Arch Pathol Lab Med.* 1992;116:777-782.

8. Skendzel LP, Barnett RN, Platt R. Medically useful criteria for analytical performance of laboratory tests. *Am J Clin Pathol*. 1985;83:200-205.

9. Fraser CG, Hyltoft Petersen P, Ricos C, Haeckel R. Proposed quality specifications for the imprecision and inaccuracy of analytical systems for clinical chemistry. *Eur J Clin Chem Clin Biochem.* 1992;30:311-317.

10. Hyltoft Petersen P, deVerdier C-H, Groth T, Aronsson T. Clinically based quality goals; a NORDKEM project. *Eur J Haematol*. 1990;45(Suppl 53):6-8.

11. Parvin CA, Gronowski AM. Effect of analytical run length on quality-control (QC) performance and the QC planning process. *Clin Chem*. 1997;43:2149-2154.

12. Westgard JO. Error budgets for quality management: Practical tools for planning and assuring the analytical quality of laboratory testing processes. *Clin Lab Manag Review.* 1996;10:377-403.

13. Koch DD, Oryall JJ, Quam EF, Felbruegge DH, Dowd DE, Barry PL, Westgard JO. Selection of medically useful QC procedures for individual tests on a multi-test analytical system. *Clin Chem.* 1990;36:230-3.

14. Mugan K, Carlson IH, Westgard JO. Planning QC procedures for immunoassays. *J Clin Immunoassay.* 1994;17:216-22.

15. Neubauer A, Wolter C, Falkner C, Neumeier D. Optimizing the frequency and number of controls for automatic multichannel analyzers. *Clin Chem.* 1998;44:1014-1023.

16. Taylor TK. *Quality Assurance of Chemical Measurements.* Chelsea, MI: Lewis Publishers Inc.;1987.

17. Lawson NS, Haven GT, Williams GW. Analyte stability in clinical chemistry quality control materials. *CRC Crit. Rev. Clin. Lab. Sci.* 1982;17:1-50.

18. Statland BE. *Clinical Decision Levels for Laboratory Tests*. 2nd ed. Oradell, NJ: Medical Economics Books;1987.

19. Westgard JO, Groth T, Aronsson T, et al. Performance characteristics of rules for internal quality control: Probabilities for false rejection and error detection. *Clin. Chem.* 1977;*23*: 1857-1867.

20. Westgard JO, Groth T. A predictive value model for quality control: Effects of the prevalence of errors on the performance of control procedures. *Am. J. Clin. Pathol*; 1983;80:49-56.

References (Continued)

21. Westgard JO, Groth T. Power functions for statistical control rules. *Clin. Chem*. 1979;25:863-869.

22. Levey S, Jennings ER. The use of control charts in the clinical laboratory. *AM J Clin Pathol.* 1950;20:1059-66.

23. Westgard JO, Groth T, Aronsson T, deVerdier C-H. Combined Shewhart-Cusum control chart for improved quality control in clinical chemistry. *Clin. Chem.* 1977;23:1881-1887.

24. Neuhauer AS. The EWMA control chart: properties and comparison with other quality-control procedures by computer simulation. *Clin. Chem.* 1997;43:594-601.

25. Hainline A. Quality assurance: Theoretical and practical aspects. In: Faulkner WR, and Meites S, eds. *Selected Methods of Clinical Chemistry,* Vol. 9. *Selected Methods for the Small Clinical Chemistry Laboratory.* Washington, D.C.: AACC; 1982:17-31.

26. Westgard JO, Carey RN, Wold S. Criteria for judging precision and accuracy in method development and evaluation. *Clin Chem.* 1974;20:825-833.

27. Hyltoft Petersen P, Ricos C, Stockl D, Libeer JC, Baadenhuijsen H, Fraser C, Thienpont L. Proposed guidelines for the internal quality control of analytical results in the medical laboratory. *Eur J Clin Chem Clin Biochem.* 1996;34:983-999.

28. Linnet K. Choosing quality-control systems to detect maximum clinically allowable analytical errors. *Clin Chem.* 1989;35:284-288.

Summary of Comments and Committee Responses

C24-A: *Internal Quality Control Testing: Principles and Definitions; Approved Guideline*

General Comments

1. Most hematologists (and heme lab personnel) have no comprehension of what the chemical jargon, "matrix" means. You want a reasonably wide audience to benefit from this document.

