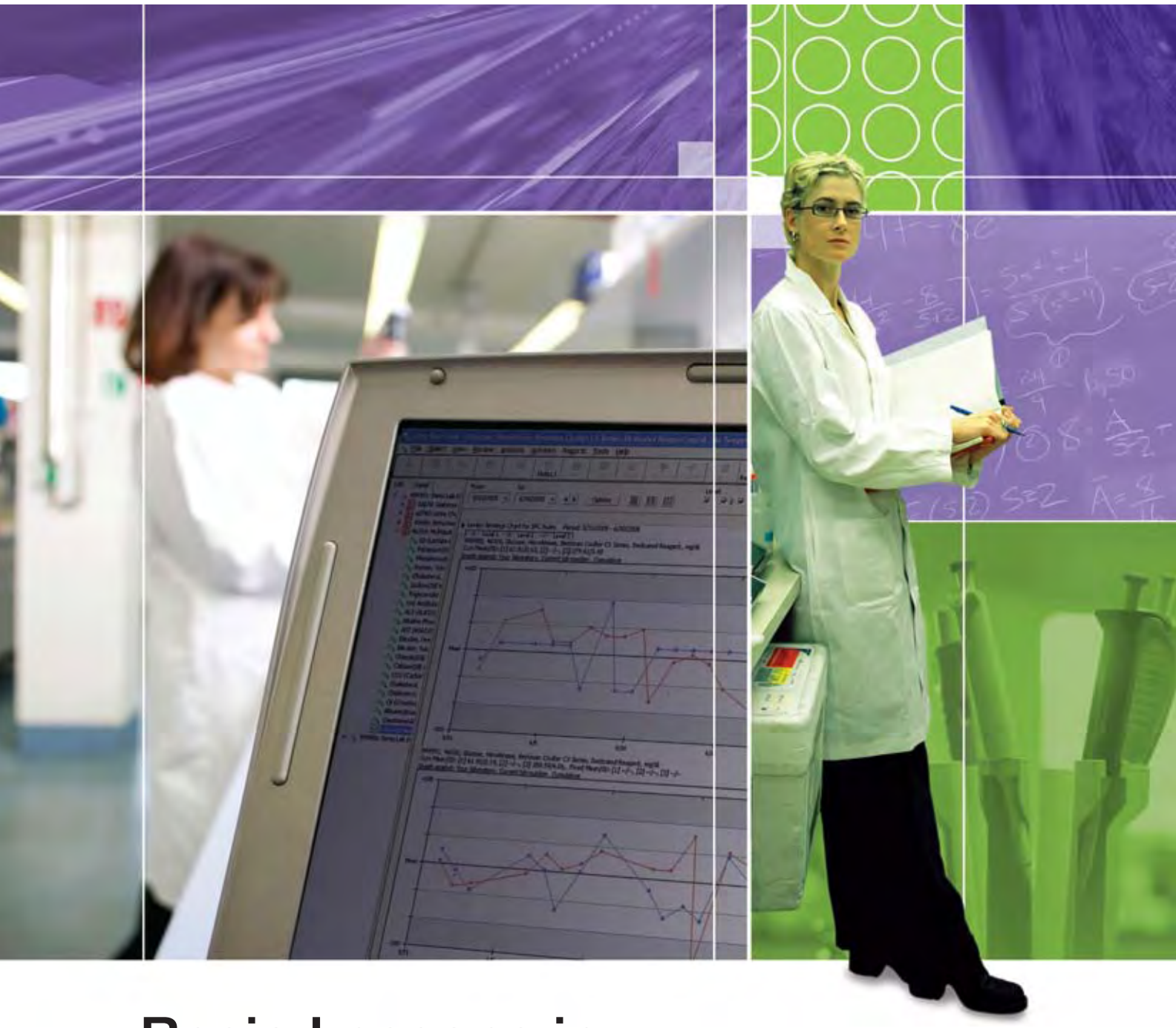

Basic Lessons in Laboratory Quality Control

QC Workbook

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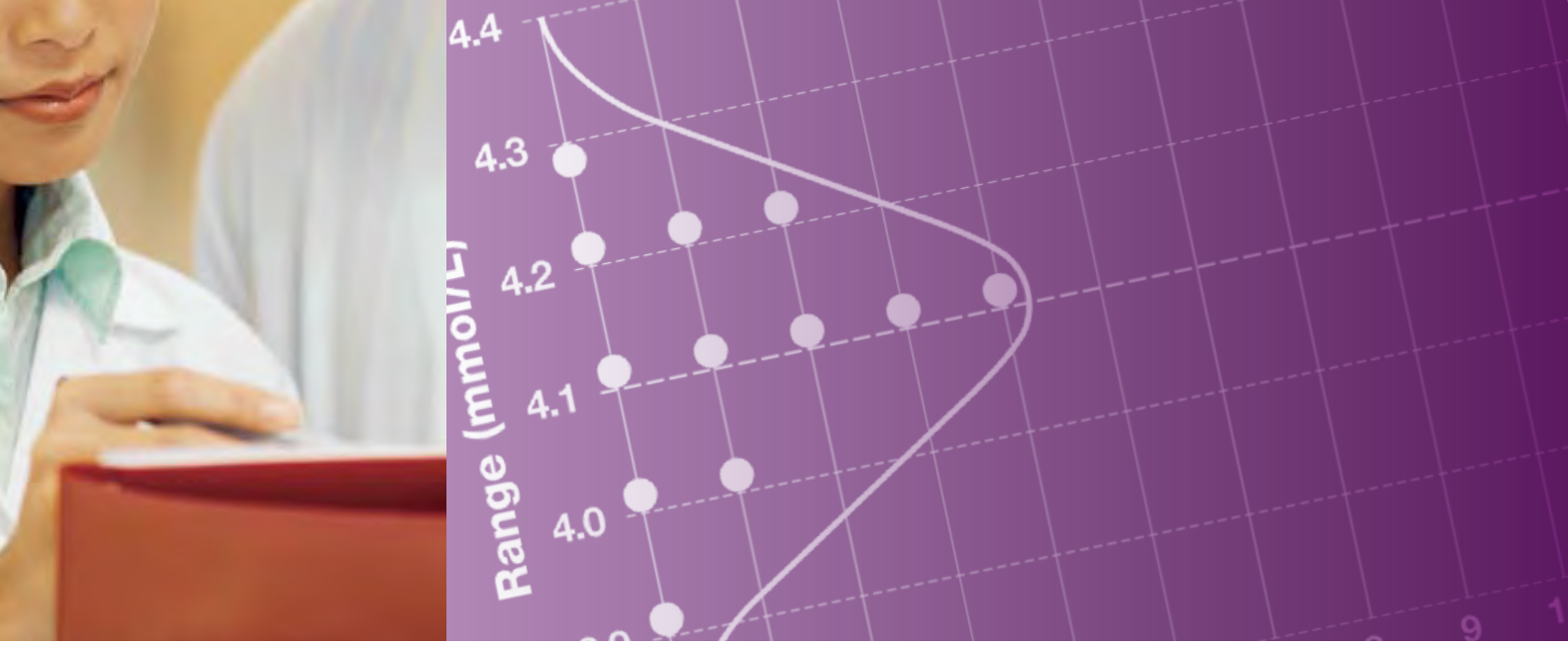

Basic Lessons in Laboratory Quality Control

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Table of Contents

CHAPTER 4: Additional Quality Control Statistics

CHAPTER 5: Choosing a Quality Control Product

CHAPTER 6: Final Examination & Evaluation

Index & Resources

Foreword

Achieving quality in the medical laboratory requires the use of many tools. These include procedure manuals, maintenance schedules, calibrations, a quality assurance program, training and quality control.

This workbook explains and illustrates the basic knowledge required to set up a simple but effective quality control system using statistical process control. Statistical process control is a set of rules that is used to verify the reliability of patient results. It is based on statistics calculated from the regular testing of quality control products.

