A Practical Guide to Internal Quality Control (IQC) for Quantitative Tests in Medical Laboratories

(Proposed Guidelines)

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For

Hong Kong Association of Medical Laboratories Ltd.

September 2009

Educational Material

Disclaimer

The guidelines are compiled based, in most cases on published professional recommendations from national or international expert bodies or individuals. The guidelines are not, and never intended to be a complete primer or a "how-to" guide for the best internal quality control (IQC) practice in medical laboratories. And most importantly, neither the Editor nor the Hong Kong Association of Medical Laboratories Ltd. assumes responsibility for the accuracy of, or for errors or omissions in these guidelines.

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Revision date : March 2010

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HKAML gratefully acknowledges the help of Bio-Rad Pacific Limited with the printing of this book.

Foreword

The Hong Kong Association of Medical Laboratories is pleased to present to members and colleagues this "Practical Guide to Internal Quality Control". There is no doubt that Dr Richard Pang, PhD, has more than the required experience or qualifications to write about quality control. Dr Pang, former scientific officer at Dept of Pathology and Clinical Biochemistry at Queen Mary Hospital, having practical experience of more than 30 years in the field, is now retired, and has turned his energies to part time professional speaking and consultancy in quality control.

This guide describes the processes that are needed to fulfill the internal quality control requirements of modern day laboratories. The way to perform quality control has changed with the times. With international consensus on what is expected from a medical lab in terms of monitoring quality of medical testing, we now have much more to do in the laboratory. However, with the assistance of inexpensive computer programs, we can monitor our testing precision on a daily basis knowing that we can spot and prevent erroneous results from reaching patients.

For those planning to do ISO 15189 accreditation, you should find, in addition to the guide, that the appendices are useful. It contains tables and procedures, Westgard's Multirule QC procedure chart, QC for multiple analyzers and even Sigma Metrics, the latest new measure of performance, and perhaps, new to many of us.

In conclusion, this guide is for all of us in the lab field. Our thanks to Dr. Pang for his contribution to HKAML's mission - the advancement of medical laboratories in Hong Kong, and good laboratory practice.

Marianne Leung
Chairman, HKAML

Contents

1. Scope

There is a requirement for good laboratory practice (GLP) in Internal Quality Control (IQC), according to the local authoritative body HOKLAS accreditation standard for Medical Testing and ISO 15189:2007 - Medical laboratories - Particular requirements for quality and competence. The internal QC involves in-house procedures for continuously and concurrently assessing laboratory work so that results produced by the laboratory can then be decided whether they are reliable enough to be released for supporting quality patient care. Quality must be designed from the front end, not tested on the back end. The laboratory should establish its own IQC policy and standard practice guidelines, prospectively. In fact, the standard procedure guideline described by the laboratory accreditation organization is only the basic requirement for quality control. The final goal is promoting our medical laboratory service quality, achieving a good cost-effectiveness outcome, and providing the best patient care. It could effectively cut down the probability of false rejection (P_{fr}) and increase the probability of error detection (P_{ed}). When the results of IQC exceed the control provision, there should have technical processes to make corrections and effective mechanisms to prevent the recurrence. These actions will be the basis of continuous quality improvement (CQI).

Guideline Objectives

To provide healthcare professionals in the private sector with clear guidance on the management of internal quality control for quantitative tests in the laboratory.

To provide information and suggestions for good laboratory practice and for producing reliable results, regardless of where the test is performed.

1.1 Basic Principles

It is recommended that guidance on QC issues should be sought from publications of the relevant professional societies.

1.2 Compliance versus Practicality

1. *The laboratory shall design internal quality control systems that verify the attainment of the intended quality of results. It is important that the control system provide staff members with clear and easily understood information on which to base technical and medical decisions. Special attention should be paid to the elimination of mistakes in the process of handling samples, requests, examinations, reports, etc. (ISO 15189: 2007 Clause 5.6.1)*

Practicality: The laboratory shall document its quality control plan in detail, including the levels of quality control materials run each day, frequency of performing QC, types of QC materials and the QC acceptance criteria customerized for each examination procedure based on that procedure's capabilities.

2. *Control materials need to be <u>different</u> from the calibrator materials to ensure that the QC procedure provides an independent assessment of system performance. (CLSI C24-A3: 2006)*

Practicality: The laboratory is encouraged to use control material similar to or identical with patient sample matrix.

3. *Controls <u>independent</u> of those produced by the manufacturer of the test or analyzer should be used. (Supplementary Requirements for accreditation in the field of Medical Testing, NATA, July 2009)*

Practicality: The laboratory should use independent QC material, where available. In case independent controls are not available, the laboratory may use controls provided by the manufacturer or prepared in-house from patient pools.

4. *Laboratories should establish their own means and ranges rather than use product insert ranges. (CLSI C24-A3: 2006)*

Practicality: The mean and SD values must be calculated or evaluated before a new lot of QC material is used. The SD value should be derived from the laboratory established precision goals for each analyte.

5. *Acceptable ranges (confidence limits) must be defined for internal quality control material. Where acceptable ranges are set to limits other than ± 2SD based on current analytical performance, the rationale for the limits should be documented. (Supplementary Requirements for accreditation in the field of Medical Testing, NATA, July 2009)*

Practicality: The selection of QC levels should be optimized for clinical decision and patient management.

6. *It is recommended that there should be a strong emphasis on troubleshooting the measurement process to detect a root cause of an 'out-of-control' condition. (European Quality Association of Laboratory Medicine (EQALM) EQA-Organizers Working Group)*

Practicality: The laboratory must incorporate in the procedure, appropriate statistical QC rules used to detect systematic (trends or shifts) and random errors.

Practicality: The Laboratory must also establish and document procedures for monitoring, evaluating and resolving 'out-of-control' situations.

Practicality: The laboratory must maintain stability of analytical measuring systems by conducting regular audits and reviews aiming for improvement.

2. Definitions

Accuracy

"Closeness of the agreement between the result of a measurement and a true value of the measurand. Usually expressed in the same units as the result, as the difference between the true value and the value, or as a percentage of the true value that the difference represents; expressed this way the quantity is more correctly termed 'inaccuracy.'" [CLSI]. The closeness of measurements to the true value is indicative of the "accuracy"of the assay.

Precision

"Closeness of agreement between quantity values obtained by replicate measurements of a quantity, under specified conditions" [ISO]. The degree of fluctuation or the agreement of replicate values in the measurement system is indicative of the "precision"of the assay. "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." [CLSI] is indicative of the "imprecision" of the assay.

Mean

The arithmetic average of a group of values. This is determined by summing the values and dividing by the number of values.

Standard Deviation

A statistic which describes the dispersion about the mean. The standard deviation is related to the width of a normal curve.

Range

Range refers to the difference or spread between the highest and lowest observations. It is the simplest measure of dispersion.

Total Error

Total error is defined as the total allowable difference from the accepted reference value seen in the deviation of a single measurement from the target value. Total Error limits can be defined by medical usefulness or by external proficiency testing criteria such as the RCPA or CAP, biologic specifications for imprecision and accuracy and the US CLIA criteria for Total Error. There are also CLSI guidelines for Total Error.

Random Error

Random Error is defined as the dispersion of independent test results obtained under specified conditions. It is expressed as the maximum allowable coefficient of variation (CV%) of the results in a set of replicate measurements.

Systematic Error

Systematic Error is defined as the expressed difference between the average result obtained by a procedure under specified conditions and an accepted reference value or the deviation of the mean from the target value. Bias is expressed as the maximum allowable difference (Delta diff) of an average result in a set of replicate measurements and its expected reference value.

Trend

A trend is a sustained increase or decrease in a quality control value over a period of four or more days with the latest value at or beyond the 2 SD limits. If no action is taken, the QC limit may be breached.

Shift

A shift is a sudden change in the mean value of the accumulated quality control values. Precision is not affected but the plotted points stay consistently to one side or the other of the calculated mean value, indicating a shift in the distribution of control values with a new mean.

Drift

A drift is a gradual change of more than one set of controls that show a shift between the beginning and end of a run in the same direction.

Calibrator

A solution which has a known amount of analyte weighed in or has a value determined by repetitive testing using a reference or definitive test method.

Control

Material or preparation used to monitor the stability of the test system within predetermined limits.

Independent (Third-Party) Control

QC materials that are independent of the calibration materials or obtained from a different supplier of the analyzing system.

Analytical Run

Generally defined by CLIA as an 8 hour to 24 hour interval during which control materials must be analyzed. According to CLSI C24, a 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."

Additional definitions:

http://www.eurogentest.org/web/info/public/unit1/qmanagement/definitions_v1.xhtml
http://www.westgard.com/glossary.htm

3. Purposes

"The main objective of internal quality control (IQC) is to ensure day-to-day consistency"(WHO 1981)

There are three purposes of IQC:

1. To monitor the accuracy and precision of the complete analytical process;
2. To detect immediate errors that occur due to test-system failure, adverse environmental conditions, and operator performance; and
3. To monitor over time the accuracy and precision of test performance that may be influenced by changes in test system performance and environmental conditions, and variance in operator performance.

As defined in the Harmonized Guidelines for Internal Quality Control in Analytical Chemistry Laboratories : '*internal quality control (IQC) is a set of procedures undertaken by laboratory staff for the continuous monitoring of operations and the results of measurements in order to decide whether results are reliable enough to be released*.' (Thompson and Wood, 1995). Above all, IQC is a control of the precision of your analytical process with the aim of assuring a long-term constancy of the results. It can also be a control of trueness depending of the control material used. The main objective is to ensure the constancy of the results day-to-day and their conformity with defined criteria.

4. QC Planning

General guidelines for planning and design of IQC procedures have been provided by CLSI (formerly NCCLS, National Committee for Clinical Laboratory Standards). The essential steps for planning a statistical QC procedure are presented as follows:

1. Define the quality requirement for the test.
2. Determine method precision and bias.
3. Identify candidate IQC procedures.
4. Predict IQC performance.
5. Set goals for IQC performance.
6. Select an appropriate IQC procedure.

Source:
Westgard JO. Internal quality control: planning and implementation strategies. Ann Clin Biochem 2003; 40: 593-611.