- **The term matrix has been defined in Section 3.**

Key Words

2. You should distinguish clearly between "calibration interval" and "calibration."

- **The working group and area committee decided to omit the brief section on calibration from C24-A2 rather than expanding this discussion to adequately treat this topic.**

Section 2.0

3. The last paragraph in this section points out, in its second sentence, the key consideration relative to a methods analytical performance. In this day of governmental involvement in testing, the statement is most pertinent and I believe applies very specifically to the congressional and regulatory discussions relative to the "complexity model of testing." I realize that currently this is a draft document, but it would be nice if we were able to quote this—if not as NCCLS members, at least individually or representatives of our organizations.

- **Addition of Section 5, on** "Planning a Quality Control Procedure," **should help laboratories consider their particular requirements and apply QC to meet the needs of their patients and physicians.**

Section 4.0 (New Section 6.0)

4. The definition of the word "matrix" should be added, in very simple language.

- **Matrix is now defined in Section 3.**

5. Definitions for instruments performance, stray light, bandwidth, and filter types should be included.

- **Definitions have been added in Section 3 for performance terms such as bias, imprecision, random error, and systematic error, which are the terms most relevant for this document.**

6. Definitions for random error and system error should be added.

- **These definitions have been added in Section 3.**

7. The discussion of user defined run length (UDRL) suggesting a 24-hour time limit is currently inconsistent with the capabilities of modern clinical laboratory testing systems and should be corrected.

- **The committee recognizes that instrument systems may be stable for longer than 24 hours. However, 24 hours still seems to be a reasonable maximum based on an instrument s potential susceptibility to problems, which is the other side of the coin and an equally important consideration. There often are changes being made in a 24-hour period, such as new reagents,**

new bottles of calibrators, system maintenance, and different operators. There may be new approaches developed that will allow run lengths to be established in a more scientific manner, which is now recognized in the new paragraph in Section 6.6. This paragraph provides the flexibility for manufacturers and users to establish run lengths by other approaches that are properly investigated, peer-reviewed, and documented.

Section 5.2 (New Section 7.2)

8. The "type of QC" should be changed to "the unmodified QC."

- **The committee prefers the original wording. "Type of QC" here refers to statistical control using stable materials. Modified or "unmodified QC " has a different implication in today's regulatory environment. Both modified and unmodified QC procedures could be statistical control using stable materials.**

Section 5.3 (New Section 7.3)

9. "A different batch (lot number) than the" should be changed to "a different supply of." Also, "the same lot of material" should be changed to "the same material."

This section has been modified to emphasize the need for independent calibrators and controls. The present language considers that the "pool used to manufacture the control materials should be a different lot from the pool used to manufacture calibration materials."

Section 5.4.1 (New Section 7.4.1)

10. I would suggest that the following parenthetical statement be added at the end of the second sentence: (patient specimens assayed in prior runs or on different analyzers may serve as matrix control specimens as appropriate).

- **This document doesn t cover the details of patient data QC that would be necessary if this statement were included. For example, the planning of patient data QC procedures is more complicated and the manner in which control limits and control rules are established is different.**

Section 5.4.2 (New Section 7.4.2)

11. When selecting a general purpose multiconstituent control, all analytes may not be available within instrument range. Using material that requires dilution diminishes the utility of quality control testing.

- **The intention is to recommend that analytes be selected to reflect important clinical levels "where possible."The "where possible" recognizes that there will be some difficulties in doing this for all analytes when using multiconstituent controls.**

Section 5.6 (New Section 8.2)

12. I believe that the information included in the discussion of User Defined Run Length (UDRL) is inconsistent with many comments on this subject expressed at the NCCLS National Congress on CLIA '88. The statement in this guideline suggesting a 24-hour time limit has been converted by HCFA into a mandatory time limit in CLIA "88. I suggest the committee quickly review this concern as the guideline is currently inconsistent with the capabilities of modern clinical laboratory testing systems.

- **Section 6.4 has been changed in C24-A2. A footnote has been included to indicate that the 24-hour maximum is the current CLIA mandate for U.S. laboratories, rather than a mandate in this**

document. The new Section 6.6 allows some flexibility for manufacturers and users, but requires that alternate approaches for establishing run lengths be well documented.

Sections 5.7.1 and 5.7.2 (New Section 8.3)

13. There are statements relative to random and fixed placement of quality control samples within the run. However, there is no recommendation as to which is appropriate and when. The document would be improved if some sort of a statement were made in this regard rather than the somewhat less than adequate implications.

