Dear Colleagues,

A Practical Guide to Internal Quality Control (IQC)
For Quantitative Tests in Medical Laboratories, Version 2.0
February 2015

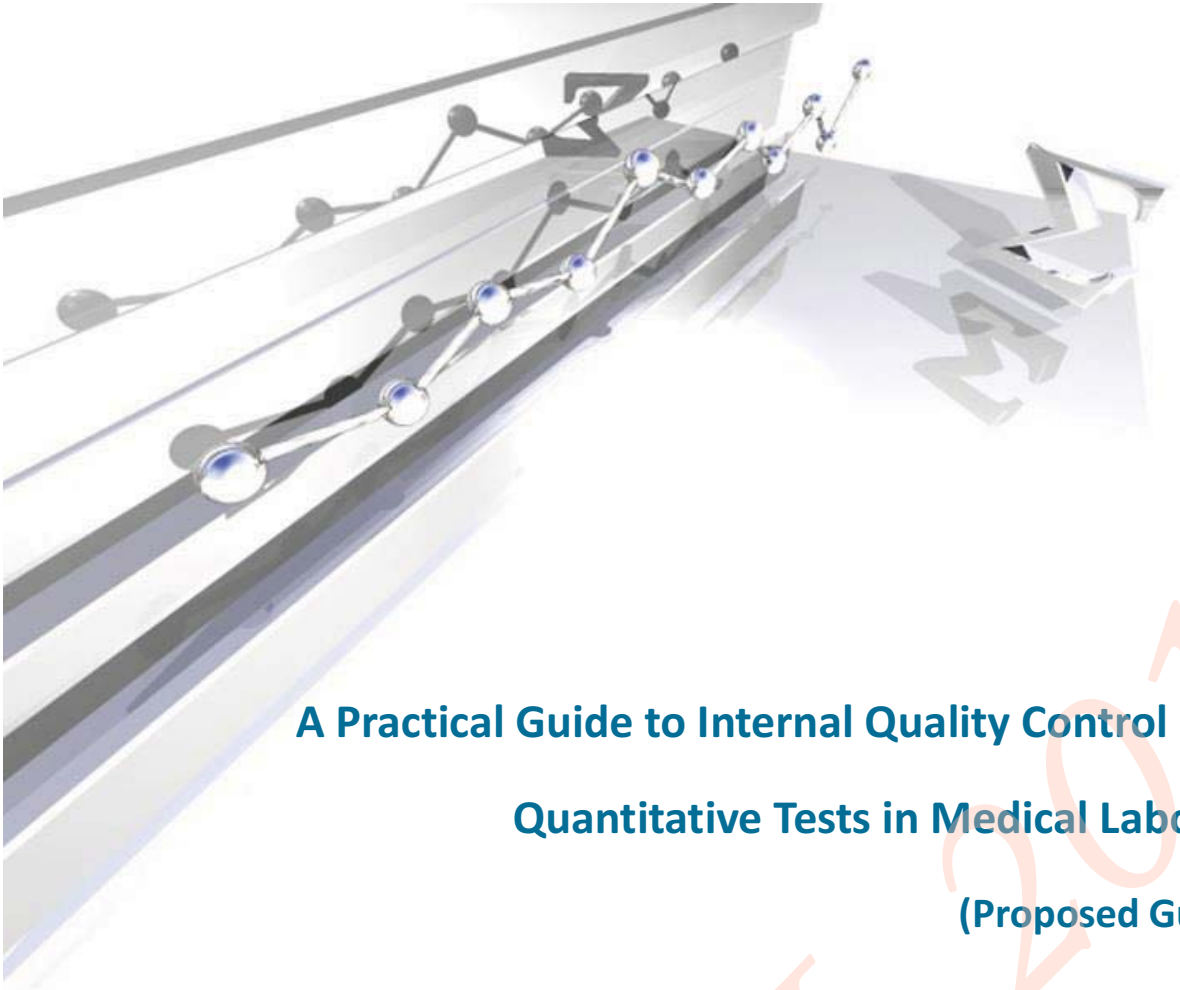
Time flies!
This is a substantial revision of the previous edition, involving a reorganization of old materials and the addition of new concepts and requirements. Nowadays, we are on the edge of an era where 'one-size-fits-all' QC approach doesn't work all the time with different analytical systems. The focus in this revision is entirely on risk-based QC management and its practical applications to IQC. The length of the book has NOT increased tremendously (Total pages ~ 60), with a hope that it is still practical, quick and easy reference. The major changes are as follows:

One new chapter on QC practices and risk management and its corresponding appendix to give readers additional information from the supplementary internet resources have been added. Our aim has been to focus on preventive measures and to facilitate understanding of the conceptual framework of QC and patient risk management through hyperlinks to other websites of some key presentations.

We would like to express our thanks to those professional colleagues who have contributed valuable comments on the procedures and/or the reorganization of the materials in the revised chapters.

Best wishes,

Richard Pang
Editor



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

(Proposed Guidelines)

Version 2.0

Edited by

Richard Pang, PhD, FACB

Senior Consultant

Pro Q Consulting Services

Hong Kong

For

Hong Kong Association of Medical Laboratories Limited

HONG KONG ASSOCIATION OF MEDICAL LABORATORIES LIMITED

香港醫務化驗所總會

Educational Material

February 2015

(This page is intentionally left blank)

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.

Editor: Richard Pang

Coordinators:
Winnie Cheung
Vicky Chu
Chi-Lim Kwok
Jason Lam
Marianne Leung
Adrian Li
Alex Li
Jacky Ng
Emily Yeh
Thomas Yeung

The Editor welcomes comments on this document which may be addressed to:
ProQ@live.hk

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

Preface

Quality can imply different features in different products and services. For food, it can be how tasty it is. For a computer, it can be how fast it is. For a laboratory test or service, it would be how accurate and how reliable it is. However, the management of test accuracy is more complicated than many people think. Accurate results depend on test methods employed, test analyzer types, reagents selected, system processes involved and even the laboratory personnel engaged. Quality assurance, is the key to accurate results, it reflects a collective result of the overall performance of a laboratory.

Internal Quality Control (IQC) is an indispensable element of every quality laboratory. It is a most important part of a quality assurance scheme. This guide highlights the important IQC elements from A to Z. Those who are going to set up an IQC system and those who are going to refine their existing IQC system will surely benefit.

Being an association of private medical laboratories in Hong Kong, HKAML is always committed to quality and professional ethics. On behalf of HKAML, we would like to thank Dr Richard Pang, our Honorary Advisor and Editor-in-Chief of this Practical Guide, for his dedicated commitment and energy put to this revision. We are sure that these guidelines will be a major driving force of the profession to move ahead in the area of quality control.

We would also like to express our appreciation to all the coordinators and corporate partners of this meaningful & educational activity for their contributions and continuing support. We hope this guide can continue to be updated periodically to equip our profession with the most up-to-date QC information.

Lastly, let's make good use of this QC guide to bring the quality of our services to a new high.

Alex Li
Chairman, HKAML

Foreword

(Version 1.1, 2010)

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 (2002-2012), 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 15189:2012 - Medical laboratories - 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 be technical processes to make corrections and effective mechanisms to prevent the recurrence. These actions will be the basis of risk management and 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 ensure the quality of examinations by performing them under defined conditions. (ISO 15189: 2012 Clause 5.6.1)*

Practicality: Appropriate pre and post-examination processes shall be implemented, and the laboratory shall not fabricate any results. (See ISO 15189: 2012 Clauses 4.14.7, 5.4, 5.7 and 5.8).

2. *The laboratory shall design internal quality control procedures that verify the attainment of the intended quality of results. (ISO 15189: 2012 Clause 5.6.2.1)*

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 customized for each examination procedure based on that procedure's capabilities.

Practicality: The laboratory should do proper QC design and documentation to select appropriate rules to apply in their care setting, and the selection of QC levels should be optimized for clinical decisions and patient management.

3. *"Quality control materials should be different from the calibrator materials to ensure that the QC procedure provides an independent assessment of the measurement procedure's performance in its entirety, including the procedure for calibration of the measurement." (CLSI C24-A3: 2006)*

Practicality: The laboratory is encouraged to use control material similar to or identical with patient sample matrix. If a calibrator is also used as a control, then the control will closely mimic the calibrator. In this situation, the control may not be able to detect shifts in values that could be caused by a degrading calibrator.