4.1 Define the Quality Requirement

Analytical Performance Goals

The laboratory should established analytical goals for all assays that incorporate both the requirements for acceptable clinical performance and the capabilities of current procedures. A performance standard in this context is a synonym for Total Allowable Error (TEa) or Allowable Limits of Error (ALE). At present, there is no consensus on how to define and calculate TEa or ALE. A fundamental reality is that no single approach is universally applicable. Consequently, multiple approaches must be used.

The major approaches are:

- Traditional Approach: The state-of-the-art of analysis, opinions of the clinicians, fraction of the reference interval (Tonks' formula).
- Biological Variation Approach: The amount of error which will allow one to calculate the probability that a result is significantly different from the previous result for that patient (Appendix I).
- Regulatory Approach: e.g. CLIA '88 PT limits (Appendix II).

TEa/ALEs are presented in the following ways:

a) As absolute concentration limits, e.g. target value ± 0.06 mmol/L for calcium.
b) As a percentage, e.g. target value ± 15% for AST and ALT.
c) As the distribution of an External Assurance Program peer group, e.g. target value ± 3 SD for TSH in the CAP or RCPA Surveys.
d) In a few cases, more than one set of limits is given, e.g. target value of ± 0.20 mmol/L or ± 6% for glucose depending on the concentration range of the analyte.

4.2 Measurement of Variability (Method Precision and Bias)

Control charts are set up based on estimates mean and SD (the standard deviation of the mean) calculated with a limit number of runs during a preliminary period. During that period, the assessment of mean and SD and later the acceptable range is a pivotal step for the set up of the QC chart. The goal is to differentiate between variability due to chance from that due to error.

4.3 Identify Candidate IQC Procedures

The basic approach to IQC involves the analysis of control materials alongside the routine test samples. The laboratory must establish the frequency, type and number of QC that monitor the entire analytical process:

4.3.1 Frequency of QC

Although minimum regulatory standards exist for determining QC testing frequency, decisions regarding when and how to run QC samples are not standardized. Most QC testing strategies test control samples at fixed time intervals, often placing the samples in the same position on an instrument during subsequent QC events and leaving large gaps of time when control samples are never run, yet patient samples are being tested.

Strategies for QC Testing Schedules

- Strategy 1: QC events scheduled at fixed time intervals.
- Strategy 2: QC events randomly scheduled within fixed time intervals.
- Strategy 3: QC events scheduled at random intervals.
- Strategy 4: QC events scheduled at a random interval, followed by a series of *n* QC events scheduled at fixed intervals.

- Strategy 5: The average interval between QC events was set at eight hours for all of the evaluated scheduling strategies.

Scheduling QC tests at fixed intervals yields an average time between the occurrence of an out-of-control error condition and the next scheduled QC test that is equal to half of the fixed time interval. This performance was the best among the QC scheduling strategies investigated. Near-optimal performance, however, was achieved by randomly selecting time intervals between QC events centered on the desired expected interval length, a method that provides variation in QC testing times throughout the day.

Source: Tilting at perfect timing for QC. CAP Today. October 2007
Parvin C, Robbins S. Evaluation of the Performance of Randomized versus Fixed Time Schedules for Quality Control Procedures. Clin Chem 2007; 53: 575-580.

Commentary
Analytical run generally defined by CLIA as an 8 hour to 24 hour interval during which control materials must be analyzed. According to CLSI C24, a 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."

The level of QC applied in the laboratory varies according to the number of analytical runs and the specimens analyzed per day. The following protocol may be adopted by the laboratories according to the total number of specimens analyzed per analyte:

- Less than 50 per day - apply at least one level QC once a day.
- Between 50-100 per day - apply two level QCs at least once a day.
- More than 100 per day - apply two level QCs at least twice a day for such analytes.

IMPORTANT
One should consider to review and perform more maintenance rather than to perform more QC in response to a QC failure.

Patient-based Quality Goals

Evaluating a QC specimen with each patient will minimize patient risk, but is not practical. The expected number of patient results reported with an unacceptable amount of error due to an undetected error condition - E(Nu) - can be used as a design goal. Using the number of patients tested between QC specimens as a design parameter allows one to design QC strategies that meet specified patient-based quality goals. The QC utilization rate can be minimized to balance the error detection (P_{ed}) and false rejection (P_{fr}) characteristics of statistical QC procedures, as well as to maximize run length in a QC design for a given E(Nu). The QC-utilization rate achievable depends on how close analytical imprecision is to the TEa. To optimize the QC planning process a reliability analysis of the analytical system and a risk analysis of the measurement error are needed. Then it is possible to rationally estimate the optimal QC sampling time intervals to sustain an acceptable residual risk with the minimum QC related cost.

Source: Parvin CA. Assessing the Impact of the Frequency of Quality Control Testing on the Quality of Reported Patient Results. Clin Chem 2008; 54: 2049-2054 and visit the following open-access article for more details:
http://www.plosone.org/article/info:doi%2F10.1371%2Fjournal.pone.0005770

4.3.2 Number of QC

The application of Six Sigma (σ) principles and metrics would greatly improve the IQC process and provide a scientific basis for recommendations on the amount of QC that is needed.

- For analytic processes whose performance characteristics are known, i.e., whose precision (s) and accuracy (bias) can be estimated directly from experimental data, define the “tolerance limit” in the form of an allowable total error, TEa, such as specified in the CLIA proficiency testing criteria for acceptable performance, and calculate the sigma from the following equation:

Sigma = (TEa – bias)/s

- For a 6 sigma process (or higher), use 3.5 SD control limits with N=2;
- For a 5 sigma process, use 3.0 SD control limits with N=2;
- For a 4 sigma process, use 2.5 SD control limits or a multirule procedure with N=4;
- For a 3 sigma process, use a multirule procedure with N of 6 or 8.
- For less than 3 sigma, method performance must be improved before the method can be used for routine production.

Thus, with the aid of Six Sigma principles and metrics, it is possible to assess the quality of laboratory testing processes and the QC that is needed to ensure that the desired quality is achieved. When assessing quality on the σ scale, the higher the σ metric, the better the quality. CLIA's minimum QC of TWO levels per day should apply only to measurement procedures that demonstrate 5 sigma quality or higher.

Source: http://www.westgard.com/essay40.htm

James O. Westgard, Sten A. Westgard. The Quality of Laboratory Testing Today: An Assessment of Sigma Metrics for Analytic Quality Using Performance Data From Proficiency Testing Surveys and the CLIA Criteria for Acceptable Performance. Am J Clin Pathol 2006; 125: 343-354.

Source: http://www.westgard.com/cliafinalrule9.htm

4.4 Predict IQC Performance

Operational Process Specifications (OPSpecs) Charts

"Operational process specifications" have been derived from an analytical quality-planning model to assess the precision, accuracy, and quality control (QC) needed to satisfy Proficiency Testing (PT) criteria. These routine operating specifications are presented in the form of an "OPSpecs chart," which describes the operational limits for imprecision and inaccuracy when a desired level of quality assurance is provided by a specific QC procedure. OPSpecs charts can be used to compare the operational limits for different QC procedures and to select a QC procedure that is appropriate for the precision and accuracy of a specific measurement procedure.

1. Determine TEa for the analyte from biological variation tables or CLIA regulations (e.g. Appendix I or II).
2. Using the Operational Process Specifications (OPSpecs) charts obtainable from the Westgard website at www.westgard.com, calculate which Westgard rules are optimal based on the precision and accuracy of each analyte in relation to the permitted biological variation or CLIA regulations.

4.5 Set Goals for IQC Performance

The goal of IQC is to catch ***ALL*** significant errors without repeating tests unnecessarily

A significant error is defined as a wrong answer that causes a change in the diagnosis or treatment of a patient; or a failure in proficiency testing (PT).

4.6 Select an Appropriate IQC Procedure

Analytes show varying biological variation and assays show varying accuracy and precision. Therefore, in order to detect clinically significant errors, it is best to determine QC rules for an assay that are specifically based on:

1. Its Total Allowable Error (TEa) and
2. Its specific performance.

TEa = allowable error based on CLIA requirements for proficiency testing or determined from individual and group biological variance.

The appropriate IQC procedure is one that has at least a 0.90 probability or 90% chance of detecting medically important errors ($P_{ed} \geq 0.90$) and a maximum 0.05 probability or 5% chance of false rejections ($P_{fr} \leq 0.05$), preferably 1% or less.

5. QC Protocols

The first essential in setting up QC protocols in the clinical laboratory is to select the proper IQC program to implement, i.e. choosing the statistical criteria or control rules, and the number of control measurements, according to the quality required for the test and the observed performance of the method. Then the right IQC procedure must be properly implemented.

Commentary

How to implement an IQC program

1. Establish written policies and procedures.
2. Assign responsibility for monitoring and reviewing.
3. Train staff.
4. Obtain control materials.
5. Collect data.
6. Set target values (mean, SD).
7. Establish Levey-Jennings charts.
8. Routinely plot control data.
9. Establish and implement troubleshooting and corrective action protocols.
10. Establish and maintain system for documentation.

General Requirements:

5.1. Control specimens should be tested in the same manner and by the same personnel as patient samples.

5.2. If a calibrator obtained from an outside supplier is used as a control, it should be a different lot number from that used to calibrate the method.

5.3. For each new lot of QC material, numeric QC data, quality control statistics (mean, SD and CV) should be calculated at least 20-30 data intervals to define analytic imprecision (Appendix III).

5.4. Results of controls must be recorded or plotted to readily detect a malfunction in the instrument or in the analytic system. These control records must be readily available to the person performing the test.

5.5. To detect problems and evaluate trends, testing personnel or supervisory staff must review quality control data on days when controls are run.

5.6. The results of controls should be verified for acceptability before reporting patient results.

5.7. The laboratory director or designee must review QC data at least monthly.

5.8. Controls must be run prior to reporting patient results after a change of analytically critical reagents, major preventive maintenance, or change of a critical instrument component.

Identical Methods and Instrumentation

- Considerations of clinical need, workload, patient population, costs etc., may necessitate a laboratory facility employing more than one of the same, or different, analytical systems to measure the same analyte at the same or different locations.
- Quality assurance data demonstrate that even with identical methods and instrumentation, a variable such as location can impact measurably on analytical performance, presumably through factors such as differing work and equipment maintenance practices, staff skills, and environmental and reagent storage conditions.
- The analyzers should be of the same manufacture, employ the same analytical principles, reagent formulations and calibrators, and be located within the same laboratory site (Appendix IV).