- **These original sections on random and fixed placement have been changed to provide a more generic description that identifies some of the factors that will influence the placement of controls.**

Section 5.8 (New Section 8.1)

14. In the third sentence of the paragraph, the term "data" is used in a way that could be very broadly interpreted. My concern is that some readers of the document might assume that raw data developed by manufacturers might be something to which they are entitled. I believe that an appropriate qualifying statement relative to the use of the word data would be appropriate.

- **That statement has been changed to indicate that data should be available to validate quality control recommendations.**

Section 6.2

15. In sentence number 5, I would strongly suggest the phrase "though not necessarily" be added after the word customarily. By doing this, one maintains the intent of the document without making statistical limits mandatory. I believe that, again, in the light of regulatory involvement, reasonable flexibility must be promoted. Even though the NCCLS documents are not intended for regulatory use, they are frequently quoted by the regulators, and I believe we must be sensitive to these issues.

- **The implication of this comment is that nonstatistical limits may be used. With the addition of the new Section 5 on planning a quality control procedure, the medical and analytical requirements for quality should be considered up-front and the statistical limits or rules be selected to assure the defined quality is achieved.**

Section 6.3 (New Section 8.4.1)

16. I would suggest strongly that a statement similar to the following be added at the end of the last paragraph of this section: "Specific rules chosen should be based on the analytical and clinical goals of the particular assay and this clearly may be different for different analytes and clinical needs."

- **The new Section 5 on planning a quality control procedure recognizes the importance of defining the analytical or clinical quality needed in the first step of the planning process.**

Section 8.2

17. The cost savings and convenience of multiconstituent controls can be offset by problems with cross-reactivity.

- **This statement and the separate recommendations for the "low test volume environment" have been eliminated in C24-A2.**

Section 8.3.2

18. I would suggest that the second sentence be modified to read "The process of establishing actual target values must include repeating of analytical testing in the laboratory. Incorporation of manufacturers' and other information including general laboratory experience may be part of the final mechanism for determining the laboratory values."

- **The word "target" has been eliminated in the new document to avoid confusion with the use of "target values" in the CLIA regulations. A strong emphasis is still maintained on the laboratory's need to establish its own mean and standard deviation that will reflect the performance being achieved in the individual laboratory.**

Summary of Delegate Comments and Responses

C24-A2: *Statistical Quality Control for Quantitative Measurements: Principles and Definitions; Approved Guideline Second Edition*

General

1. Change name "Internal Quality Control" to "In-House" or "User Established" to eliminate the confusion with "Internal Quality Control" used by manufacturers and FDA, CLIA to mean QC internal to the device.

- **The title of the document has been changed to "Statistical Quality Control for Quantitative Measurements: Principles and Definitions." The word "internal" has been replaced with "statistical" throughout the guideline.**

2. I would suggest that the relationship between accuracy and systematic error and precision and random error be discussed in further detail.

- **Other NCCLS documents, particularly the evaluation protocols series, provide in depth discussions of accuracy and precision. In this guideline, only standard definitions are included.**

3. A section with examples and problem solving would be useful.

- **Examples and detailed directions for the implementation of statistical QC and construction of control charts can be found in References 1-6. Examples of the planning of statistical QC procedures are provided in References 12-14, 27 and 28.**

4. The document should more strongly state the acceptability of alternate QC practices (electronic QC, procedural controls, etc.)

- **This document deals only with statistical QC. The third paragraph of the Foreword states that this document does not attempt to describe alternatives to statistical process control. Because of the focus on statistical QC, there are no recommendations about the acceptability or non-acceptability of alternative QC procedures. Another NCCLS subcommittee is considering alternative QC practices.**

Introduction

5. My concern is that the scope of this guideline is much too broad and does not address the needs of small laboratories (contrary to the first sentence in Scope, 2) that might be using instruments and systems that self monitor in part or in the whole. When the laboratory elects to use statistical monitoring, this document provides a very useful guide to important considerations and concerns that need to be controlled and/or monitored.

- **The title of the document has been changed to, "Statistical Quality Control for Quantitative Measurements: Principles and Definitions; Approved Guideline Second Edition," to clarify that these recommendations and guidelines apply when a laboratory elects to use statistical monitoring. Large and small laboratories alike may use this document for guidance in implementing appropriate statistical QC procedures.**

6. The last sentence of the introduction should be changed: "...it is still useful to monitor the outcome of the whole analytical process by traditional statistical quality control." This might not be true for several reasons, including the monitoring capability of the system, the economics of the testing environment, the specificity and compatibility of the control material. An acceptable change is "...it is *often* useful to monitor the outcome of the whole analytical process by

traditional statistical quality control. However, alternative acceptable quality practices can be established to accommodate such factors as internal or self-monitoring capability, availability of suitable control materials, the expectation of when a significant change in performance is anticipated to occur, and economics to optimize testing frequency.