4. *Controls independent of those produced by the manufacturer of the test or analyzer should be used. (Medical Testing Field Application Document, Interpretation of NPAAC Requirements and ISO 15189, NATA, November 2013)*

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.

5. *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.

6. *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.*

(Medical Testing Field Application Document, Interpretation of NPAAC Requirements and ISO 15189, NATA, November 2013)

Practicality: The 2SD limits are generally not desirable because of the high P_{fr}, except occasionally they are necessary for low sigma analytes.

7. *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.

8. *The laboratory shall determine action to eliminate the causes of potential nonconformities in order to prevent their occurrence. Preventive actions shall be appropriate to the effects of the potential problems. (ISO 15189: 2012 Clause 4.11) i.e., risk management and patient safety measures.*

Practicality: Preventive action is a proactive process for identifying opportunities for improvement rather than a reaction to the identification of problems or complaints (i.e. nonconformities). In addition to review of the operational procedures, preventive action might involve analysis of data, including trend and risk analyses and external quality assessment (proficiency testing).

Practicality: The Quality Control Plan (QCP), based on the identified risk(s), is a comprehensive strategy that includes all control procedures to reduce residual risk and methods to immediately detect errors, using both prevention and monitoring strategies. The QCP is intended to proactively address potential risks before they occur and result in failures, compared to the practice of addressing failures after they occur.

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."

Commentary

This traditional definition of an analytical run is ambiguous. Recent concepts, by changing the focus of QC to the patient safety and risk management, statistical software could assess risk and help determine appropriate QC frequency based upon the number of patients between QC events, which is more meaningful.

Patient Safety

Patient safety is a new healthcare discipline that emphasizes the reporting, analysis, and prevention of medical errors that often leads to adverse healthcare events. The World Health Organization (WHO) calls patient safety an endemic concern (WHO website: http://www.who.int/en/).

Risk Management

Risk management is defined as the systematic application of management policies, procedures, and practices to the tasks of analyzing, evaluating, controlling, and monitoring risk (ISO 14971: 2007).

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.

Commentary

*******This statement often leads laboratory personnel to incorrectly believe that QC will always catch errors, when in fact; it's the QC rule and frequency that determines if an out of control condition (OOC) will be caught. A poorly selected rule may not catch a smaller OOC condition until many many QC events have passed.*

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. Quality 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.

The CLIA Individualized Quality Control Plan (IQCP) is a recently developed, risk-based, objective approach to performing quality control testing. The IQCP is based on assessment of the unique laboratory testing in use, patient populations, and other aspects (for example, internal quality checks built into new instruments).

The IQCP incorporates key concepts from the Clinical and Laboratory Standards Institute document *CLSI EP23: Laboratory Quality Control Based on Risk Management; Approved Guideline*. The concepts include (1) Risk Assessment, (2) the Quality Control Plan, and (3) Quality Assessments (surveillance). While providing a scientific basis for QC strategies, EP23 is not prescriptive. It describes risk assessment elements; quality system essentials; quality control tools, strengths and weaknesses; information to be gathered; and surveillance and follow-up guidelines. Laboratories will need to assess their current quality practices as they apply to test systems, clinical use of technologies, patient populations, etc.

The Quality Control Plan (QCP), based on the identified risk(s), is a comprehensive strategy that includes all control procedures to reduce residual risk and methods to immediately detect errors, using both prevention and monitoring strategies. The QCP is intended to proactively address potential risks *before* they occur and result in failures, compared to the practice of addressing failures *after* they occur.

Source:
http://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/CLIAbrochure11.pdf

4.1 Define the Quality Requirement

4.1.1 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 little 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 first major approach is based on medical need. The following approaches are ranked in accordance with the Stockholm Consensus Hierarchy:

- Evaluation of the effect of analytical performance on clinical outcomes in specific clinical situations: e.g. Diabetes Control and Complications Trial – DCCT.
- Evaluation of the effect of analytical performance on clinical decisions in general: e.g. biological variation database (Appendix I), opinions of the clinicians, and fraction of the reference interval (Tonks' formula).
- Published professional recommendations: e.g. National Cholesterol Education Program (NCEP), American Diabetes Association (ADA), National Academy of Clinical Biochemistry (NACB), and professional expert panels or individuals.
- Regulatory approach: e.g. performance goals set by CLIA '88 PT limits (Appendix II), or Allowable Limits of Performance (ALP) of the RCPAQAP. http://www.rcpaqap.com.au/wp-content/uploads/2014/02/chempath/docs/ALP.pdf
- Performance goals based on the state-of-the-art technologies as found in current publications of methodology or as demonstrated by data from EQA or PT schemes.

  Source: Petersen PH, Fraser CG, Kallner A, Kenny D. Strategies to set global analytical quality specificationsin laboratory medicine. Scan J Clin Lab Invest 1999; 59: 475–585.

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.

4.1.2 Within-Subject Biological Variation in Disease

Biological Variation is a random variation for healthy subjects. It is important to determine what clinically significant changes in diseased patients are. It has become common practice to use Reference Change Value (RCV) estimated from healthy subjects to detect significant changes in the status of patients. But, the use of RCVs from healthy subjects may not be the most appropriate strategy for this task because the underlying pathology may modify the set-point in diseased patients. This could mean that RCV derived from healthy within-subject coefficient of variation may not be appropriate for monitoring patients in certain diseases.

Source: http://www.westgard.com/biological-variation-in-patients-with-disease.htm

The database contained information from 66 quantities estimated in 34 diseases, obtained from 45 papers published in 15 scientific journals. The results obtained in each paper, organized by quantity and disease, are shown in Appendix1 of the original article appeared as Within-subject biological variation in disease: collated data and clinical consequences in *Ann Clin Biochem* 2007; 44: 343-352. This set of biologic variation data is unique in that it represents the biologic variation not from healthy individuals, but from patients with various diseases. Hence, disease-specific RCVs may be clinically useful.

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 shall establish the frequency, type and number of QC that monitor the entire analytical process, and the laboratory must also establish the statistical QC rules.

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.

The above-mentioned QC strategies are NOT equally acceptable and they are NOT ranked in order of preferability. 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, and 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."

This traditional definition of an analytical run is ambiguous. More recent concepts, by changing the focus of QC to the patient safety and risk management, statistical software could assess risk and help determine appropriate QC frequency based upon the number of patients between QC events, which is more meaningful. The level of QC applied in the laboratory varies according to the number of analytical runs and the specimens analyzed per day where decreasing frequency of QC which would have an adverse effect on patient safety. An example of 2 laboratories A and B that run the CLIA minimum of 2 QCs per 24 hours, does lab A that runs 1000 patients a day have the same risk as lab B that runs 50? The answer would be obviously not.

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 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 6σ process (or higher), use 3.5 SD control limits with N=2;
- For a 5σ process, use 3.0 SD control limits with N=2;
- For a 4σ process, use 2.5 SD control limits or a multirule procedure with N=4;
- For a 3σ process, use a multirule procedure with N of 6 or 8.
- For less than 3σ, 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.

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.

IMPORTANT: 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/cliafinalrule9.htm

4.3.3 Medical Decision Levels

Those tables of medical decision levels on http://www.westgard.com/decision.htm provide possible critical decision levels - where you can assess performance (CV, bias) and determine the Sigma-metrics and appropriate QC procedures.

These figures are quoted from Statland BE. Clinical Decision Levels for Laboratory Tests, Second Edition [Oradell NJ; Medical Economics Books, 1987].

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 http://www.westgard.com/downloads/calculators-downloads-1/43-normalized-opspecs-calculator.html, 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.