Workbook Overview

- Learn how to calculate the required and other useful statistics
- Learn how to recognize patterns in quality control data that may indicate the test system is operating outside of specifications
- Learn how to investigate and troubleshoot when certain patterns exist
- Discover important items to consider when purchasing a control product

Self Test questions appear throughout the workbook, and the answers to these questions can be found at the end of this publication along with a self exam. A Certificate of Completion will be awarded to those who score a 70% or higher.

Bio-Rad Laboratories is approved as a provider for Category 1 Continuing Education by the PACE Program through the American Society of Clinical Laboratory Science. This basic to intermediate self-instructional course is approved for 2.5 contact hours. This course is also approved for California clinical licensees under the PACE California Accrediting Agency License No. 0001.

What You Will Learn?

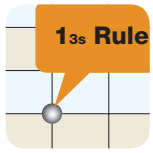
1

Quality Control Basics

2

Calculations & Statistics

3



Westgard Rules

4

Levey-Jennings Charts

5

QC Product Awareness

- Define and apply the basic elements of quality control, and implement a quality control program in the laboratory
- Define, calculate and apply the following statistics: mean, standard deviation, coefficient of variation, coefficient of variation ratio and standard deviation index
- Describe, choose and apply each of the Westgard rules
- Identify which Westgard rules identify random error and which rules identify systematic error
- Identify and differentiate trend and shift
- Identify and differentiate random error and systematic error
- Construct a Levey-Jennings chart and evaluate graphed data for out of control events
- Assess instruments, reagents, and control products using the coefficient of variation
- Evaluate within lab precision using the coefficient of variation ratio
- Evaluate laboratory accuracy using the standard deviation index
- Choose and/or recommend control materials based on shelf life, box pricing, clinically relevant decision levels, matrix effects and interlaboratory comparison programs

What Do You Want to Learn?

CHAPTER 1

Quality Control

Introduction:
What is Quality Control?

Quality control in the medical laboratory is a statistical process used to monitor and evaluate the analytical process that produces patient results.

Requirements for the Statistical Process

Regular testing of quality control products along with patient samples.

Comparison of quality control results to specific statistical limits (ranges).

When a diagnostic test is performed in the medical laboratory, the outcome of the test is a result. The result may be a patient result or it may be a quality control (QC) result. The result may be quantitative (a number) or qualitative (positive or negative) or semi-quantitative (limited to a few different values).[1]

QC results are used to validate whether the instrument is operating within pre-defined specifications, inferring that patient test results are reliable. Once the test system is validated, patient results can then be used for diagnosis, prognosis, or treatment planning. For example, when a patient's serum is assayed (tested) for potassium, the test result tells us how much potassium (concentration) is present in the blood. This result is then used by the physician to determine whether the patient has a low, normal or high potassium.

Let's assume the measured value of potassium in a patient's serum is 2.8 mmol/L (a unit of measure, millimoles per liter).[2] This result is abnormally low and indicates an inappropriate loss of potassium. But how does the person performing the test know that this result is truly reliable? It could be possible that the instrument is out of calibration and the patient's true potassium value is 4.2 mmol/L – a normal result. The question of reliability for most testing can be resolved by regular use of quality control materials and statistical process control.

1 This workbook will deal only with the quality control of quantitative data.
2 Potassium can be measured as milliequivalents per liter (mEQ/L) as well.

Quality Control Products

A quality control product is a patient-like material ideally made from human serum, urine or spinal fluid.[3] A control product can be a liquid or freeze-dried (lyophilized) material and is composed of one or more constituents (analytes) of known concentration. Control products should be tested in the same manner as patient samples.

A quality control product usually contains many different analytes. For example, a general chemistry control can contain any number of chemistry analytes including potassium, glucose, albumin and calcium.

A normal control product contains normal levels for the analyte being tested. An abnormal control product contains the analyte at a concentration above or below the normal range for the analyte. For example, the normal range for a potassium level is about 3.5 – 5.0 mmol/L. A normal control would contain potassium at a level within this range. An abnormal control would contain potassium at a level below 3.5 mmol/L or above 5.0 mmol/L.