6. QC Materials

QC materials may be provided by the instrument manufacturer or by an independent control manufacturer.

General Requirements:

The CLSI C24-A3 "Statistical Quality Control for Quantitative Measurements: Principles and definitions – Approved Guideline, 2006" recommends that:

- Control materials need to be different from calibrator materials

The AS 4633 (ISO 15189) Field Application Document - "Supplementary Requirements for accreditation in the field of Medical Testing, NATA, July 2009" also recommends that:

1. The QC material used must cover the analytical concentrations encountered. Low/normal/high, normal/abnormal controls, as appropriate for the test, must be performed.
2. Controls independent of those produced by the manufacturer of the test or analyzer should be used.

Properties of a QC Material

1. It should resemble human sample (blood, plasma, serum, CSF etc).
2. The analyte concentration should be at medically significant levels. It should span the clinically important range of analyte's concentration.
3. The material matrix should be as much as like the human sample as possible.
4. Constituents should be stable for a long period of time.
5. After the vial has been opened and material prepared it should be stable during the period of use.
6. The control material should be ready to use and require minimum preparation.
7. Convenient size of aliquots/vials can be prepared and vial to vial variability should be low.
8. It should be reasonably priced (optional).
9. The control material should be tested in the same manner as patient specimens.

- Control material must be matrix matched where available.

  Note: It is acknowledged that this may not always be possible for analyses which have specific QC requirements e.g. electronic QCs in POCT.

Dependent Controls

- Materials manufactured by the same company which supplies the analytical instruments/reagents. The analytical values are set by the manufacturer.
- In normal routine, a dependent control may always give a correct value, giving the "false" appearance of a test system in control though the patient samples may be giving wrong results.

Commentary

- A control material that is made from the same material as the calibrator does not provide an independent assessment of the testing system. If the calibrator values have shifted, a control made from the same material may also shift in a similar way.
- Under such circumstances, laboratories using in-kit controls may NOT detect changes in patient values that could occur with a new lot of reagent or calibrator.

Independent Controls

- Control materials that can provide independent assessment of the testing system by peer-group data comparison. They are not enhanced by the manufacturer of reagents to only work with a particular method.
- An advantage of using independent QC material is that it may show up problems with calibration of the assay.

Commentary

- There are specific occasions where package QCs with reagent-lot-specific target values would compromise our ability to detect lot-to-lot variations.
- The most effective way to reduce the challenges and frustrations of reagent lot validation, particularly for these lot related changes is to use independent or third-party QCs with peer group comparison data to see if other users are seeing the same reagent lot related shift.
- If the laboratory suspects a problem under these circumstances, it should

consider running patient specimens on the old and new lots of reagent to reassure the repeatability of patient results.

- If independent commercial QC material is unavailable the following approaches should be considered:

    1. where QC material is obtained from the manufacturer of the analyzer system, information on the production of QC material should be sought from the manufacturer to determine the extent of independence from the kit calibration process. This should include the source of the QC material, traceability (including value assignment) and matrix matching.
    2. use pooled patient samples.

7. QC Rules and Procedures

CAUTION

DON'T use the same control rules for all tests!

There's no *one* rule or one *set* of rules that's right for *all* tests and methods. Some methods have better precision than others; therefore different QC procedures should be used. The most cost-effective operation is possible when the QC procedures are selected for the individual tests on the basis of the quality required for the test and the performance observed for the method.

Source: http://westgard.com/essay27.htm

7.1 Statistical QC Rules

IQC enables the detection of day to day performance problems and assures the precision and accuracy of clinical laboratory tests. The QC results are evaluated against various sorts of statistical QC rules, e.g., Westgard rules (Appendix V), which define specific performance limits and are designed to detect both random and systematic errors. It is not possible to establish a common control system which can be used for all quantities and analytical procedures in the laboratory; on the contrary, each procedure should have its particular efficient IQC system.

Westgard Multirules

The Westgard multirules are used to detect trends or shifts by examining individual values to determine the status of the measuring system. Westgard rules are based on sigma and are hence calculated without regard to constant sample sizes. These rules are commonly used with Levey-Jennings chart.

7.2 QC Procedures

The following steps highlight the procedure for verification of QC results for acceptability based on the Westgard rules. This procedure is applicable for using two or three QCs. IQC results must be verified before accepting the analytical run and reporting patient results.

Monitoring of IQC Data

- Use Levey-Jennings chart.
- Plot control values each run, make decision regarding acceptability of run.
- Monitor over time to evaluate the precision and accuracy of repeated measurements.
- Review charts at defined intervals, take necessary action, and document.

Clearly there is a play-off between type-1 (the false detection of an out-of-control condition or the probability for error detection, P_{ed}) and type-2 errors (the false rejection of an in-control condition or probability for false rejection, P_{fr}). The wider the limits are set then the more likely it is that a good run will be accepted and a poor run not rejected.

The choice of two or three SDs and the use of Westgard rules require careful thought, as the consequences of making a poor decision will be an unacceptable level of type-1 or type-2 errors.

Beware of False Rejection

- With 2 controls, there is ~10% chance that the run will be rejected when there is NOTHING wrong
- With 3 controls per run, there is ~15% chance of rejection when there is NOTHING wrong

There are some hints and tips on using the Westgard rules:
http://www.medialabinc.net/spg113782/tips_on_using_the_westgard_rules.aspx

7.2.1 Acceptance of Analytical Run:

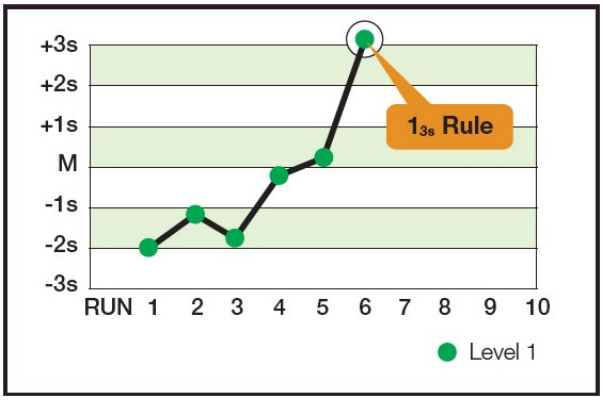
All controls are within 2 SD limits.

Two controls are within 2 SD limits and the other is within 3 SD limits.

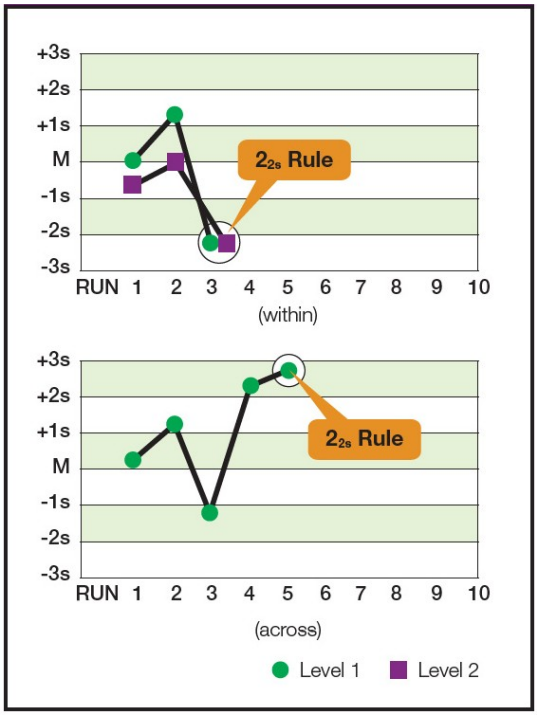
7.2.2 Rejection of Analytical Run:

Precision Flagged

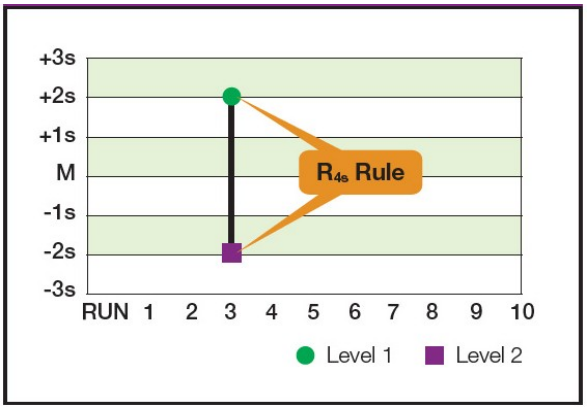
pi. One control is outside 3 SDs.



pii. Two controls are outside ± 2 SDs in the same or consecutive runs.

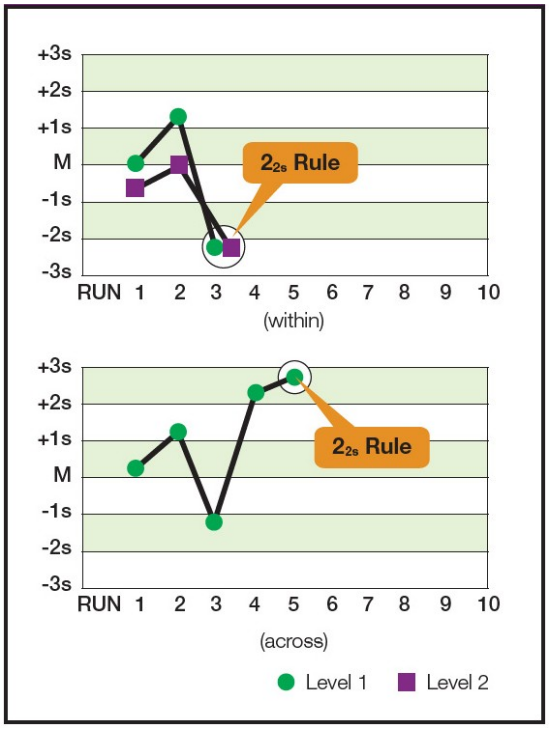


piii. The range (difference) between the maximum and minimum QC value exceeds 4 SDs in the last 6 QC assays.