4.7 Choosing QC Rules Based on Risk Management (Error Rates)

Critical Systematic Error (SEc) reaches zero when 5% of results exceed the TEa limit. SEc uses a z-value of 1.65

$$\mathbf{SE_c = [(TEa\text{-}bias)/s] - z}$$

Error Rate Categories

Low= method that experiences <3% QC flags/year

Moderate= method that experiences 3-10% QC flags/year

High= method that experiences >10% QC flags/year

ΔSE_c	Low	Moderate	High
>3	1-3.5s	1-3s	1-2.5s (D,I)
2-3	1-3s	1-2.5s	1-2s (D,I)
1-2	1-2.5s (D)	1-2s (D,+)	1-2s (D,+,I)
<1	1-2s (D,I)	1-2s (D,+,I)	1-2s (D,+,I)

D: Examine QC chart **D**aily

+: Increase control frequency

I: **I**nitiate corrective action

Source: By courtesy of Alan Wu, PhD, FACB (Personal communication)

5. QC Protocols

The first essential step 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 Medical Testing Field Application Document, Interpretation of NPAAC Requirements and ISO 15189, NATA, November 2013 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. The Clinical users should bear in mind that electronic QC should not supplant QC material. It is a supplement and gives the user confidence that the instrument electronics are performing properly. It does not assess whether the instrument appropriately reads a "wet" sample (patient or QC sample).

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 (refer to: ISO Guide 80 (2014) Guidance for the in-house preparation of Quality Control Materials).

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 SD 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

For the use of a 1-2s rule:

- 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:

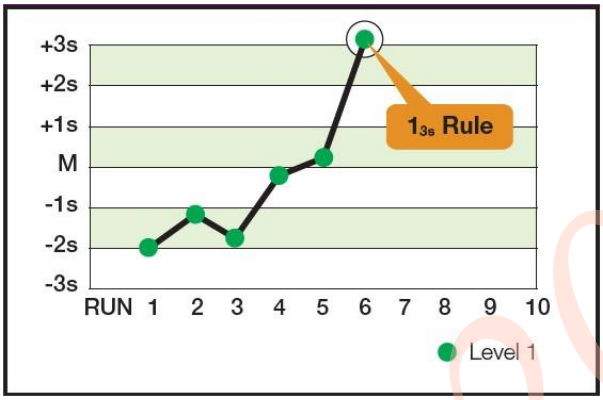
All controls are within 2 SD limits.

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

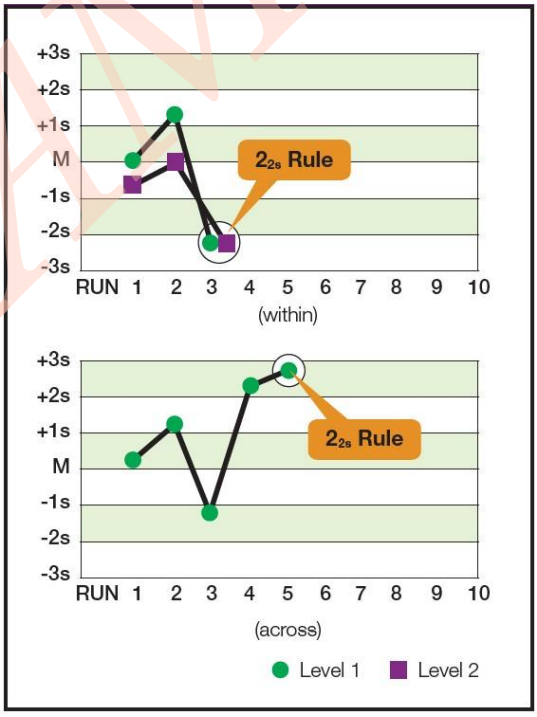
7.2.2 Rejection of Analytical Run:

Precision Flagged

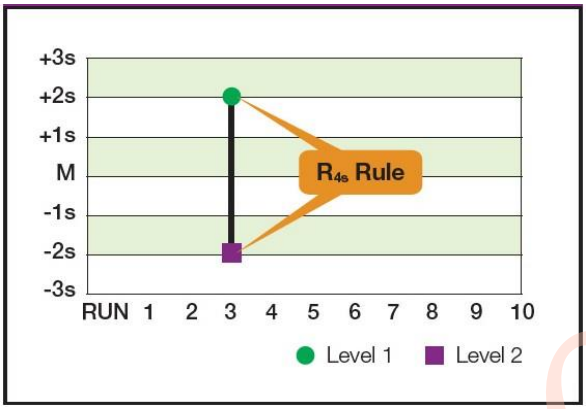
pi. One control is outside 3 SD.



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

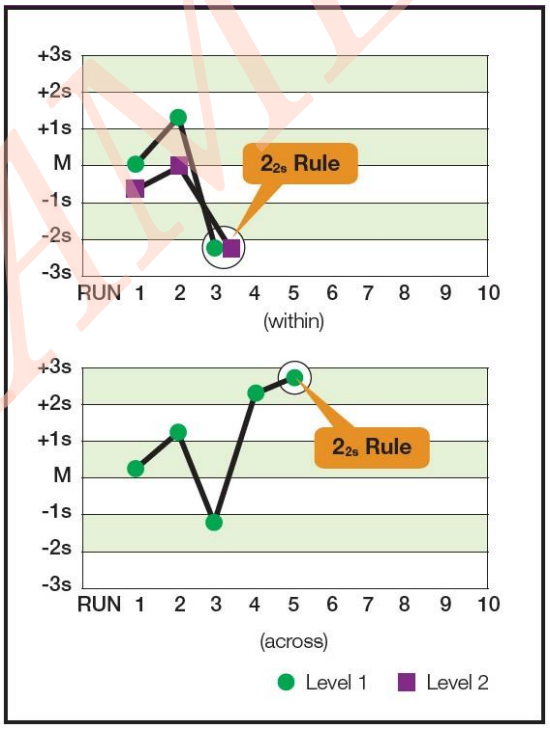


piii. The range (difference) between the maximum and minimum QC value exceeds 4 SD in the last 6 QC assays.

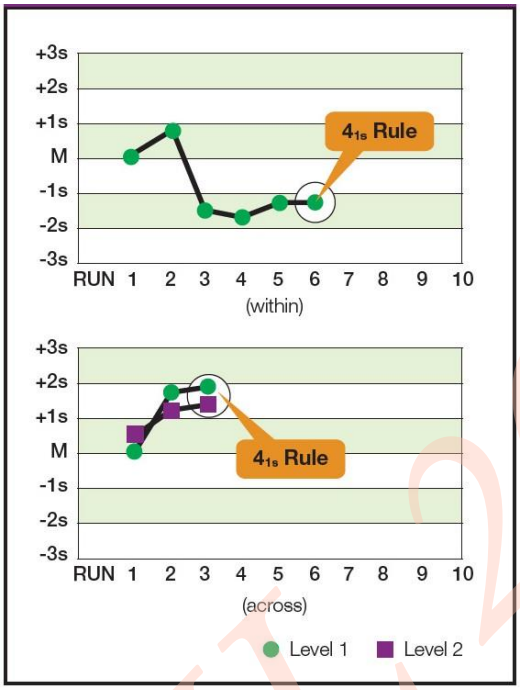


Bias (Accuracy) Flagged

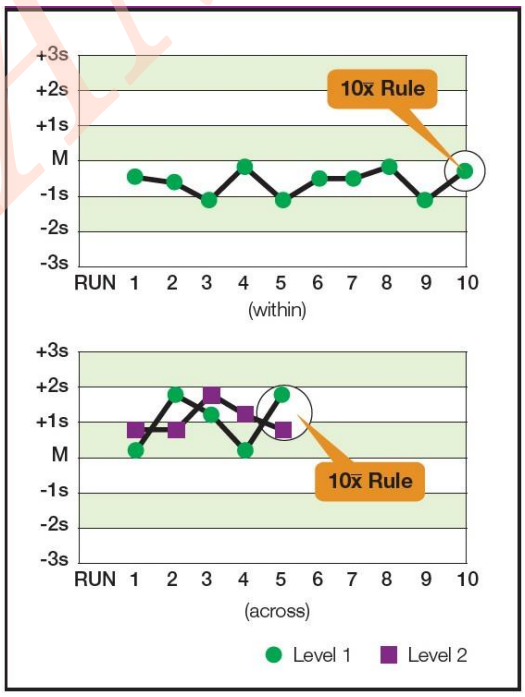
bi. Two consecutive controls are outside the same 2 SD i.e. >+2 SD or <-2 SD.