Regular Testing

Good laboratory practice requires testing normal and abnormal controls for each test at least daily to monitor the analytical process. If the test is stable for less than 24 hours or some change has occurred which could potentially affect the test stability, controls should be assayed more frequently.[4,5]

Regular testing of quality control products creates a QC database that the laboratory uses to validate the test system. Validation occurs by comparing daily QC results to a laboratory-defined range of QC values. The lab-defined range is calculated from QC data collected from testing of normal and abnormal controls. Please examine the contents of Table 1 before proceeding to the next section.

3 Sometimes control products are not human. Control products can be animal in origin, aqueous solutions or a commercially prepared organic matrix.

4 In the United States, the Final CLIA Rule (January 2003) requires that two control materials, each material being of a different concentration, be assayed on each day the test is performed, unless the laboratory can demonstrate the test qualifies for an alternative QC scheme known as equivalent QC. (Equivalent QC requires more than a basic understanding of QC principles, so is not covered in this workbook.) So, without going into the few exceptions allowed under the Final CLIA rule, if you test patient samples for potassium on Wednesday, you must assay at least two concentrations of control material (e.g. one normal and one abnormal control product) for potassium on Wednesday.

5 As with any government regulation, these requirements can undergo change as a result of the regulatory or political process.

Comparison of Quality Control Results to Specific Statistical Limits

In Table 1, there are two ranges reported. The acceptable range for the Level I (Normal Control) is 3.7 – 4.3 mmol/L. The range for Level II (Abnormal Control) is 6.7 – 7.3 mmol/L. When the daily QC result obtained for the normal control is compared to the range calculated for the normal control, it becomes apparent that each result lies somewhere within the expected range. This indicates that the analytical process is "in control" at the normal level on that day of testing.

When the daily QC result for the abnormal control (high potassium) is compared to the defined range for the abnormal control, the analytical process is shown to be "in control" for each day of testing except for the last day (11/7). On November 1 through November 6, both controls were "in control" and patient values could be reliably reported. However, the laboratory was "out of control" for abnormal high potassiums on November 7 because the value obtained for the QC material (8.0 mmol/L) was outside the acceptable range (6.7 – 7.3 mmol/L).

This means that some error occurred which may have made some patient results unreliable. The laboratory should not report any patient samples with an abnormally high potassium result until the error is resolved and the abnormally high sample(s) are re-tested.[6]

Perhaps it is now apparent that the range defined for each level of control is fundamental to the quality control system. The next section describes how to calculate the basic statistics required to develop an acceptable control range.

Table 1: Example of a QC Log with Patient Results

Test: Potassium	**Instrument:** Instrument No. 1		**Unit of Measure:** mmol/L
	Level I Normal Control	**Level II Abnormal Control**	
Range ▸	3.7 – 4.3 mmol/L	6.7 – 7.3 mmol/L	**Patient Results**
1 November	4.0	7.0	4.2, 4.0, 3.8, 5.0, 5.8, 4.2
2 November	4.1	7.0	3.8, 4.4, 4.6, 3.9, 4.8, 4.4, 3.9
3 November	4.0	6.9	4.4, 3.9, 3.7, 4.7
4 November	4.2	7.1	4.7, 5.6, 4.2, 3.7, 4.3
5 November	4.1	7.0	4.2, 4.3, 4.1, 4.3
6 November	4.1	7.0	4.6, 4.4, 5.5, 3.8, 3.2
7 November	4.2	8.0	2.8, 4.6, 4.2, 3.2, 3.9, 4.1, 6.0, 4.3

6 A test system can malfunction or begin to malfunction at any time since the last successful QC. In this example, it would be good laboratory practice to re-test all patient samples that were reported with abnormally high potassium levels or near the upper limit of normal since the last QC was performed. Re-testing a random sample of patients versus all samples, is an acceptable, although risky practice. In the case of some analytes like potassium, the amount of time the plasma or serum has been in contact with cellular elements must be taken into consideration.

Self Test #1
Quality Control

1. **What is quality control?**

2. **Name two components of quality control in the medical laboratory?**

a.

b.