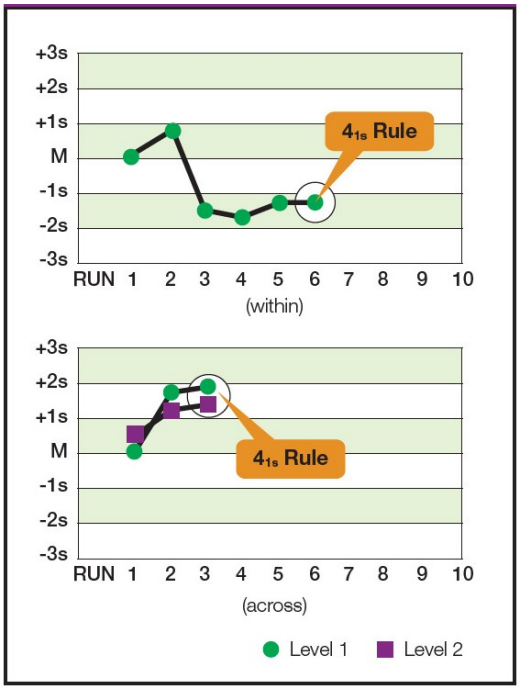


Bias (Accuracy) Flagged

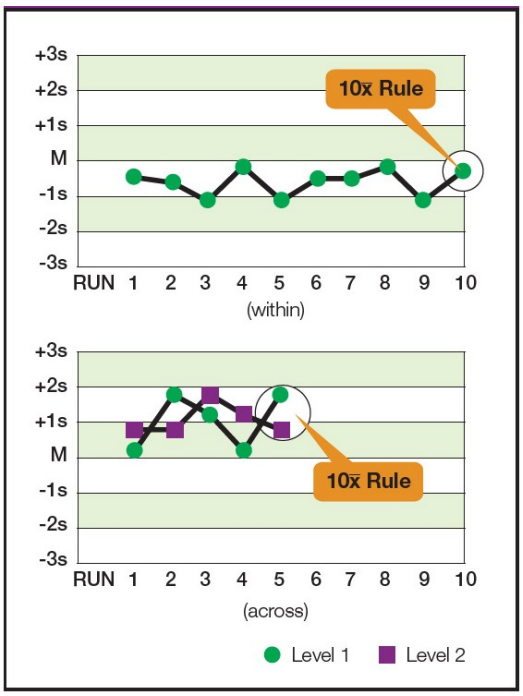
bi. Two consecutive controls are outside the same 2 SD i.e. >+2 SD or <-2 SD.



bii. Four consecutive controls are on one side of the mean and further than 1 SD from the mean i.e. > +1 SD or < -1 SD.



biii. Ten consecutive controls are on the one side of the mean.



7.2.3 Summary of Rejection Characteristics:

The table below summarizes the responses of different control rules to different error conditions. Identified which other rules are most sensitive for detection of probable **False Rejection**, **Random** or **Systematic** errors.

Error Condition	Westgard Rule
False rejection	1_{2s}
Random error	1_{3s}, R_{4s}
Systematic error	2_{2s}, 4_{1s}, 10_{x}

7.2.4 Action to be taken if a test run is rejected:

Corrective action must be taken and documented when control results exceed defined tolerance limits:

i. Patient test results will not be reported when controls do not yield acceptable results.
ii. The monthly mean is compared to the cumulative mean. If the monthly mean varies by more than ±1SD from the cumulative mean, it must be investigated and documented.
iii. The monthly CV is compared to the cumulative CV. If the monthly CV is greater than twice the cumulative CV, it must be investigated and documented. Any significant change may indicate a change in instrument calibration or a fault in its function.
iv. Other corrective actions in response to Shifts, Drifts and Trends, etc.

The laboratory personnel performing the test should determine the appropriate action to be taken for QC data that fall outside the established tolerance limits. Corrective action should be documented with the technician's Initials and Date.

In response to the failed QC results, one of three options can be chosen:

1. **CONTINUE** - continue without change, if false alarm/rejection is identified.
2. **PAUSE** - Stop performing the assay - troubleshoot and continue when fixed.
3. **STOP** - Stop releasing results - troubleshoot and rerun previous samples after corrective action(s).

Commentary

Identifying Systematic Errors

A systematic error affects all specimens equally in a proportionate or constant manner. Improper instrument calibration or loss of calibration secondary to malfunction, are causes of systematic error. The QC program should detect such errors.

- Many factors contribute to a systematic error. For some analytes, the use of daily patient mean provides additional confidence that the assay performance is stable.
- Very similarly to the process used for monitoring quality control results, the operator may define patient mean tolerance limits and apply control rules versus baseline or target.
- This is a very useful tool to identify clinically relevant shifts occurring in the patient mean.

Identify Instrument-Specific Problems

Short Sampling:

A short sample can occur if the sample flow is restricted during aspiration, or there is insufficient blood in the tube. This is sometimes apparent when low analyte concentrations are seen in a relatively healthy ambulatory patient; this should raise suspicion about incomplete aspiration.

Improper Calibration:

Errors in calibration will create errors for all patient samples, so this is the most critical step for each laboratory. Accuracy of calibration must be verified periodically; under most accreditation requirements, this must perform at least every 6 months, no matter how stable the analytical system.

Maintenance Schedules:

Each analyzer has specific maintenance schedules detailed in the Operator's Manual. It is important for each laboratory to perform the specified activities in order to keep instrument performance within specifications and reduce the possibility of error. Specific cleaning instructions are provided for each analyzer system, and daily background checks must be performed to detect any such build-up of interfering material.

Identifying Random Errors

Random errors occur without a defined pattern or frequency. Delta checks and precision checks, can aid in identification of random errors.

1. Delta Checks: A delta check identifies random errors by comparing the current result with a previous result from the same patient and monitors the difference (delta) between the two results. Delta limits take into account analyzer imprecision and drift (systematic errors) as well as physiological variations. Delta checks can also be used to monitor instruments for random error. It is important to confirm a result that fails a delta check.

2. Paired Runs: The within-run reproducibility (imprecision) is usually stated within the Performance Specifications section of the Operator's Manual for each analyzer system. Each laboratory should verify that its specific instrument meets those values with multiple assays of the same specimen. Additionally, periodic paired imprecision runs can be used to detect random analytical errors. If an imprecision check fails, perform troubleshooting to identify the reason(s) for the failure.

Lean Sigma Approaches

Setting up appropriate QC protocols and control rules with the aid of a QC software package which has a high probability of detecting an error together with a low rejection rate is an example of the Lean Sigma approaches in routine QC practice that could reduce unnecessary sample re-runs and unnecessary corrective actions due to QC failures (Appendix VI).

Source:
http://www.westgard.com/essay41.htm and http://www.westgard.com/essay94.htm

8. IQC Audits

Audit is an essential part of any quality control program in a laboratory. Audit is a means of assessing whether the laboratory is achieving its stated objectives. There are five key questions in the audit process:

1. What should we do?
2. What do we do?
3. Are we doing what we should be doing?
4. Can we improve what we do?
5. Have we improved?

"A systematic, independent and documented process for obtaining audit evidence and evaluating it objectively to determine the extent to which audit criteria are fulfilled" (ISO 9000:2005 3.9.1)

Review of procedures as defined by the QMS: aspects of the structure, processes, and outcomes are selected and systematically evaluated against explicit criteria (for example, the requirements of an accreditation standard). Where indicated, changes are implemented and further monitoring is used to confirm improvement.

Audit is a process of critical review of the functioning and evaluation of services. Internal audit is the systematic, independent and documented process for obtaining audit evidence and evaluating it objectively to determine the extent to which the specific criteria are complied with. Internal audit can be effectively carried out by examining documents, specimens, equipment, environmental conditions, examination procedures and personnel competence. Effective internal audit will identify the problems and weak points in the system and suggest remedial measures.

Procedure

1. One or more auditors conducting an audit, supported if needed by technical experts.
2. The person involved should have demonstrated personal attributes, capable of review of procedures as defined by the QMS and the requirements of an accreditation standard, and most importantly, competence to conduct an audit.
3. The audit process then begins with the auditor drawing up an audit checklist compiled from the QMS of the part being audited. The auditor then checks compliance, non-compliance or possible non-compliance against this checklist and

write a report.

4. Corrective action requests may then be submitted as part of the report.

The quality system itself can be audited by a non-technical person, whereas technical activities must be audited by a person with sufficient technical background. In general, it is better to have a series of small audits rather than a single large audit. Any faults identified by an audit should lead to immediate corrective action and appropriate changes in documentation, which should be discussed in management reviews.

QC/QA Meetings

Regular QC/QA meetings are encouraged to discuss and solve the problems arising from the daily operation of the laboratory. It should be a part of QMS focused on increasing the ability to fulfil quality requirements in order to enhance its ability to meet requirements. So that continual improvement can be achieved by carrying out internal audits, performing management reviews, analysing data, and implementing corrective and preventive actions.

Commentary

Corrective actions are steps that are taken to remove the causes of an existing non-conformity or to make quality improvements. Corrective actions address actual problems. In general, the corrective action process can be thought of as a problem-solving process.

Preventive actions are steps that are taken to remove the causes of potential non-conformities or to make quality improvements. Preventive actions address potential problems, ones that have not yet occurred. In general, the preventive action process can be thought of as a risk analysis process.

Source: http://www.praxiom.com/iso-definition.htm

9. References

1. CLSI/NCCLS C24-A3 Statistical Quality Control for Quantitative Measurements: Principles and Definitions: Approved Guideline – Third Edition - 2006.

2. ISO 15189:2007 Medical laboratories – Particular requirements for quality and competence (ISO 15189:2007).

3. James O. Westgard. Assuring the Right Quality Right. Westgard QC, Inc. 2007. ISBN 1-886958-24-6.

4. HOKLAS 015. Technical Criteria for Laboratory Accreditation (Medical Laboratories) - Third Edition. July 2007. Hong Kong Accreditation Service.

5. Protocols for QA Review. Co-ordinating Committee (COC) for Scientific Officers (Medical) in Pathology, Hospital Authority, Hong Kong. February 1998.

6. AS 4633 (ISO 15189) Field Application Document - Supplementary Requirements for accreditation in the field of Medical Testing, NATA, July 2009.