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. The laboratory shall also evaluate the patient results that were examined after the last successful QC event. When a retest is indicated there shall be criteria (e.g. any clinically significant errors) and written instructions on how to decide which to retest.
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. When an original report is revised there shall be written instructions regarding the revision so that the clinical users are aware of the revision. 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

Identify 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.

Identify 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?

"Review the quality management system at planned intervals to ensure a suitable, adequate, and effective system" (ISO 9001:2015 9.3.1)

Review of procedures as defined by the Quality Management System (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, analyzing 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. QC Practices and Risk Management

Why medical laboratories need QC and Risk Assessment?
Excessive product and process complexity contributes to both excessive variation and unnecessary mistakes. The CLSI Laboratory Quality Control Based on Risk Management; Approved Guideline EP23 was published in October 2011 as a primer on risk management. EP23 can help laboratorians take a more comprehensive view of their operations that builds on the real-world consequences and sources of errors. This document describes Good Laboratory Practice (GLP) for developing and maintaining a Quality Control Plan (QCP) for medical laboratory testing using internationally recognized risk management principles. An individual QCP should be established, maintained, and modified as needed for each measuring system. The QCP is based on the performance required for the intended medical application of the test results.

9.1 Patient Safety

The whole purpose of quality control is to give you confidence in the quality of the results that you are reporting. Those metrics should include measurements to determine if control systems are actually in control. EP23 says; "Medical judgment is used to estimate the overall probability of harm due to receiving an incorrect result…" and hence, Patient Safety (Appendix VII).

There are three ways to improve Patient Safety:

- ✓ Increase Detectability
- ✓ Decrease Frequency (of Errors)
- ✓ Reduce Severity

Detect Immediate Errors

- "Detect immediate errors that occur due to test system failure, adverse environmental conditions, and operator performance" (CLIA 493.1256).
- Most importantly, perform corrective actions to "recover" before reporting of test results.

9.2 Risk Assessment

Why laboratories should perform Risk Assessment (Analysis and Evaluation)?
Currently manufacturers of devices do NOT give much, if any information about device risk. Complex and ever-changing national or international regulations controlling the marketing of medical in-vitro diagnostic (IVD) devices are forcing

manufacturers to provide risk assessment of their IVD products including their QC procedures but NO global consensus or harmonization yet.

Relevant ISO 15189: 2012 Clauses:

- 4.15.1. Laboratory management shall review the quality management system at planned intervals to ensure its continuing suitability, adequacy and effectiveness and support of patient care.
- 4.15.3. The quality and appropriateness of the laboratory's contribution to patient care shall, to the extent possible, also be objectively evaluated.

CLSI (EP23) also recommends the use of risk management for customizing QC in the laboratory. In this approach for "alternate QC," IVD manufacturers would make a risk assessment of their analytic system, eliminate risks of failure when possible, mitigation those risks, and report the "residual risks" to the laboratory, which should then help the laboratory customize its QC system. This customization could employ a variety of mechanisms for prevention and control, a primary one being the adjustment of the QC frequency to monitor the remaining risks.

9.3 Sigma Metrics and Risk Management

"Sigma" standard, its definition "DPM" Defects Per Million by itself is already a risk assessment. If probability estimates are not easily quantifiable, EP23 suggests using descriptive categories (EP23-A 7.2.1).

- For each possible failure, assess the likelihood of that failure occurring and the severity of consequences if it occurs.
  - Construct a table for each identified failure.
  - Use all of the information gathered in order to make these assessments.
- Error Rate Categories

  Low= method that experiences <3% QC flags/year

  Moderate= method that experiences 3-10% QC flags/year

  High= method that experiences >10% QC flags/year

9.4 Sigma Metrics and QC Frequency

Use sigma (σ) metrics to divide tests into groups. The following is an example of the approach – the specifics should be adjusted for patient volume and other relevant factors.

1. >6σ (excellent performance) – evaluate with one QC per day (alternating levels between days) and a 1-3.5s rule.
2. 4σ–6σ (suited for purpose) – evaluate with two levels of QC per day and the 1-2.5s rule.
3. 3σ–4σ (poor performance) – use a combination of rules with two levels of QC twice per day.
4. <3σ (problematic) – maximum QC, three levels, three times a day. Consider testing specimens in duplicate.

Using sigma metrics for QC design should be modulated with other considerations e.g.

a) risk assessment,
b) clinical utility,
c) number of tests performed (volume),
d) level of education of staff performing the test, and
e) external minimal legal requirements.

Source: Cooper G, DeJonge N, Ehrmeyer S, Yundt-Pacheco J, Jansen R, Ricos C, Plebani M. Collective opinion paper on findings of the 2010 convocation of experts on laboratory quality. Clin Chem Lab Med 2011; 49: 793-802.

10. References

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

2. ISO 15189:2012 Medical laboratories – Requirements for quality and competence (ISO/IEC 15189:2012).

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). Hong Kong Accreditation Service. Fifth Edition - April 2013.

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

6. Medical Testing Field Application Document – Requirements for Accreditation, Medical Testing ISO 15189 Standard Application Document (including the application of NPAAC requirements), NATA, November 2013.

7. CLSI EP23-A: Laboratory Quality Control Based on Risk Management; Approved Guideline. October 2011.

8. 中国国家标准化管理委员会. 临床实验室定量测定室内质量控制指南 GB/T 20468-2006. 中华人民共和国国家质量监督检验检疫总局 发布

See also: Appendix VII
Conceptual Framework of QC and Patient Risk Management (Internet Resources)

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.

Biological Variation Values

Desirable Analytical Quality Specifications for Imprecision, Bias and Total Error 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, Hernandez 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 **2014**. ***(denotes updated values)**

S = serum; U = urine; P = plasma; B = blood
CV_w = within-subject biological variation; CV_b = between-subject biological variation; Imp = imprecision; TE_a = total allowable error

		BIOLOGICAL VARIATION		DESIRABLE SPECIFICATIONS			
	ANALYTE	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	50.4	9.8	13.5	29.7	36.4
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	α1-Acid glycoprotein	11.3	24.9	5.7	6.8	16.2	20.0
S	α1-Antitrypsin	5.9	16.3	3.0	4.3	9.2	11.2
S	α1-Globulin	11.4	22.6	5.7	6.3	15.7	19.6
S	α2-Globulins	10.3	12.7	5.2	4.1	12.6	16.1
U	α1-Microglobulin	33.0	58.0	16.5	16.7	43.9	55.1
S	α2-Macroglobulin	3.4	18.7	1.7	4.8	7.6	8.7
P	α-Aminobutyric Acid (AABA)	24.7	32.3	12.4	10.2	30.5	38.9
S	α-Amylase	8.7	28.3	4.4	7.4	14.6	17.5
U	α-Amylase	94.0	46.0	47.0	26.2	103.7	135.7
S	α-Amylase, pacreatic	11.7	29.9	5.9	8.0	17.7	21.7
S	Acid phosphatase (ACP)	8.9	8.0	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
S	Adenosine Deaminase (ADA)	11.7	25.5	5.9	7.0	16.7	20.6
P	Adiponectin	18.8	51.2	9.4	13.6	29.1	35.5
S	AFP	12.2	45.6	6.1	11.8	21.9	26.0
P	Alanine	14.7	55.8	7.4	14.4	26.6	31.6
S	* Alanine aminotransferase	19.4	41.6	9.7	11.5	27.5	34.1
S	* Albumin	3.2	4.75	1.6	1.4	4.1	5.2
U	* Albumin	35	35	17.5	12.4	41.2	53.1
U	Albumin: Creatinine Ratio	30.5	32.5	15.3	11.1	36.3	46.7
S	Aldosterone	29.4	40.1	14.7	12.4	36.7	46.7
U	* Aldosterone concentration, 24 h	39.4	40.1	19.7	14.1	46.6	60.0
S	* Alkaline phosphatase	6.45	26.1	3.2	6.7	12.0	14.2
S	Alkaline phosphatase, bone	6.2	37.4	3.1	9.5	14.6	16.7
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	15.8	38.8	7.9	10.5	23.5	28.9
S	Anion Gap	9.5	10.1	4.8	3.5	11.3	14.5
P	Antiplasmin activity	6.2		3.1			
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)	26.0	31.0	13.0	10.1	31.6	40.4
P	* Ascorbic Acid (Vitamin C)	20	21	10.0	7.3	23.8	30.6