3. **What is mmol/L?**

4. **How often should quality control products be tested?**

5. **If the QC result for the normal level of control is outside the range defined for that control level, normal patient results may be reported. (Circle the answer below)**

   True

   False

Answers to Self Test on Page 54

What Do You Want to Learn?

CHAPTER 2

Calculations

Calculation and Use of QC Statistics

QC statistics for each test performed in the laboratory are calculated from the QC database collected by regular testing of control products. The data collected is specific for each level of control. Consequently, the statistics and ranges calculated from this data are also specific for each level of control and reflect the behavior of the test at specific concentrations. The most fundamental statistics used by the laboratory are the mean [$\bar{x}$] and standard deviation [s].

Calculating a Mean [$\bar{x}$]

The mean (or average) is the laboratory's best estimate of the analyte's true value for a specific level of control.

To calculate a mean for a specific level of control, first, add all the values collected for that control. Then divide the sum of these values by the total number of values. For instance, to calculate the mean for the normal control (Level I) in Table 1, find the sum of the data {4.0, 4.1, 4.0, 4.2, 4.1, 4.1, 4.2}. The sum [Σ] is 28.7 mmol/L. The number of values is 7 (n = 7). Therefore, the mean for the normal potassium control in Table 1 from November 1–7 is 4.1 mmol/L (or 28.7 mmol/L divided by 7).

Formula 1: Calculating the Mean [$\bar{x}$]

$$\Sigma x_n / n$$

Where:

Σ = sum

x_n = each value in the data set

n = the number of values in the data set

Self Test #2
Calculating the Mean

Calculate the normal and/or abnormal control mean for each of the following sets of control data.

Laboratory A

Level I (Normal Control)
Unassayed Chemistry Control, Lot No. 12345
Test: Creatine Kinase
Instrument: ABC
Units: U/L

Control Values are:
{94, 93, 97, 95, 95, 100, 100, 99, 100, 99}

Level II (Abnormal Control)
Unassayed Chemistry Control, Lot No. 12345
Test: Creatine Kinase
Instrument: ABC
Units: U/L

Control Values are:
{327, 325, 321, 323, 315, 308, 304, 298, 327, 334}

Laboratory B

Level II (Abnormal Control)
Unassayed Chemistry Control, Lot No. 12345
Test: Aspartate Aminotransferase (AST)
Instrument: ABC
Units: U/L

Control Values are:
{183, 185, 182, 181, 182, 180, 182, 181, 179, 181}

Laboratory C

Level I (Normal Control)
Unassayed Chemistry Control, Lot No. 12345
Test: Creatine Kinase
Instrument: XYZ
Units: U/L

Control Values are:
{86, 93, 97, 90, 95, 100, 103, 99, 104, 92}

Level II (Abnormal Control)
Unassayed Chemistry Control, Lot No. 12345
Test: Creatine Kinase
Instrument: ABC
Units: U/L

Control Values are:
{342, 325, 321, 323, 315, 298, 288, 298, 327, 350}

Answers to Self Test on Page 54

Calculating a Standard Deviation [s]

Standard deviation is a statistic that quantifies how close numerical values (i.e., QC values) are in relation to each other. The term precision is often used interchangeably with standard deviation. Another term, imprecision, is used to express how far apart numerical values are from each other. Standard deviation is calculated for control products from the same data used to calculate the mean. It provides the laboratory an estimate of test consistency at specific concentrations. The repeatability of a test may be consistent (low standard deviation, low imprecision) or inconsistent (high standard deviation, high imprecision). Inconsistent repeatability may be due to the chemistry involved or to a malfunction. If it is a malfunction, the laboratory must correct the problem.

It is desirable to get repeated measurements of the same specimen as close as possible. Good precision is especially needed for tests that are repeated regularly on the same patient to track treatment or disease progress. For example, a diabetic patient in a critical care situation may have glucose levels run every 2 to 4 hours. In this case, it is important for the glucose test to be precise because lack of precision can cause loss of test reliability. If there is a lot of variability in the test performance (high imprecision, high standard deviation), the glucose result at different times may not be true.