7. 中國國家標準化管理委員會. 臨床實驗室定量測定室內質量控制指南 GB/T 20468-2006. 中華人民共和國國家質量監督檢驗檢疫總局 發佈

Appendix I

Desirable Analytical Quality Specifications

Biological Variation Values This table provides desirable analytical quality specifications for imprecision, bias and total error based upon biological variation.

Source: http://www.qcnet.com/Portals/0/PDFs/BVValues1Final.pdf

By courtesy of Bio-Rad Laboratories, Inc.

Information updates:
http://www.westgard.com/guest36.htm

Biological Variation Values

Desirable Analytical Quality Specifications for Imprecision, Bias and Total Error Based Upon Biological Variation

The following values are provided as a service to Bio-Rad Customers and are based upon desirable performance. The values are derived from Ricos C, Alvarez V, Cava F, Garcia-Lario JV, Hernadez A, Jimenez CV, Mininchela J, Perich C, Simon M. "Current databases on biologic variation: pros, cons and progress" Scand J Clin Lab Invest 1999;59:491-500. These values are updated/modified with the most recent specifications made available in 2008.

S = serum; U = urine; P = plasma; B = blood; Plat = platelets; Ery = erythrocytes; Hb = hemoglobin; Leu = leukocytes; Pt = patient; Sa = saliva

CV_w = within-subject biological variation; CV_b = between-subject biological variation; Imp = imprecision; TE = total error

	ANALYTE	BIOLOGICAL VARIATION		DESIRABLE SPECIFICATIONS			
		CV_w	CV_b	Imp (%)	Bias (%)	TE_a (%) p<0.05	TE_a (%) p<0.01
S	11-Deoxycortisol	21.3	31.5	10.7	9.5	27.1	34.3
S	17-Hydroxyprogesterone	19.6	52.4	9.8	14.0	30.2	36.8
U	5-HIAA concentration, 24 h	20.3	33.2	10.2	9.7	26.5	33.4
S	5'Nucleotidase	23.2	19.9	11.6	7.6	26.8	34.7
S	a1-Acid glycoprotein	11.3	24.9	5.7	6.8	16.2	20.0
S	a1-Antitrypsin	5.9	16.3	3.0	4.3	9.2	11.2
S	a1-Globulin	11.4	22.6	5.7	6.3	15.7	19.6
S	a2-Globulins	10.3	12.7	5.2	4.1	12.6	16.1
S	a2-Macroglobulin	3.4	18.7	1.7	4.8	7.6	8.7
S	a-Amylase	8.7	28.3	4.4	7.4	14.6	17.5
U	a-Amylase	94	46	47.0	26.2	103.7	135.7
S	a-Amylase, pancreatic	11.7	29.9	5.9	8.0	17.7	21.7
S	Acid phosphatase (ACP)	8.9	8	4.5	3.0	10.3	13.4
P	Activated partial thromboplastin time	2.7	8.6	1.4	2.3	4.5	5.4
P	Adiponectin	18.8	51.2	9.4	13.6	29.1	35.5
S	AFP	12	46	6.0	11.9	21.8	25.9
S	Alanine aminotransferase	24.3	41.6	12.2	12.0	32.1	40.4
S	Albumin	3.1	4.2	1.6	1.3	3.9	4.9
U	Albumin	36	55	18.0	16.4	46.1	58.4
S	Aldosterone	29.4	40.1	14.7	12.4	36.7	46.7
U	Aldosterone concentration, 24 h	32.6	39	16.3	12.7	39.6	50.7
S	Alkaline phosphatase	6.4	24.8	3.2	6.4	11.7	13.9
U	Aminolevulinic Acid	16	27	8.0	7.8	21.0	26.5
U	Ammonia output, 24 h	24.7	27.3	12.4	9.2	29.6	38.0
S	Androstendione	11.5	51.1	5.8	13.1	22.6	26.5
S	Angiotensin converting enzyme	12.5	27.7	6.3	7.6	17.9	22.2
P	Antithrombin III	5.2	15.3	2.6	4.0	8.3	10.1
S	Apolipoprotein A1	6.5	13.4	3.3	3.7	9.1	11.3
S	Apolipoprotein B	6.9	22.8	3.5	6.0	11.6	14.0
S	Ascorbic Acid (Vitamin C)	26	31	13.0	10.1	31.6	40.4
S	Aspartate aminotransferase	11.9	17.9	6.0	5.4	15.2	19.2
S	a-Tocopherol	13.8	13.3	6.9	4.8	16.2	20.9
S	b2-Microglobulin	5.9	15.5	3.0	4.1	9.0	11.0
B	Basophils, count	28	54.8	14.0	15.4	38.5	48.0
B	Basophils, count	28	54.8	14.0	15.4	38.5	48.0
S	b-Globulins	10.1	9.1	5.1	3.4	11.7	15.2
S	Bilirubin, conjugated	36.8	43.2	18.4	14.2	44.5	57.1
S	Bilirubin, total	23.8	39	11.9	11.4	31.1	39.1
S	C Peptide	9.3	13.3	4.7	4.1	11.7	14.9

	ANALYTE	BIOLOGICAL VARIATION		DESIRABLE SPECIFICATIONS			
		CV_W	CV_b	Imp (%)	Bias (%)	TE_a (%) p<0.05	TE_a (%) p<0.01
S	C3 complement	5.2	15.6	2.6	4.1	8.4	10.2
S	C4 complement	8.9	33.4	4.5	8.6	16.0	19.0
S	CA 125	24.7	54.6	12.4	15.0	35.4	43.8
S	CA 15.3	5.7	42.9	2.9	10.8	15.5	17.5
S	CA 19.9	24.5	93	12.3	24.0	44.3	52.6
S	CA 549	9.1	33.4	4.6	8.7	16.2	19.3
S	Calcium	1.9	2.8	1.0	0.8	2.4	3.1
U	Calcium	27.5	36.6	13.8	11.4	34.1	43.5
U	Calcium, Ionized	1.7	2.2	0.9	0.7	2.1	2.7
S	Carbohydrate deficient transferrin	7.1	38.7	3.6	9.8	15.7	18.1
S	Carcinoembryonic antigen (CEA)	12.7	55.6	6.4	14.3	24.7	29.1
S	Carnitine, Free	7.6	15.2	3.8	4.2	10.5	13.1
S	Carnitine, Total	7.7	13.8	3.9	4.0	10.3	12.9
B	CD4	25		12.5			
S	Ceruloplasmin	5.7	11.1	2.9	3.1	7.8	9.8
S	Chloride	1.2	1.5	0.6	0.5	1.5	1.9
S	Cholesterol	5.4	15.2	2.7	4.0	8.5	10.3
S	Cholinesterase	7	10.4	3.5	3.1	8.9	11.3
S	CK MB, activity	19.7	24.3	9.9	7.8	24.1	30.8
S	CK MB, mass	18.4	61.2	9.2	16.0	31.2	37.4
P	Copper	8	19	4.0	5.2	11.8	14.5
S	Copper	4.9	13.6	2.5	3.6	7.7	9.3
S	Cortisol	20.9	45.6	10.5	12.5	29.8	36.9
S	C-Reactive protein	42.2	76.3	21.1	21.8	56.6	71.0
S	Creatine kinase	22.8	40	11.4	11.5	30.3	38.1
S	Creatinine	5.3	14.2	2.7	3.8	8.2	10.0
U	Creatinine	24	24.5	12.0	8.6	28.4	36.5
S	Cyfra 21.1	22.5	31.1	11.3	9.6	28.2	35.8
S	Cystatin C	4.6	13	2.3	3.4	7.2	8.8
P	Cysteine	5.9	12.3	3.0	3.4	8.3	10.3
S	Dehydroepiandrosterone sulfate	4.2	29.3	2.1	7.4	10.9	12.3
B	Eosinophils, count	21	76.4	10.5	19.8	37.1	44.3
B	Erythrocytes, count	3.2	6.1	1.6	1.7	4.4	5.5
S	Estradiol	18.1	19.7	9.1	6.7	21.6	27.8
P	Factor VII	6.8	19.4	3.4	5.1	10.7	13.1
P	Factor VIII	4.8	19.1	2.4	4.9	8.9	10.5
S	Ferritin	14.2	15	7.1	5.2	16.9	21.7
P	Fibrinogen	10.7	15.8	5.4	4.8	13.6	17.2
S	Folate	24	73	12.0	19.2	39.0	47.2
B	Folate	12	66	6.0	16.8	26.7	30.8
S	Follicle stimulating hormone	8.7	18	4.4	5.0	12.2	15.1
S	Free thyroxine (FT4)	7.6	12.2	3.8	3.6	9.9	12.4
S	Fructosamine	3.4	5.9	1.7	1.7	4.5	5.7
S	Globulins, total	5.5	12.9	2.8	3.5	8.0	9.9
S	Glucose	5.7	6.9	2.9	2.2	6.9	8.9
B	Glucose-6-Phosphate Dehydrogenase	32.8	31.8	16.4	11.4	38.5	49.6
B	Glutathione peroxidase	7.2	21.7	3.6	5.7	11.7	14.1
S	Glycated albumin	5.2	10.3	2.6	2.9	7.2	8.9
P	Haptoglobin	20.4	36.4	10.2	10.4	27.3	34.2
S	Haptoglobin	20.4	36.4	10.2	10.4	27.3	34.2
P	HDL cholesterol	7.1	19.7	3.6	5.2	11.1	13.5
S	HDL cholesterol	7.1	19.7	3.6	5.2	11.1	13.5
B	Hematocrit	2.8	6.4	1.4	1.7	4.1	5.0
B	Hemoglobin	2.8	6.6	1.4	1.8	4.1	5.1