		BIOLOGICAL VARIATION		DESIRABLE SPECIFICATIONS			
	ANALYTE	CV_w	CV_b	Imp (%)	Bias (%)	TE_a (%) p<0.05	TE_a (%) p<0.01
P	Asparagine	12.3	28.0	6.2	7.6	17.8	22.0
S	* Aspartate aminotransferase	12.3	23.1	6.2	6.5	16.7	20.9
P	Aspartic Acid	31.2	55.1	15.6	15.8	41.6	52.2
P	Arginine	19.3	34.1	9.7	9.8	25.7	32.3
S	α-Tocopherol	13.8	15.0	6.9	5.1	16.5	21.2
S	β2-Microglobulin	5.9	15.5	3.0	4.1	9.0	11.0
B	Basophils, count	28.0	54.8	14.0	15.4	38.5	48.0
S	β-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	39.0	11.9	11.4	31.1	39.1
S	C Peptide	16.6	23.2	8.3	7.1	20.8	26.5
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	6.1	62.9	3.1	15.8	20.8	22.9
S	* CA 19.9	15.95	131	8.0	32.9	46.0	51.4
S	CA 549	9.1	33.4	4.6	8.7	16.2	19.3
S	* Calcium	2.1	2.5	1.1	0.8	2.5	3.3
U	* Calcium	26.2	27	13.1	9.4	31.0	39.9
S	* Calcium, Ionized	1.7	1.9	0.9	0.6	2.0	2.6
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	8.05	16.7	4.0	4.6	11.3	14.0
S	* Carnitine, Total	8.85	11.8	4.4	3.7	11.0	14.0
P	* Carotene	18	48	9.0	12.8	27.7	33.8
S	* Carotene	36	39.7	18.0	13.4	43.1	55.3
B	CD4	25.0		12.5			
S	Ceruloplasmin	5.8	11.1	2.9	3.1	7.9	9.9
S	Chloride	1.2	1.5	0.6	0.5	1.5	1.9
S	* Cholesterol	5.95	15.3	3.0	4.1	9.0	11.0
S	Cholinesterase	6.1	18.2	3.1	4.8	9.8	11.9
P	Chromogranin A	12.8	26.3	6.4	7.3	17.9	22.2
P	Citrulline	21.4	43.9	10.7	12.2	29.9	37.1
S	CK MB, activity	19.7	24.3	9.9	7.8	24.1	30.8
S	* CK MB, mass	18.4	56.6	9.2	14.9	30.1	36.3
P	Copper	8.0	19.0	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
P	* Cortisol	21.7	46.2	10.9	12.8	30.7	38.0
S	C-Reactive protein	42.2	76.3	21.1	21.8	56.6	71.0
S	* CRP, High Sensitive	49.7	89.2	24.9	25.5	66.5	83.4
S	Creatine kinase	22.8	40.0	11.4	11.5	30.3	38.1
S	Creatinine	6.0	14.7	3.0	4.0	8.9	11.0
U	* Creatinine	11	23	5.5	6.4	15.4	19.2
S	* C-telopeptide (CTx)	10.85	30.6	5.4	8.1	17.1	20.8
S	Cyfra 21.1	22.2	31.1	11.1	9.6	27.9	35.4
S	Cystatin C	5	13.0	2.5	3.5	7.6	9.3

		BIOLOGICAL VARIATION		DESIRABLE SPECIFICATIONS			
	ANALYTE	CV_w	CV_b	Imp (%)	Bias (%)	TE_a (%) p<0.05	TE_a (%) p<0.01
P	Cystatin C	5.5		2.8			
P	Cystine	38.3	48.5	19.2	15.4	47.0	60.1
P	* D-dimer	23.3	26.5	11.7	8.8	28.0	36.0
S	* Dehydroepiandrosterone sulfate	6.35	30.7	3.2	7.8	13.1	15.2
U	* Deoxypyridinoline/creatinine, 24h	15.35	30.3	7.7	8.5	21.2	26.4
P	* Elastase	12.4	15.1	6.2	4.9	15.1	19.3
B	Eosinophils, count	21.0	76.4	10.5	19.8	37.1	44.3
B	* Erythrocytes, count	3.25	6.3	1.6	1.8	4.5	5.6
S	Estradiol	22.8	24.4	11.4	8.3	27.2	34.9
U	Estradiol	30.4		15.2			
U	Estradiol, free	38.6		19.3			
P	Factor V	3.6		1.8			
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
P	* Factor X	5.35		2.7			
S	Ferritin	14.2	15.0	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	19.2	39.0	47.2
B	* Folate	12	66	6	16.8	26.7	30.8
S	* Follicle stimulating hormone	11	47.2	5.5	12.1	21.2	24.9
S	Free thyroxine (FT4)	5.7	12.1	2.9	3.3	8.0	10.0
S	Free triiodothyronine (FT3)	7.9	17.6	4.0	4.8	11.3	14.0
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	5.6	7.5	2.8	2.3	7.0	8.9
P	Glucose	4.5	5.8	2.3	1.8	5.5	7.1
B	Glucose-6-Phosphate Dehydrogenase	32.8	31.8	16.4	11.4	38.5	49.6
P	Glutamic Acid	46.4	79.9	23.2	23.1	61.4	77.2
P	Glutamine	12.1	22.0	6.1	6.3	16.3	20.4
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	Glycine	11.8	40.3	5.9	10.5	20.2	24.2
S	* HA (Hyaluronic Acid)	62		31.0			
S	Haptoglobin	20.4	36.4	10.2	10.4	27.3	34.2
P	Haptoglobin	20.0	27.9	10.0	8.6	25.1	31.9
P	* HDL cholesterol	7.3	21.2	3.7	5.6	11.6	14.1
S	* HDL cholesterol	7.3	21.2	3.7	5.6	11.6	14.1
B	* Hematocrit	2.7	6.41	1.4	1.7	4.0	4.9
B	* Hemoglobin	2.85	6.8	1.4	1.8	4.2	5.2
B	* Hemoglobin A1C (IFCC)	1.85	5.7	0.9	1.5	3.1	3.7
B	* Hemoglobin A1C (JDS)	1.85	5.7	0.9	1.5	3.0	3.7
B	* Hemoglobin A1C (Mono-S)	1.85	5.7	0.9	1.5	3.0	3.7
B	* Hemoglobin A1C (NGSP)	1.85	5.7	0.9	1.5	3.0	3.7
B	* Hemoglobin A2	0.7	7.7	0.4	1.9	2.5	2.7
S	High Sensitivity C-Reactive protein	42.2	76.3	21.1	21.8	56.6	71.0
P	Histidine	9.7	27.2	4.9	7.2	15.2	18.5