Figure 1: Example of Good Precision & Accuracy

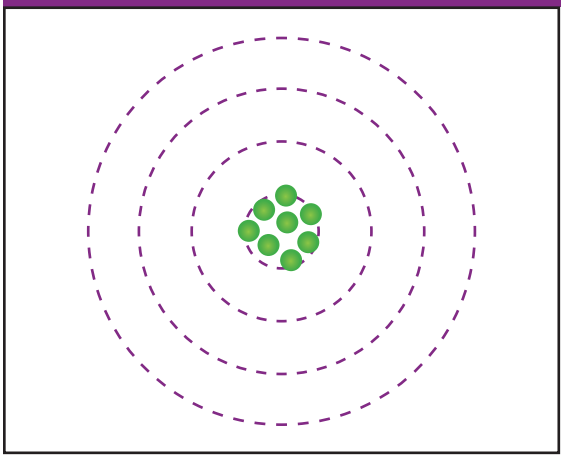
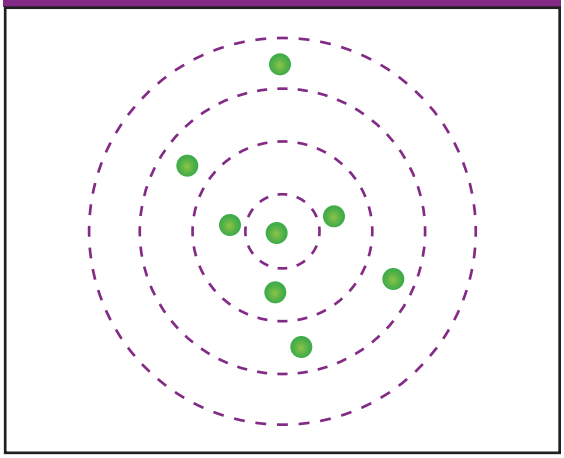


Figure 2: Example of Poor Precision (High Imprecision)



Standard deviation may also be used to monitor on-going day-to-day performance. For instance, if during the next week of testing, the standard deviation calculated in the example for the normal potassium control increases from .08 to 0.16 mmol/L, this indicates a serious loss of precision. This instability may be due to a malfunction of the analytical process. Investigation of the test system is necessary and the following questions should be asked:

- Has the reagent or reagent lot changed recently?
- Has maintenance been performed routinely and on schedule?
- Does the potassium electrode require cleaning or replacement?
- Are the reagent and sample pipettes operating correctly?
- Has the test operator changed recently?

Formula 2: Calculating a Standard Deviation [s] For a Set of QC Values

$$s = \sqrt{\frac{\sum(x_n - \bar{x})^2}{n - 1}}$$

Where:

- s = standard deviation
- $\bar{x}$ = mean (average) of the QC values
- $\Sigma(x_n - \bar{x})^2$ = the sum of the squares of differences between individual QC values and the mean
- n = the number of values in the data set

Although most calculators and spreadsheet programs automatically calculate standard deviation, it is important to understand the underlying mathematics.

To calculate the standard deviation for the normal level of control (Level I) in Table 1, begin by calculating the mean [$\bar{x}$]:

$\bar{x}$ = 4.0 + 4.1 + 4.0 + 4.2 + 4.1 + 4.1 + 4.2 mmol/L ÷ 7

$\bar{x}$ = 28.7 mmol/L ÷ 7

$\bar{x}$ = 4.1 mmol/L

Calculate the standard deviation [s] as follows:

$$s = \sqrt{\frac{\sum(x_n - \bar{x})^2}{n - 1}}$$

$$s = \sqrt{\frac{(4 - 4.1)^2 + (4.1 - 4.1)^2 + (4 - 4.1)^2 + (4.2 - 4.1)^2 + (4.1 - 4.1)^2 + (4.2 - 4.1)^2}{6}}$$

$$s = \sqrt{\frac{(-0.1)^2 + (0.0)^2 + (-0.1)^2 + (+0.1)^2 + (0.0)^2 + (0.0)^2 + (+0.1)^2}{6}}$$

$$s = \sqrt{\frac{0.01 + 0.0 + 0.01 + 0.01 + 0.0 + 0.0 + 0.01}{6}}$$

$$s = \sqrt{\frac{0.04}{6}}$$

s = 0.082 OR 0.1 (Rounded)

The standard deviation for one week of testing of the normal potassium control level is 0.082 mmol/L.[7] Now that the amount of precision is known, some assumptions can be made about how well this test is performing.