	ANALYTE	BIOLOGICAL VARIATION		DESIRABLE SPECIFICATIONS			
		CV_W	CV_b	Imp (%)	Bias (%)	TE_a (%) p<0.05	TE_a (%) p<0.01
B	Hemoglobin	2.8	6.6	1.4	1.8	4.1	5.1
B	Hemoglobin A1C	3.4	5.1	1.7	1.5	4.3	5.5
S	High Sensitivity C-Reactive protein	42.2	76.3	21.1	21.8	56.6	71.0
P	Homocysteine	9	40.3	4.5	10.3	17.7	20.8
U	Hydroxyproline	36.1	38.8	18.1	13.2	43.0	55.3
S	Immunoglobulin A	5.4	35.9	2.7	9.1	13.5	15.4
S	Immunoglobulin G	4.5	16.5	2.3	4.3	8.0	9.5
S	Immunoglobulin M	5.9	47.3	3.0	11.9	16.8	18.8
S	Insulin	21.1	58.3	10.6	15.5	32.9	40.1
S	Iron	26.5	23.2	13.3	8.8	30.7	39.7
S	k-Chains	4.8	15.3	2.4	4.0	8.0	9.6
B	Lactate	27.2	16.7	13.6	8.0	30.4	39.7
S	Lactate dehyrogenase (LDH)	8.6	14.7	4.3	4.3	11.4	14.3
S	l-Chains	4.8	18	2.4	4.7	8.6	10.2
S	LD1	6.3	10.2	3.2	3.0	8.2	10.3
S	LD2	4.9	4.3	2.5	1.6	5.7	7.3
S	LD3	4.8	5.5	2.4	1.8	5.8	7.4
S	LD4	9.4	9	4.7	3.3	11.0	14.2
S	LD5	12.4	13.4	6.2	4.6	14.8	19.0
S	LDL cholesterol	8.3	25.7	4.2	6.8	13.6	16.4
B	Leukocytes, count	10.9	19.6	5.5	5.6	14.6	18.3
S	Lipase	23.1	33.1	11.6	10.1	29.1	37.0
S	Lipoprotein (a)	8.5	85.8	4.3	21.6	28.6	31.5
S	Luteinizing hormone	14.5	27.8	7.3	7.8	19.8	24.7
B	Lymphocytes, count	10.4	27.8	5.2	7.4	16.0	19.5
S	Magnesium	3.6	6.4	1.8	1.8	4.8	6.0
U	Magnesium	45.4	37.4	22.7	14.7	52.2	67.6
B	Mean corpuscular hemoglobin (MCH)	1.6	5.2	0.8	1.4	2.7	3.2
B	Mean corpuscular hemoglobin conc. (MCHC)	1.7	2.8	0.9	0.8	2.2	2.8
B	Mean corpuscular volume (MCV)	1.3	4.8	0.7	1.2	2.3	2.8
B	Mean platelet volume (MPV)	4.3	8.1	2.2	2.3	5.8	7.3
B	Monocytes, count	17.8	49.8	8.9	13.2	27.9	34.0
S	Mucinous carcinoma-associated antigen (MCA)	10.1	39.3	5.1	10.1	18.5	21.9
S	Myoglobin	13.9	29.6	7.0	8.2	19.6	24.4
S	NT-proBNP	17.2	28.8	8.6	8.4	22.6	28.4
S	Osmolality	1.3	1.2	0.7	0.4	1.5	2.0
S	Osteocalcin	6.3	23.1	3.2	6.0	11.2	13.3
B	pCO2	4.8	5.3	2.4	1.8	5.7	7.4
B	PH	3.5	2	1.8	1.0	3.9	5.1
S	Phenylacetate	6.6	25.2	3.3	6.5	12.0	14.2
S	Phosphate	8.5	9.4	4.3	3.2	10.2	13.1
S	Phospholipids	6.5	11.1	3.3	3.2	8.6	10.8
B	Platelets	9.1	21.9	4.6	5.9	13.4	16.5
U	Porphobilinogen	17	31	8.5	8.8	22.9	28.6
U	Porphyrins, Total	40		20.0			
S	Potassium	4.8	5.6	2.4	1.8	5.8	7.4
U	Potassium	27.1	23.2	13.6	8.9	31.3	40.5
S	Prealbumin	10.9	19.1	5.5	5.5	14.5	18.2
S	Prolactin (men)	6.9	61.2	3.5	15.4	21.1	23.4
S	Prostatic specific antigen (PSA)	18.1	72.4	9.1	18.7	33.6	39.7
U	Protein	39.6	17.8	19.8	10.9	43.5	57.0
P	Protein C	5.8	55.2	2.9	13.9	18.7	20.6
P	Protein S	5.8	63.4	2.9	15.9	20.7	22.7
S	Protein, total	2.7	4	1.4	1.2	3.4	4.4

	ANALYTE	BIOLOGICAL VARIATION		DESIRABLE SPECIFICATIONS			
		CV_W	CV_b	Imp (%)	Bias (%)	TE_a (%) p<0.05	TE_a (%) p<0.01
P	Prothrombin, time	4	6.8	2.0	2.0	5.3	6.6
U	Pyridinoline/creatinine	8.7	17.6	4.4	4.9	12.1	15.0
B	Pyruvate	15.2	13	7.6	5.0	17.5	22.7
B	Red cell distribution wide (RDW)	3.5	5.7	1.8	1.7	4.6	5.7
S	Reticulocyte, count	11	29	5.5	7.8	16.8	20.6
P	Retinol	6.2	21	3.1	5.5	10.6	12.7
S	Retinol	13.6	19	6.8	5.8	17.1	21.7
S	Rheumatoid factor	8.5	24.5	4.3	6.5	13.5	16.4
S	SCC	39.4	35.7	19.7	13.3	45.8	59.2
B	Selenium	12	14	6.0	4.6	14.5	18.6
S	Sex hormone binding globulin (SHBG)	12.1	42.7	6.1	11.1	21.1	25.2
S	Sodium	0.7	1	0.4	0.3	0.9	1.1
U	Sodium	24	26.8	12.0	9.0	28.8	37.0
S	T3-uptake	4.5	4.5	2.3	1.6	5.3	6.8
S	Testosterone	9.3	23.7	4.7	6.4	14.0	17.2
S	Thyroglobulin	0.2	0.4	0.1	0.1	0.3	0.3
S	Thyroglobulin antibody	8.5	82	4.3	20.6	27.6	30.5
S	Thyroid peroxidase antibody	11.3	147	5.7	36.9	46.2	50.0
S	Thyroid stimulating hormone (TSH)	19.3	19.7	9.7	6.9	22.8	29.4
S	Thyrotropin receptor antibody	4.8		2.4			
S	Thyroxin binding globulin (TBG)	4.4	12.6	2.2	3.3	7.0	8.5
S	Thyroxine (T4)	4.9	10.9	2.5	3.0	7.0	8.7
S	Tissue polypeptide antigen (TPA)	36.1	108	18.1	28.5	58.3	70.5
U	Total catecholamines, concentration, 24 h	24	32	12.0	10.0	29.8	38.0
S	Transferrin	3	4.3	1.5	1.3	3.8	4.8
S	Triglyceride	20.9	37.2	10.5	10.7	27.9	35.0
S	Triiodothyronine (T3)	8.7	17.2	4.4	4.8	12.0	15.0
S	Urate	9	17.6	4.5	4.9	12.4	15.4
U	Urate	24.7	22.1	12.4	8.3	28.7	37.1
S	Urea	12.3	18.3	6.2	5.5	15.7	19.8
U	Urea concentration	22.7	25.9	11.4	8.6	27.3	35.1
U	Vanilmandelic acid concentration, 24 h	22.2	47	11.1	13.0	31.3	38.9
P	Vitamin B1	4.8	12	2.4	3.2	7.2	8.8
B	Vitamin B12	5.2	40	2.6	10.1	14.4	16.1
B	Vitamin B2	5.8	10	2.9	2.9	7.7	9.6
B	Vitamin B6	1.4	44	0.7	11.0	12.2	12.6
P	Von Willebrand factor	0.001	28.3	0.0005	7.1	7.1	7.1
P	Von Willebrand factor antigen	5	18	2.5	4.7	8.8	10.5
S	y-Globulin	14.6	12.3	7.3	4.8	16.8	21.8
S	y-Glutamyltransferase	13.8	41	6.9	10.8	22.2	26.9
P	Zinc	11	14	5.5	4.5	13.5	17.3
S	Zinc	9.3	9.4	4.7	3.3	11.0	14.1

Appendix II

CLIA Proficiency Limits

CLIA Proficiency Limits This table provides CLIA's criteria for acceptable proficiency performance per 42 CFR Ch. IV (10-1-03 Edition).

Source: http://www.qcnet.com/Portals/0/PDFs/CLIALimits(3-3-04).pdf

By courtesy of Bio-Rad Laboratories, Inc.

CLIA Proficiency Limits

Analyte or Test	CLIA Criteria for Acceptable Performance
Alcohol, Blood	± 25%
Alanine Aminotransferase (ALT/SGPT)	± 20%
Albumin	± 10%
Alkaline Phosphatase	± 30%
Alpha-1 Antitrypsin	Target value ± 3 SD
Alpha-Fetoprotein (Tumor Marker) AFP	Target value ± 3 SD
Amylase	± 30%
Antinuclear Antibody	Target value ± 2 dilutions or positive/ negative
Antistreptolysin O	Target value ± 2 dilutions or positive/ negative
Anti-Human Immunodeficiency Virus	Reactive or nonreactive
Aspartate Aminotrasnferase (AST/SGOT)	± 20%
Bilirubin, Total	Target value ± 20% or ± 0.4 mg/dL (greater)
Calcium, Total	Target value ± 1.0 mg/dL.
Carbamazepine	± 25%
Cell Identification	90% or greater consensus on identification
Chloride	± 5%
Cholesterol, High Density Lipoprotein	± 30%
Cholesterol, Total	± 10%
Complement C3	Target value ± 3 SD
Complement C3C	Target value ± 3 SD
Complement C4	Target value + 3 SD
Cortisol	± 25%
Creatine Kinase	± 30%
Creatine Kinase CK-MB	Target value ± 3 SD or presence/ absence
Creatinine	Target value ± 15% or ± 0.3 mg/dL (greater)
Digoxin	Target value ± 20% or ± 0.2 ng/mL (greater)
Erythrocyte Count RBC	± 6%
Ethosuximide	± 20%
Fibrinogen	± 20%
Free Thyroxine Free T4	Target value ± 3 SD
Gentamicin	± 25%
Glucose	Target value ± 10% or ± 6 mg/dL (greater)
Hematocrit (Excluding Spun Hematocrits) HCT	± 6%
Hemoglobin Hgb, Total	± 7%
Hepatitis (HbsAg, anti-HBc, HbeAg)	Reactive (positive) or nonreactive (negative)
Human Chorionic Gonadotropin Beta	Target value ± 3 SD or positive/ negative
Human Chorionic Gonadotropin Intact	Target value ± 3 SD or positive/ negative
Human Chorionic Gonadotropin Qualitative	Target value ± 3 SD or positive/ negative
Human Chorionic Gonadotropin Total	Target value ± 3 SD or positive/ negative
IgA	Target value ± 3 SD
IgE	Target value ± 3 SD
IgG	± 25%
IgM	Target value ± 3 SD
Infectious Mononucleotides	Target value ± 2 dilutions or positive/ negative
Iron, Total	± 20%