		BIOLOGICAL VARIATION		DESIRABLE SPECIFICATIONS			
	ANALYTE	CV_w	CV_b	Imp (%)	Bias (%)	TE_a (%) p<0.05	TE_a (%) p<0.01
P	* Homocysteine	8.3	33.5	4.2	8.6	15.5	18.3
U	Hydroxyproline	36.1	38.8	18.1	13.2	43.0	55.3
P	Hydroxyproline, Total	34.5	56.7	17.3	16.6	45.1	56.8
S	l-Chains	4.8	18.0	2.4	4.7	8.6	10.2
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
P	Isoleucine	15.5	45.5	7.8	12.0	24.8	30.1
S	* Inhibin B	10	25	5.0	6.7	15.0	18.4
S	Insulin	21.1	58.3	10.6	15.5	32.9	40.1
S	Insulin-like growth factor I (IGF-I, Somatomedin C)	14.6	45.4	7.3	11.9	24.0	28.9
S	Interleukin-8	24.0	31.0	12.0	9.8	29.6	37.8
S	Interleukin 1-β	30.0	36.0	15.0	11.7	36.5	46.7
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
P	Lactoferrin	11.8	23.7	5.9	6.6	16.4	20.4
S	LD1	2.3	8.3	1.2	2.2	4.1	4.8
S	LD2	3.3	2.4	1.7	1.0	3.7	4.9
S	LD3	2.8	3.8	1.4	1.2	3.5	4.4
S	LD4	5.9	5.3	3.0	2.0	6.9	8.9
S	LD5	8	9.6	4.0	3.1	9.7	12.4
S	* LDL cholesterol	7.8	20.4	3.9	5.5	11.9	14.5
P	Leucine	14.8	44.0	7.4	11.6	23.8	28.8
B	* Leukocytes, count	11.45	21.3	5.7	6.0	15.5	19.4
S	* Lipase	32.2	31.8	16.1	11.3	37.9	48.8
S	Lipoprotein (a)	20.8	18.1	10.4	6.9	24.1	31.1
S	* Luteinizing hormone	23	27.4	11.5	8.9	27.9	35.7
B	* Lymphocytes, count	10.2	35.3	5.1	9.2	17.6	21.1
P	Lysine	11.5	38.2	5.8	10.0	19.5	23.4
S	Magnesium	3.6	6.4	1.8	1.8	4.8	6.0
U	* Magnesium	38.3	37.6	19.2	13.4	45.0	58.0
S	Magnesium, ionized	1.9	5.1	1.0	1.4	2.9	3.6
B	* Mean corpuscular hemoglobin (MCH)	1.4	5.2	0.7	1.3	2.5	3.0
B	* Mean corpuscular hemoglobin conc. (MCHC)	1.06	1.2	0.5	0.4	1.3	1.6
B	* Mean corpuscular volume (MCV)	1.4	4.85	0.7	1.3	2.4	2.9
B	Mean platelet volume (MPV)	4.3	8.1	2.2	2.3	5.8	7.3
P	Methionine	14.7	43.4	7.4	11.5	23.6	28.6
U	* Microalbumin	35	35	17.5	12.4	41.2	53.1
B	* Monocytes, count	17.5	49.8	8.8	13.2	27.6	33.6
S	Mucinous carcinoma-associated antigen (MCA)	10.1	39.3	5.1	10.1	18.5	21.9
S	Myeloperoxidase	36.0	30.0	18.0	11.7	41.4	53.7
S	* Myoglobin	17.6	46.3	8.8	12.4	26.9	32.9
B	* Neutrophils, count	17.1	32.8	8.6	9.2	23.4	29.2
B	Norepinephrine	9.5		4.8			

		BIOLOGICAL VARIATION		DESIRABLE SPECIFICATIONS			
	ANALYTE	CV_w	CV_b	Imp (%)	Bias (%)	TE_a (%) p<0.05	TE_a (%) p<0.01
P	Norepinephrine	19.5		9.8			
U	* N-telopeptide	15.5	37.6	7.8	10.2	23.0	28.2
S	NT-proBNP	10.0	16.0	5.0	4.7	13.0	16.4
P	Ornithine	18.4	54.9	9.2	14.5	29.7	35.9
S	Osmolality	1.3	1.2	0.7	0.4	1.5	2.0
P	Osmolality	1.3	1.5	0.7	0.5	1.6	2.0
U	Osmolality	28.3	57.9	14.2	16.1	39.5	49.1
S	* Osteocalcin	6.35	30.9	3.2	7.9	13.1	15.3
U	* Oxalate	42.5	19.9	21.3	11.7	46.8	61.2
S	* PAPP-A	12.6	14	6.3	4.7	15.1	19.4
S	Parathyroid hormone (PTH, intact)	25.9	23.8	13.0	8.8	30.2	39.0
P	* Parathyroid hormone (PTH, intact)	25.3	43.4	12.7	12.6	33.4	42.0
B	pCO2	4.8	5.3	2.4	1.8	5.7	7.4
B	PH	3.5	2.0	1.8	1.0	3.9	5.1
S	Phenylacetate	6.6	25.2	3.3	6.5	12.0	14.2
P	Phenylalanine	9.5	40.6	4.8	10.4	18.3	21.5
S	* Phosphate	8.15	10.8	4.1	3.4	10.1	12.9
U	* Phosphate	18	22.6	9.0	7.2	22.1	28.2
S	Phospholipids	6.5	11.1	3.3	3.2	8.6	10.8
S	PINP (Procollagen type 1 N-terminal Propeptide)	7.4	57.3	3.7	14.4	20.5	23.1
P	Plasminogen	7.7		3.9			
B	Platelets	9.1	21.9	4.6	5.9	13.4	16.5
U	Porphobilinogen	17.0	31.0	8.5	8.8	22.9	28.6
U	Porphyrins, Total	40.0		20.0			
S	* Potassium	4.6	5.6	2.3	1.8	5.6	7.2
U	* Potassium	24.4	22.2	12.2	8.2	28.4	36.7
S	Prealbumin	10.9	19.1	5.5	5.5	14.5	18.2
S	Prolactin	23.0	35 .0	11.5	10.5	29.4	37.3
P	* Prolactin	39.2	65.1	19.6	19.0	51.3	64.7
P	Proline	17.0	104.0	8.5	26.4	40.5	46.2
S	Properdin factor B	9.5	11.2	4.8	3.7	11.5	14.7
S	Prostatic specific antigen (PSA)	18.1	72.4	9.1	18.7	33.6	39.7
U	* Protein	35.5	23.7	17.8	10.7	40.0	52.0
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	2.75	4.7	1.4	1.4	3.6	4.6
P	Prothrombin, time	4.0	6.8	2.0	2.0	5.3	6.6
U	* Pyridinoline/creatinine	19.4	23.6	9.7	7.6	23.6	30.2
B	Pyruvate	15.2	13.0	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	Procollagen type 1 n-terminal (PINP)	6.8	18.4	3.4	4.9	10.5	12.8
S	Reticulocyte, count	11.0	29.0	5.5	7.8	16.8	20.6
P	Retinol	6.2	21.0	3.1	5.5	10.6	12.7
S	Retinol	13.6	19.0	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	12.0	14.0	6.0	4.6	14.5	18.6

		BIOLOGICAL VARIATION		DESIRABLE SPECIFICATIONS			
	ANALYTE	CV_w	CV_b	Imp (%)	Bias (%)	TE_a (%) p<0.05	TE_a (%) p<0.01
P	Selenium	12.0	12.0	6.0	4.2	14.0	18.2
P	Serine	12.8	42.8	6.4	11.2	21.7	26.1
S	* Sex hormone binding globulin (SHBG)	13.05	36.4	6.5	9.7	20.4	24.9
S	* Sodium	0.6	0.7	0.3	0.2	0.7	0.9
U	* Sodium	28.7	16.7	14.4	8.3	32.0	41.7
U	Specific Gravity	0.4	1.0	0.2	0.3	0.6	0.7
S	T3-uptake	0.05		0.0			
P	* T3, Total	9.4	18.5	4.7	5.2	12.9	16.1
P	* T4, Free	7.1	9.1	3.6	2.9	8.7	11.2
P	Taurine	30.6	44.0	15.3	13.4	38.6	49.0
S	* Testosterone	9.25	22.1	4.6	6.0	13.6	16.8
P	* Testosterone	12.6	40.8	6.3	10.7	21.1	25.4
U	Testosterone	25		12.5			
S	Testosterone, free	9.3		4.7			
U	Testosterone, free	51.7		25.9			
P	Threonine	17.9	33.1	9.0	9.4	24.2	30.3
S	Thyroglobulin	14.0	39.0	7.0	10.4	21.9	26.7
S	Thyroglobulin antibody	8.5	82	4.3	20.6	27.6	30.5
S	* Thyroid stimulating hormone (TSH)	29.3	48.4	14.7	14.1	38.3	48.3
S	Thyrotropin receptor antibody	4.8		2.4			
S	Thyroxin binding globulin (TBG)	0.09	0.06	0.0	0.0	0.1	0.1
S	Thyroxine (T4)	4.9	10.6	2.5	2.9	7.0	8.6
S	Thyroid peroxidase antibody	11.3	147.0	5.7	36.9	46.2	50.0
S	Tissue polypeptide antigen (TPA)	31.1	63.7	15.6	17.7	43.4	54.0
S	Tissue polypeptide specific antigen (TPA)	36.1	108.0	18.1	28.5	58.3	70.5
U	Total catecholamines, concentration, 24 h	24.0	32.0	12.0	10.0	29.8	38.0
S	Transferrin	3.0	4.3	1.5	1.3	3.8	4.8
S	* Triglyceride	19.9	32.7	10.0	9.6	26.0	32.8
S	* Triiodothyronine (T3)	6.9	12.3	3.5	3.5	9.2	11.6
S	* Troponin-I	14.05	63.8	7.0	16.3	27.9	32.7
P	* Troponin-I	37.1	179	18.6	45.8	76.4	89.0
S	Troponin-T	30.5	90.0	15.3	23.8	48.9	59.3
P	Tryptophan	22.7	153.0	11.4	38.6	57.3	65.0
S	Tumor neucrosis factor	43.0	29.0	21.5	13.0	48.4	63.1
P	Tyrosine	10.5	61.0	5.3	15.5	24.1	27.7
S	* Urate	8.6	17.5	4.3	4.9	12.0	14.9
U	* Urate	16.8	14.4	8.4	5.5	19.4	25.1
S	* Urea	8.6	17.5	4.3	4.9	12.0	14.9
U	* Urea concentration	17.4	25.4	8.7	7.7	22.1	28.0
P	Valine	10.6	40.1	5.3	10.4	19.1	22.7
P	Vitamin B1	4.8	12.0	2.4	3.2	7.2	8.8
B	Vitamin B12	15.0	69.0	7.5	17.7	30.0	35.1
B	Vitamin B2	5.8	10.0	2.9	2.9	7.7	9.6
B	* Vitamin B6	14	24	7.0	6.9	18.5	23.3
P	* Vitamin B6	20	34	10.0	9.9	26.4	33.2
P	Vitamin E (α-tocopherol)	7.6	21.0	3.8	5.6	11.9	14.4