7 This type of standard deviation is called between run standard deviation because the data used to calculate the statistics came from different analytical runs.

Self Test #3
Calculating the Standard Deviation

Calculate the standard deviation for each data set in Self Test #2. Please note that many calculators and spreadsheet programs calculate the standard deviation in two different ways. Use the one that divides by n-1 and not by n.

Answers to Self Test on Page 54

CHAPTER 3

Levey-Jennings Charts & Westgard Rules

Creating a Levey-Jennings Chart

Standard deviation is commonly used for preparing Levey-Jennings (L-J or LJ) charts. The Levey-Jennings chart is used to graph successive (run-to-run or day-to-day) quality control values. A chart is created for each test and level of control. The first step is to calculate decision limits.

These limits are ±1s, ±2s and ±3s from the mean. The mean for the Level I potassium control in Table 1 is 4.1 mmol/L and the standard deviation is 0.1 mmol/L.[8] Formula 3 provides examples on how ±1s, ±2s and ±3s quality control limits are calculated.

Formula 3: Calculating Quality Control Limits

These ranges are used with the mean to construct the Levey-Jennings chart as shown in Figure 3.

±1s range is 4.0 to 4.2 mmol/L

4.1 – (0.1)(1) = 4.0

4.1 + (0.1)(1) = 4.2

±2s range is 3.9 to 4.3 mmol/L

4.1 – (0.1)(2) = 3.9

4.1 + (0.1)(2) = 4.3

±3s range is 3.8 to 4.4 mmol/L

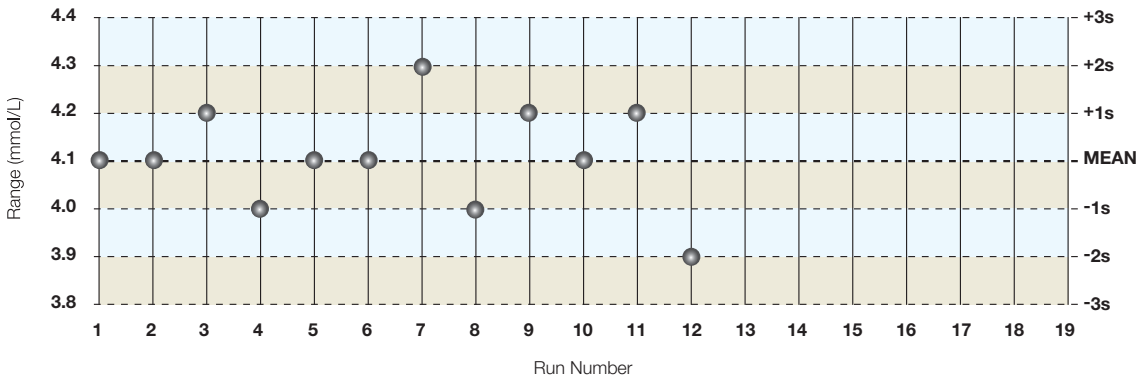
4.1 – (0.1)(3) = 3.8

4.1 + (0.1)(3) = 4.4

The Levey-Jennings chart we have developed can be overlaid onto a bell-shaped curve to illustrate the overall distribution of quality control values (see Figure 4).