Analyte or Test	CLIA Criteria for Acceptable Performance
Lactate Dehydrogenase (LDH)	± 20%
LDH Isoenzymes	Target value ± 30% or (+ or -)
LDH Isoenzymes 1	Target value ± 30% or (+ or -)
LDH Isoenzymes 2	± 30%
LDH Isoenzymes 3	± 30%
LDH Isoenzymes 4	± 30%
LDH Isoenzymes 5	± 30%
Lead	Target value ± 10% or ± 4 mcg/dL (greater)
Leukocyte Count WBC	± 15%
Lithium	Target value ± 20% or ± 0.3 mmol/L (greater)
Magnesium	± 25%
NAPA	± 25%
Partial Thromboplastin Time	± 15%
pCO2	Target value ± 8% or ± 5 mm Hg (greater)
pH	Target value ± 0.04
pO2	Target value ± 3 SD
Phenobarbital	± 20%
Phenytoin	± 25%
Platelet Count PLT	± 25%
Potassium	Target value ± 0.5 mmol/L
Primidone	± 25%
Procainamide (and metabolite)	± 25%
Prothrombin Time	± 15%
Quinidine	± 25%
Rheumatoid Factor	Target value ± 2 dilutions or positive/ negative
Rubella	Target value ± 2 dilutions or positive/ negative
Sodium	Target value ± 4 mmol/L
T3 Uptake	Target value ± 3 SD
Theophylline	± 25%
Thyroid-stimulating Hormone TSH	Target value ± 3 SD
Thyroxine T4 Total	Target value ± 20% or ± 1.0 mcg/dL (greater)
Tobramycin	± 25%
Total Protein Serum	± 10%
Triglycerides	± 25%
Triiodothyronine T3 Total	Target value ± 3 SD
Urea Nitrogen	Target value ± 9% or ± 2 mg/dL (greater)
Uric Acid	± 17%
Urine/Spinal	± 10%
Valproic Acid	± 25%
White Blood Cell Differential	Target value ± 3 SD based on the percentage of different types of white blood cells in the samples

Appendix III

Implementation of New Lot of Quality Control (QC) Materials

Procedure:

1. Over a 20 days period, assay one set of new QC material on each day along with the existing QC materials.

2. After the runs are accepted based on the exciting QC materials, calculate the mean, standard deviation (SD) and coefficient of variance (%CV) for the new QC.

3. Compare the SD and %CV with the List of Allowable Limits of Error (ALE) charts (e.g. Appendix I or II).

4. Make sure that the SD or %CV is less than half of the ALE (1/2 ALE) value that set in the ALE chart. For assayed controls, the tentative mean should fall within the manufacturer's quoted mean ± ALE. Should the requirement not be met, compare values throughout the analytic range. If the difference is consistent, there may be a standardization problem, which should be investigated. If the difference is inconsistent, the method may not be usable or usable only over a narrower analytical range than the manufacturers' claim. Follow up investigation by contacting the manufacturer of the reagent system and the QC agency to verify the quoted mean and compare the group mean of the other users using the same company kit.

5. Prepare tentative QC chart for the analyte. Set mean ± 2SD, the 95% confidence limit, as the temporary target ranges, which should be less than the mean ± ALE.

6. Ideally the new lot of QC material should overlap with the existing lot of QC for at least 20 batch of assays. Sometime this is not feasible e.g.:

    a) For manual and /or infrequent tests:
    Step 1 may be replaced with a single evaluation in which 20 replicates of the new QC are run in a single batch.

    b) For a new method or when there is a lack of practical time:
    Step 1 may be reduced to a minimum of 10 days.

Appendix IV

The Procedure for Setting up QC Limits for Multiple Identical Analyzers

Procedure:

1. There will always be a different mean and SD from one analyzer to the next. This is the result of random variability. The differences should not significant. Evaluating the significance of the difference in mean values, however, is very important. Any medically significant difference observed should be reported to the instrument manufacturer for action.

2. Separate means should be determined for each analyzer. This is important if statistical rules (e.g. 1_{3s}, 2_{2s}) are used to monitor the performance. However, the same baseline SD could be used for each analyzer.

3. The SD may be determined by averaging the observed SD from each instrument or by merely using the largest SD observed across the instruments.

4. By using the same SD to monitor daily performance, one will be able to control multiple analyzers as "one system". This is important since patient samples can, practically, be analyzed on any instrument in the laboratory.

5. Always use the same lot reagents and the same calibrators to calibrate both analyzers to minimize calibration differences.

6. It is important to review maintenance log periodically. Perform any maintenance before calibration rather than afterwards. For example, if the source lamp is about to change in one analyzer, one should consider changing it on both analyzers.

Commentary

Variability between instruments may be caused by:

a) Instrument components:
   e.g. Sample / reference metering
   Photometer / reflectometer / electrode "noise"
   Incubator temperature

b) Sample analyzed:
   e.g. Sample stability
   Sample handling

c) Reagents:
   e.g. Storage
   Warm-up protocol
   Reference fluid handling

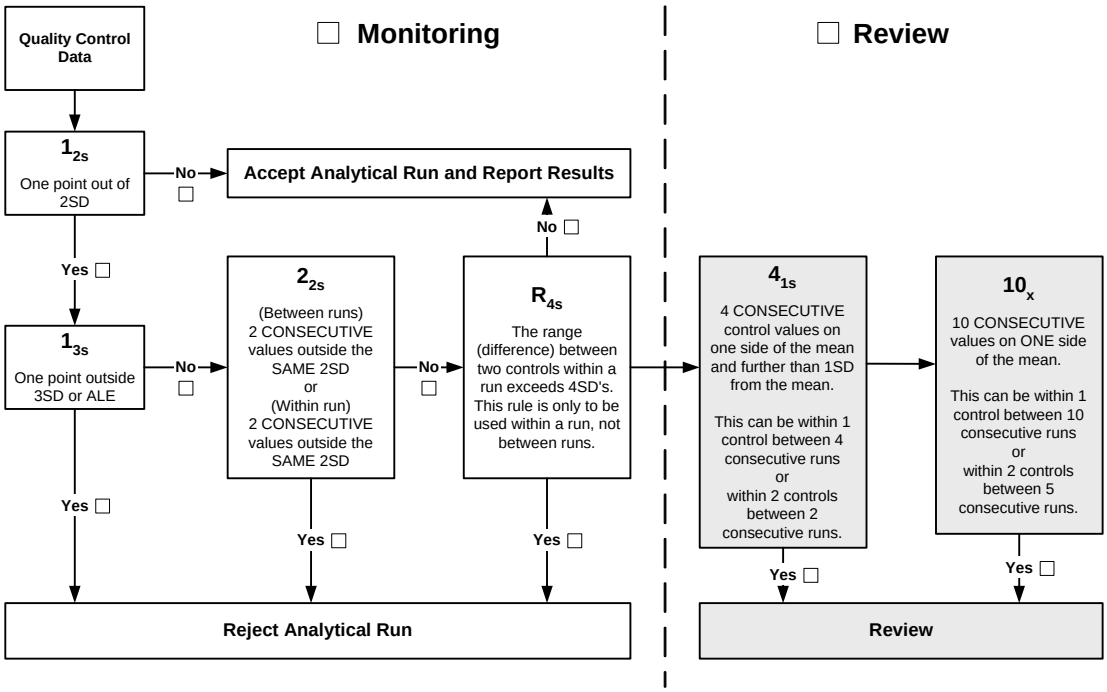
d) Laboratory:
   e.g. Adherence to maintenance and cleaning instructions
   Environment (room temperature and humidity)
   Calibration protocol

Appendix V

Westgard Multirule QC Procedure

(Generally used where 2 levels of control material are analyzed per run)

Multirule QC procedure uses a combination of decision criteria, or control rules, to decide whether an analytical run is in-control or out-of-control. The basic Westgard multirule QC procedure uses 6 different control rules to judge the acceptability of an analytical run, three are mandatory rules and the other three are warning rules.