		BIOLOGICAL VARIATION		DESIRABLE SPECIFICATIONS			
	ANALYTE	CV_w	CV_b	Imp (%)	Bias (%)	TE_a (%) p<0.05	TE_a (%) p<0.01
U	VMA	22.2	47.0	11.1	13.0	31.3	38.9
S	VLDL cholesterol	27.6		13.8			
P	Von Willebrand factor	2.5	27.3	1.25	6.9	8.9	9.8
P	Von Willebrand factor antigen	5.0	18.0	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	13.4	42.2	6.7	11.1	22.1	26.7
P	Zinc	11.0	14.0	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 be 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

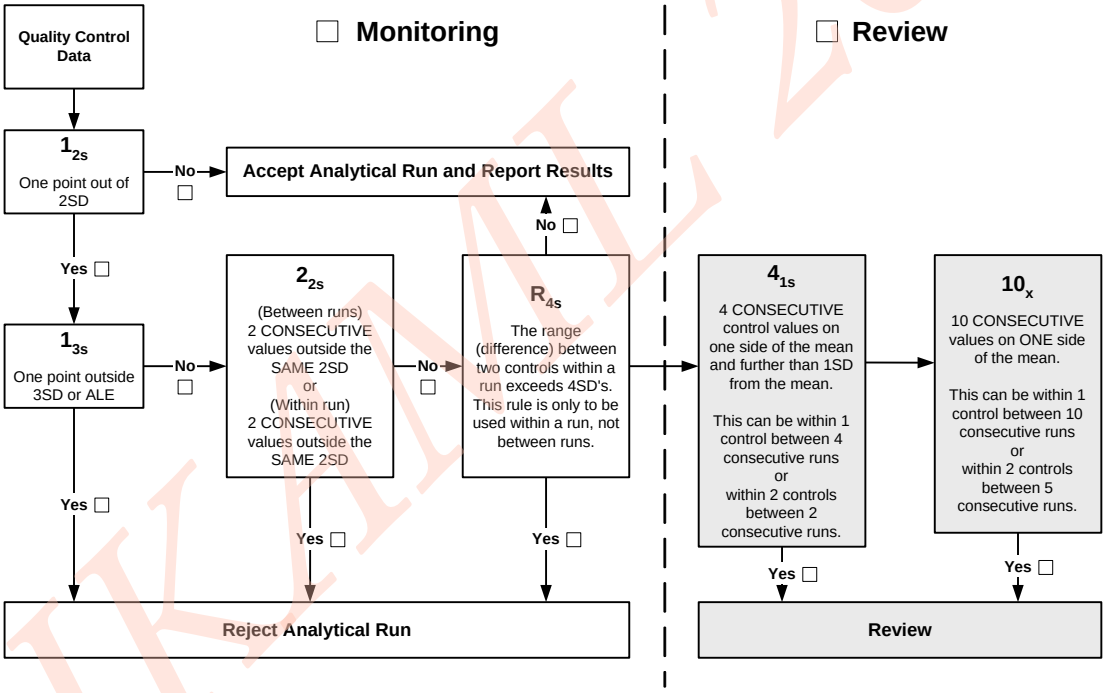
d) Laboratory:
   e.g. Adherence to maintenance and cleaning instructions
   Environment (room temperature and humidity)
   Calibration protocol

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.