- **Statistical QC can be used in most situations, even if "alternative" QC procedures are employed. Statistical QC provides an assessment of performance that is independent of an instrument's own checks and internal or self-monitoring capability. It should also be noted that statistical QC provides a way to monitor operator proficiency, which needs to be documented to satisfy regulatory requirements in some countries.**

Section 3

7. Add definition of "internal quality control" to the list of definitions. It wasn't until I got to Section 4 "Purpose of Internal Quality Control" that I truly understood.

- **The title of the document has been changed to eliminate "internal" and add "statistical" to more clearly focus on statistical QC and provide a term that is commonly understood. The document defines statistical quality control in Section 3 and "statistical quality control strategy" in Section 5.3.**

Section 5.3

8. Specific sentence and section that needs changing. 5.3 Identify Candidate QC Strategies. "A quality control strategy is defined by what control materials are used,... are evaluated." This statement describes the decisions that should be made once the QC strategy is defined, if the strategy includes statistical QC using simulated (or real) patient control materials. The introductory statement should be: "A quality control strategy is defined by the needs of the user of the results that will be reported from the clinical laboratory. The tools might include innovative practices that take advantage of the technological capability of the system or any unique attributes of the testing process. If statistical QC practices are employed, the guidance in this document should be consulted, and consideration given to what control materials are used,... are evaluated."

- **The heading of Section 5.3 was changed to "Identify Candidate Statistical QC Strategies." This confines the recommendation to statistical QC, which is the focus of this document. Alternative QC practices are currently being considered by the NCCLS Subcommittee on Unit Use Testing.**

Related NCCLS Publications*

C27-A **Blood Gas Preanalytical Considerations: Specimen Collection, Calibration, and Controls; Approved Guideline (1993).** Guidelines for collecting and handling an arterial blood specimen for pH and blood gas analysis.

EP5-A **Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline (1999).** Guidelines for designing an experiment to evaluate the precision performance of clinical chemistry devices; recommendations on comparing the resulting precision estimates with manufacturer's precision performance claims, and determining when such comparisons are valid; and manufacturer's guidelines for establishing claims.

EP9-A **Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline (1995).** This document addresses procedures for determining the bias between two clinical methods, and the design of a method-comparison experiment using split patient samples and data analysis.

EP10-A **Preliminary Evaluation of Quantitative Clinical Laboratory Methods; Approved Guideline (1998).** This guideline provides experimental design and data analysis for preliminary evaluation of the performance of an analytical method or device.

H26-A **Performance Goals for the Internal Quality Control of Multichannel Hematology Analyzers; Approved Standard (1996).** Recommended performance goals for analytical accuracy and precision based on mathematical models for the following measurements: hemoglobin concentration, erythrocyte count, leukocyte count, platelet count, and mean corpuscular volume.

H42-A **Clinical Applications of Flow Cytometry: Quality Assurance and Immunophenotyping of Lymphocytes; Approved Guideline (1998).** This document provides guidance for the immunophenotypic analysis of non-neoplastic lymphocytes by immunofluorescence-based flow cytometry; sample and instrument quality control; and precautions for acquisition of data from lymphocytes

M22-A2 **Quality Assurance for Commercially Prepared Microbiological Culture Media Second Edition; Approved Standard (1996).** Quality assurance procedures for manufacturers and users of ready-to-use microbiological culture media.

M29-A **Protection of Laboratory Workers from Instrument Biohazards and Infectious Disease Transmitted by Blood, Body Fluids, and Tissue; Approved Guideline (1997).** This document provides guidance on the risk of transmission of hepatitis viruses and human immunodeficiency viruses in any laboratory setting; specific precautions for preventing the laboratory transmission of blood-borne infection from laboratory instruments and materials; and recommendations for the management of blood-borne exposure.

NRSCL8-A **Terminology and Definitions For Use in NCCLS Documents; Approved Standard (1998).** Standard definitions for use in NCCLS standards and guidelines, and for submitting candidate reference methods and materials to the National Reference System for the Clinical Laboratory (NRSCL).

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* Proposed- and tentative-level documents are being advanced through the NCCLS consensus process; therefore, readers should refer to the most recent editions.

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