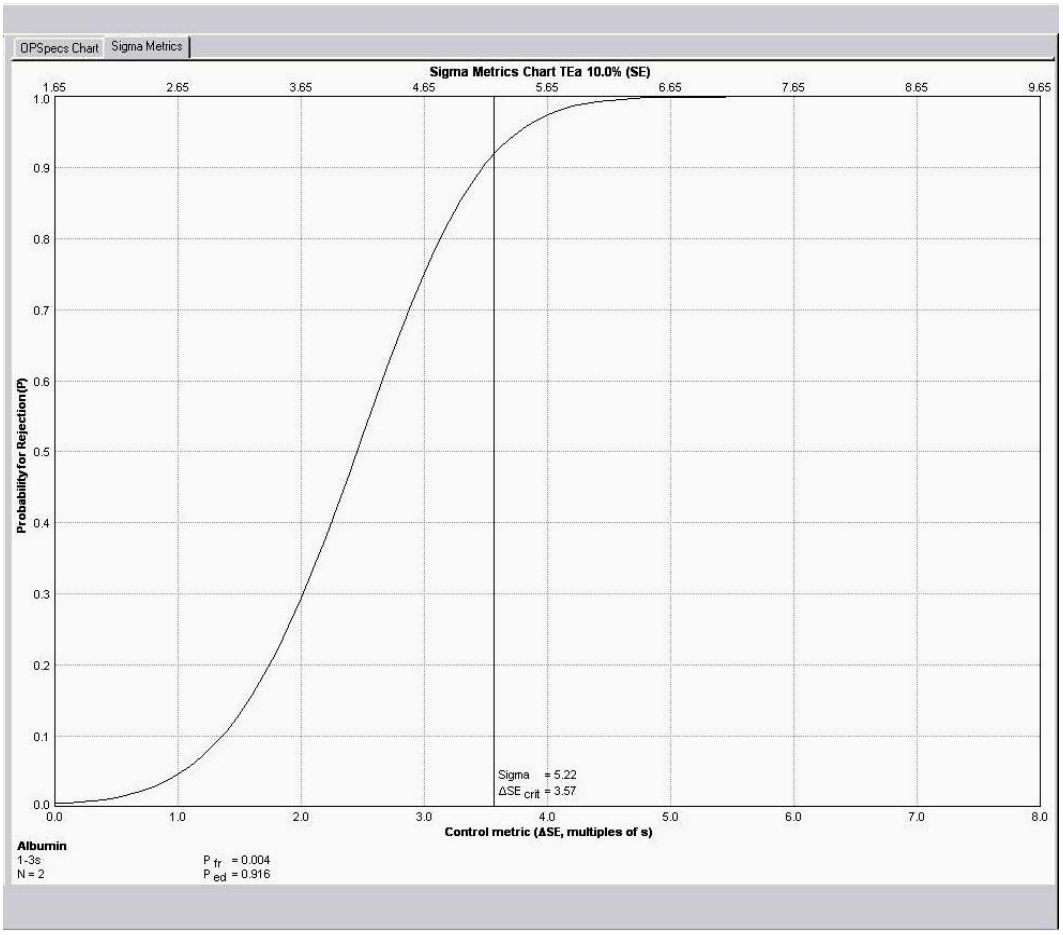


Appendix VI

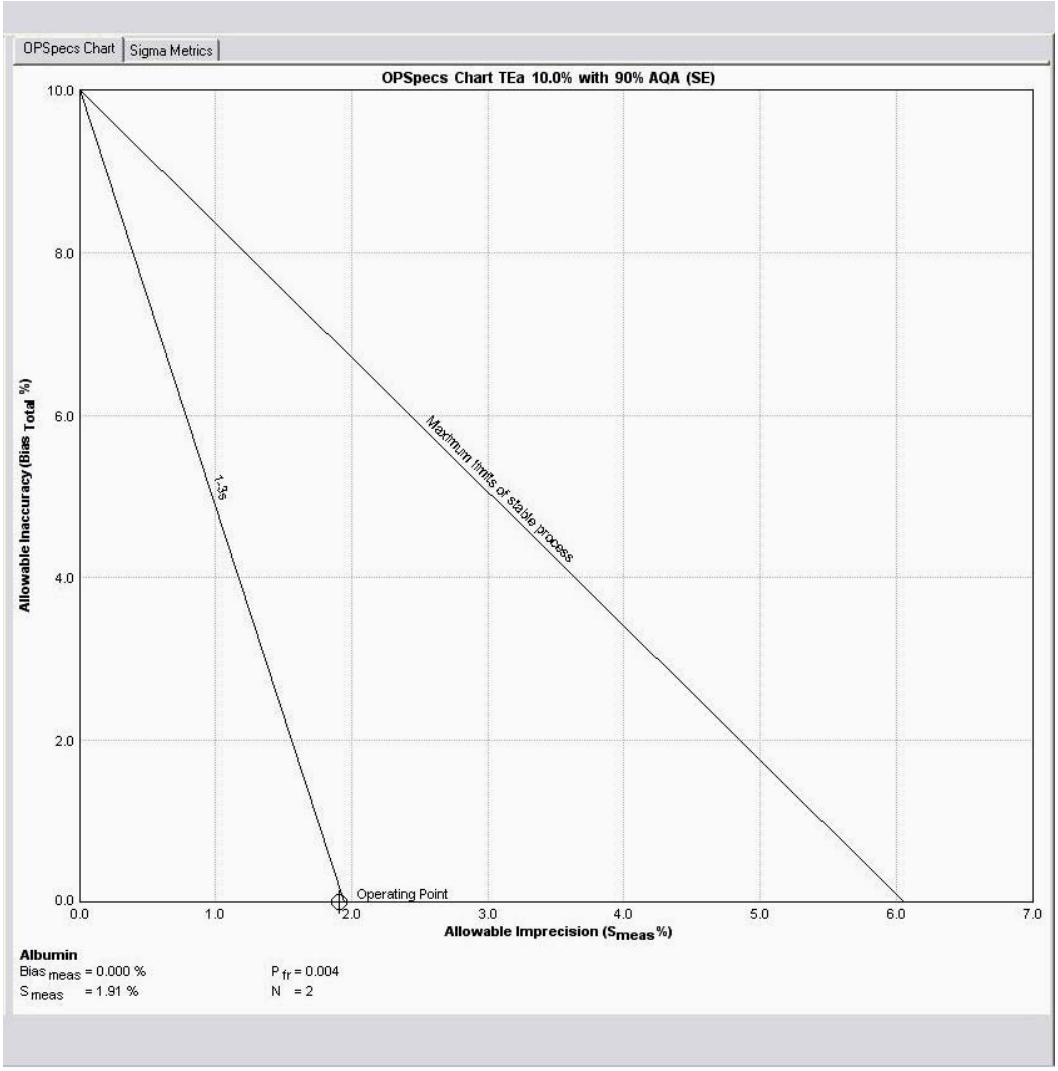
Sigma Metrics and OPSpecs Chart Application

Selected	Analyte	Level	TEa Selection	TEa	Bias %	CV	Sigma	Existing Reject Rules	Suggested Rules	N	Detection Level	False Rejections
☑	Albumin	2	CLIA	10.0	0.373	2.27	4.24	1-3s|2-2s|R-4s	1-2.5s	4	(AQA Level >= 90%)	4.00%
☑	Alkaline Phosphatase	2	CLIA	30.0	-0.158	1.88	15.8	1-5s	1-5s	2	(AQA Level >= 90%)	0.00%
☑	ALT (ALAT/GPT)	2	CLIA	20.0	3.64	1.71	9.58	1-3s|2-2s|R-4s	1-5s	2	(AQA Level >= 90%)	0.00%
☑	AST (ASAT/GOT)	2	CLIA	20.0	-2.00	1.47	12.2	1-3s|2-2s|R-4s	1-5s	2	(AQA Level >= 90%)	0.00%
☑	Bilirubin, Direct/BC (DBIL)	2	BV Minimum	66.8	-0.317	3.13	21.3	1-3s|2-2s|R-4s	1-5s	2	(AQA Level >= 90%)	0.00%
☑	Bilirubin, Total/TBIL	2	CLIA	20.0	-1.96	2.77	6.52	1-3s|2-2s|R-4s	1-4s	2	(AQA Level >= 90%)	0.00%
☑	Calcium	2	CLIA	8.49	-0.034	1.99	4.26	1-3s|2-2s|R-4s	1-2.5s	4	(AQA Level >= 90%)	4.00%
☑	Chloride	2	CLIA	5.00	-0.045	1.58	3.14	1-3s|2-2s|R-4s	1-3s|2-2s|4-1s|8-X	8	(AQA Level >= 50%)	2.00%
☑	Cholesterol, HDL	1	CLIA	30.0	0.742	2.23	13.1	1-3s|2-2s|R-4s	1-5s	2	(AQA Level >= 90%)	0.00%
☑	Cholesterol, Total	1	CLIA	10.0	-0.308	2.07	4.69	1-3s|2-2s|R-4s	1-2.5s	2	(AQA Level >= 90%)	2.80%
☑	CK (Creatine Kinase)	1	CLIA	30.0	0.373	0.423	70.0	1-3s|2-2s|R-4s	1-5s	2	(AQA Level >= 90%)	0.00%
☑	CO2 (Carbon Dioxide)	1	3SD	17.2	0.759	5.80	2.83	1-3s|2-2s|R-4s	1-3s|2-2s|4-1s|8-X	8	(AQA Level >= 50%)	2.00%
☑	Creatinine	2	CLIA	15.0	-0.332	2.09	7.02	1-3s|2-2s|R-4s	1-4s	2	(AQA Level >= 90%)	0.00%
☑	GGT (Gamma Glutamyltransferase)	2	BV Minimum	33.3	1.14	2.06	15.6	1-3s|2-2s|R-4s	1-5s	2	(AQA Level >= 90%)	0.00%
☑	Glucose	2	CLIA	10.0	-0.102	1.52	6.50	1-3s|2-2s|R-4s	1-4s	2	(AQA Level >= 90%)	0.00%
☑	Phosphorus	2	BV Minimum	15.3	-0.027	1.55	9.88	1-3s|2-2s|R-4s	1-5s	2	(AQA Level >= 90%)	0.00%
☑	Potassium	2	CLIA	8.33	-0.004	1.62	5.14	1-3s|2-2s|R-4s	1-2.5s	2	(AQA Level >= 90%)	2.80%
☑	Protein, Total, Serum	1	CLIA	10.0	0.622	1.47	6.37	1-3s|2-2s|R-4s	1-3.5s	2	(AQA Level >= 90%)	0.10%
☑	Sodium	2	BV Minimum	1.32	0.127	1.13	1.05	1-3s|2-2s|R-4s|4-1s|8-X	1-3s|2-2s|R-4s|4-1s|8-X	4	(max qc condition)	3.00%
☑	Triglycerides	1	CLIA	25.0	-0.519	1.98	12.4	1-3s|2-2s|R-4s	1-5s	2	(AQA Level >= 90%)	0.00%
☑	Urea Nitrogen	2	CLIA	9.00	-1.46	2.27	3.32	1-3s|2-2s|R-4s	1-3s|2-2s|4-1s|8-X	8	(AQA Level >= 50%)	2.00%

- The Configure TEa dialog box allows users to select the appropriate TEa (quality specification) for each test. The list above shows the available TEa options (3 SD, BV, CLIA, RCPA, User Defined, State of the Art).



- The Westgard Advisor can evaluate performance statistics from all available levels for each analyte and choose the level with the Highest Total Error (resulting in conservative settings) or Lowest Total Error (resulting in optimistic settings).



- The Chart Option allows users to see the OPSpecs chart for their rule selections.

Source: Unity Real Time Software Version URT 2.0

By courtesy of Bio-Rad Laboratories, Inc.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