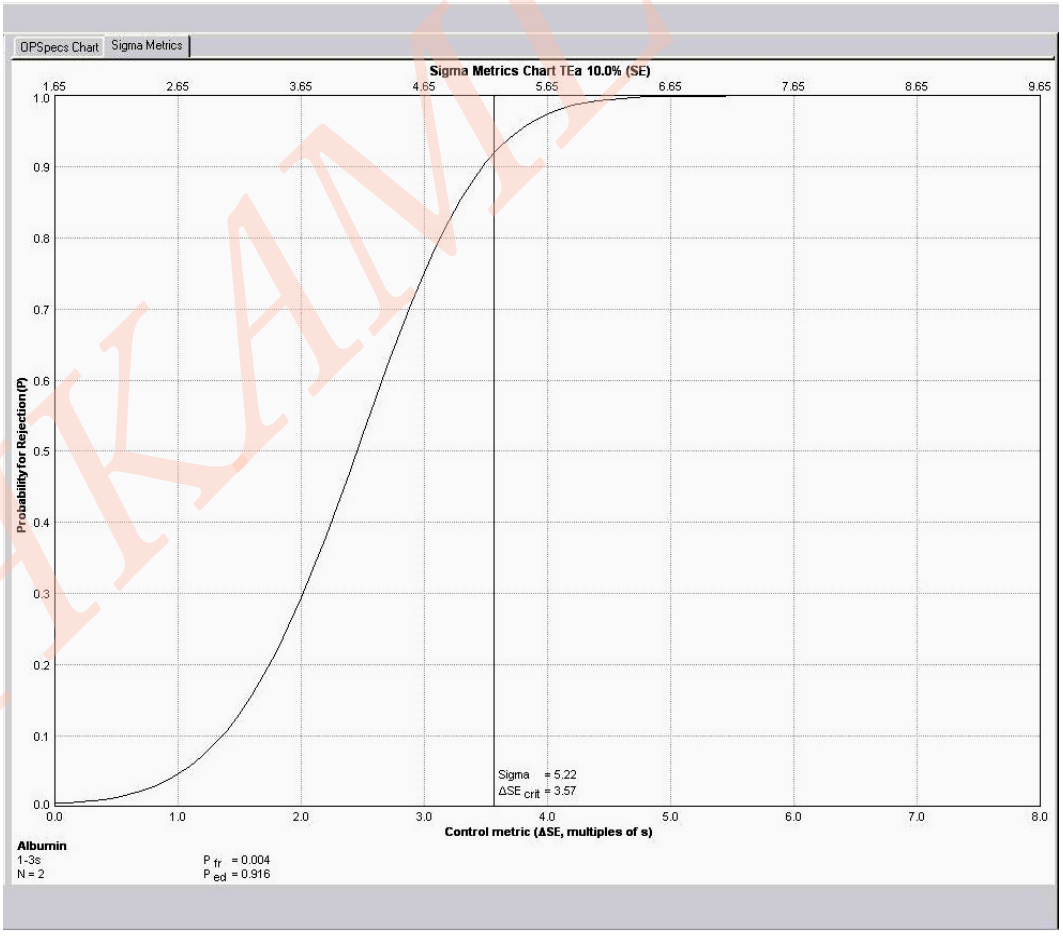


Appendix VI

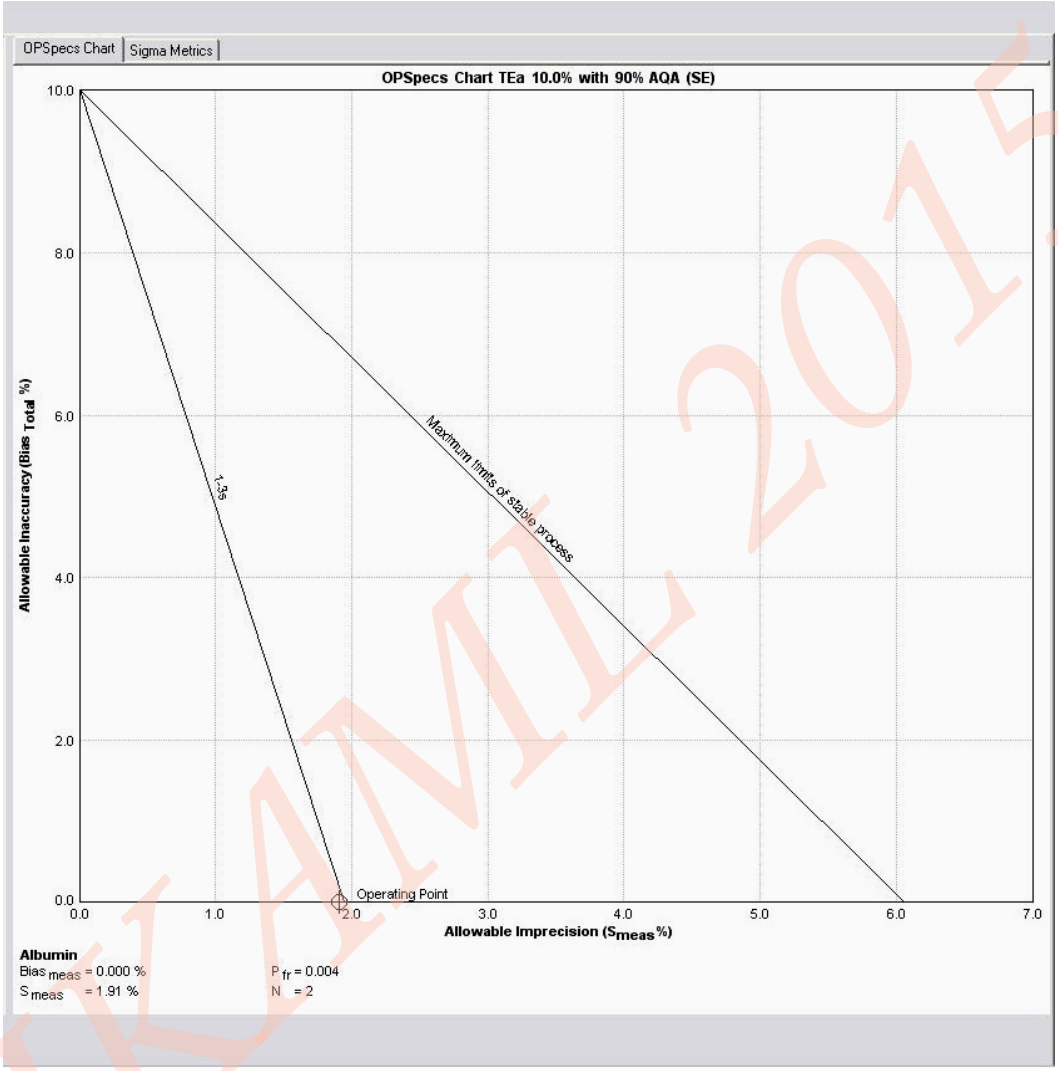
Sigma Metrics and OPSpecs Chart Application

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	(max qc condition)	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.

Appendix VII

Conceptual Framework of QC and Patient Risk Management (Internet Resources)

Reference Articles

Looking Ahead to Patient Risk Management (John Glazier)
Direct Link
http://www.qcnet.com/portals/0/PDFs/Risk_Mgmt_Paper_9_12.pdf
Link Register (best for customers)
http://www.qcnet.com/default.aspx?tabid=7631

Risk Assessment and Quality Control (Max Williams)
http://www.mlo-online.com/articles/201211/risk-assessment-and-quality-control.php

The Impact of QC Frequency on Patient Results (Curtis Parvin)
http://www.mlo-online.com/articles/200809/0908clinical_issues.pdf

QC Design: It's Easier Than You Think (Curtis Parvin)
http://www.mlo-online.com/articles/201312/qc-design-its-easier-than-you-think.php

What are the Risks of Risk Management? (Jim Westgard)
http://www.westgard.com/what-are-the-risks-of-risk-management.htm

Total Analytic Error (TEa) (Jim Westgard)
http://www.aacc.org/publications/cln/2013/september/Pages/Total-Analytic-Error.aspx

Designing QC Rules in the Presence of Laboratory Bias (Curtis Parvin)
AACC Poster
http://www.qcnet.com/Portals/0/Events/AACC%20Abst%20Poster%202012.pdf

Sigma Metrics, Total Error Budgets & QC (Curtis Parvin)
http://laboratory-manager.advanceweb.com/archives/article-archives/sigma-metrics-total-error-budgets-qc.aspx

Recovering from an Out of Control Condition (Curtis Parvin)
http://laboratory-manager.advanceweb.com/Magazine/References/References-for-Rec

overing-From-an-Out-of-Control-Condition.aspx

The Focus of Laboratory Quality Control (Curtis Parvin)
http://laboratory-manager.advanceweb.com/Archives/Article-Archives/The-Focus-of-Laboratory-Quality-Control.aspx

AACC Patient Safety Focus (Nikola Baumann)
http://www.aacc.org/publications/cln/articles/2012/october/testing-errors

Video Presentations

Risk Calculator "Teaser" http://youtu.be/44UKv9QUr6c
Video that introduces Risk Management Software (no QC Planner)

QC Simulator
Video that simulates a test explaining the risk and how it works
Part 1 - http://youtu.be/5Gvc6O0YXZM
Part 2 - http://youtu.be/qjJaQBzkQfw
Part 3 - http://youtu.be/y8RUM5Aimko
Part 4 - http://youtu.be/-ecaz_uRMGE
Total Video http://youtu.be/xUCorNTN5O8

Risk Calculator Software Demo
Video that shows how the software works. AACC demo script.
http://youtu.be/6vVdwfbz2wQ

Components of the Risk Assessment Report
% Unreliable http://youtu.be/0W6U8V_8GuY
Percent of patient results with measurement error exceeding the TEa
Part 1, 3:28 min
Risk Calculator Training, QC Services in screen shot

E(QCE) http://youtu.be/9ZX2jN4c0e4
Expected number of QC Events required to detect an out of control condition
Part 2, 4:03 min
Risk Calculator Training, QC Services in Screen shot

E(Nuf) http://youtu.be/Rbw-upWUTEM

Expected number of Unreliable patient samples after an out of control condition that have been reported and are final

Part 3, 5:57 min

Risk Calculator Training, QC Services in Header

E(Nuc) http://youtu.be/SrSnZL-GYcM

Expected number of Unreliable patient samples after an out of control condition that are correctable

Part 4, 5:27 min

Risk Calculator Training, QC Services in Header

Summary Header http://youtu.be/H1XBMAHQnwo

The summary text at the top of the Single Analyte Report

Part 5, 2:15 min

Says "QC Services" in Header

Some long pauses

Infographic http://youtu.be/qcNoWl0tmuM

Summarizes the data contained in the Single Analyte Report

Part 6, 3:38 min

By courtesy of Bio-Rad Laboratories, Inc.

Notes

(This page is intentionally left blank)


HONG KONG ASSOCIATION OF MEDICAL LABORATORIES LIMITED
HKAML
香港醫務化驗所總會