Figure 3: Levey-Jennings Chart

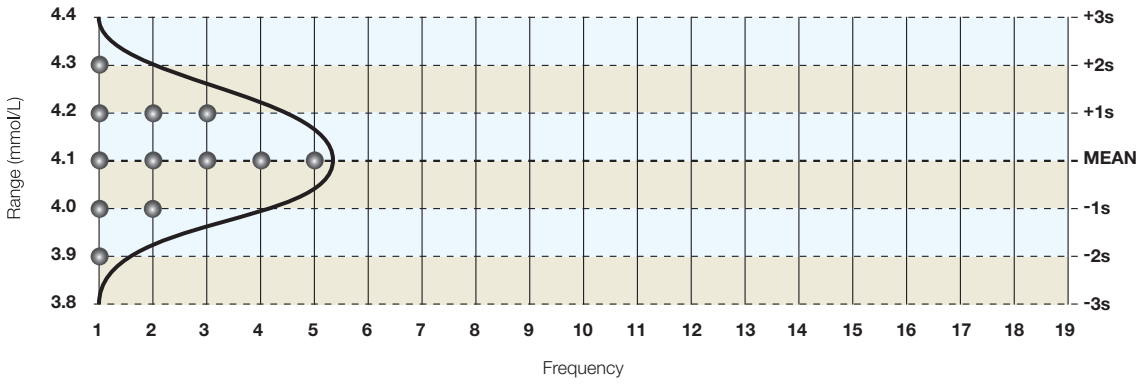
Unassayed Chemistry Control, Lot No. 12345	Level 1 (Normal Control)	**Test:** Potassium



8 Rounding of the mean and standard deviation to the nearest tenth is allowable in this example because potassium results are generated and reported to the nearest tenth. The standard deviation of 0.08 mmol/L is rounded to 0.1 mmol/L.

Figure 4: Relative Distribution of QC Values

Unassayed Chemistry Control, Lot No. 12345	Level 1 (Normal Control)	**Test:** Potassium



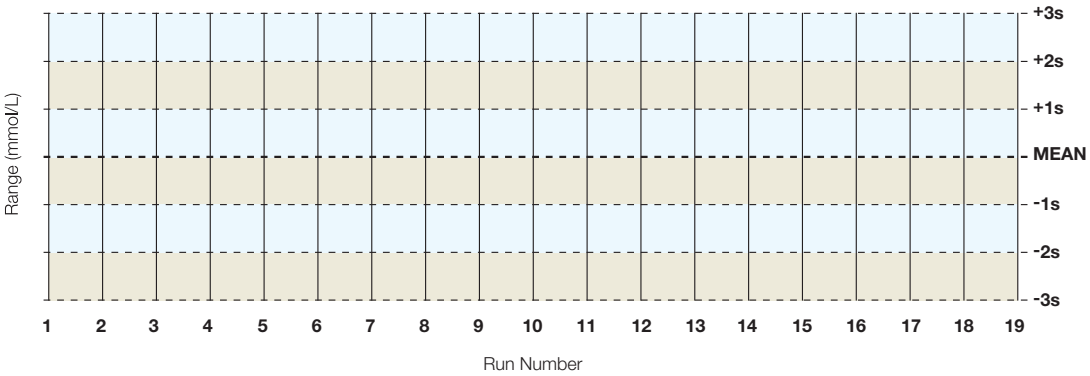
When an analytical process is within control, approximately 68% of all QC values fall within ±1 standard deviation (1s). Likewise 95.5% of all QC values fall within ±2 standard deviations (2s) of the mean. About 4.5% of all data will be outside the ±2s limits when the analytical process is in control. Approximately 99.7% of all QC values are found to be within ±3 standard deviations (3s) of the mean. As only 0.3%, or 3 out of 1000 points, will fall outside the ±3s limits, any value outside of ±3s is considered to be associated with a significant error condition and patient results should not be reported.

CAUTION: Some laboratories consider any quality control value outside its ±2s limits to be out of control. They incorrectly decide that the patient specimens and QC values are invalid. An analytical run[9] should not be rejected if a single quality control value is outside the ±2s QC limits but within the ±3s QC limits. Approximately 4.5% of all valid QC values will fall somewhere between ±2 and ±3 standard deviation limits. Laboratories that use a ±2s limit frequently reject good runs. That means patient samples are repeated unnecessarily, labor and materials are wasted, and patient results are unnecessarily delayed.

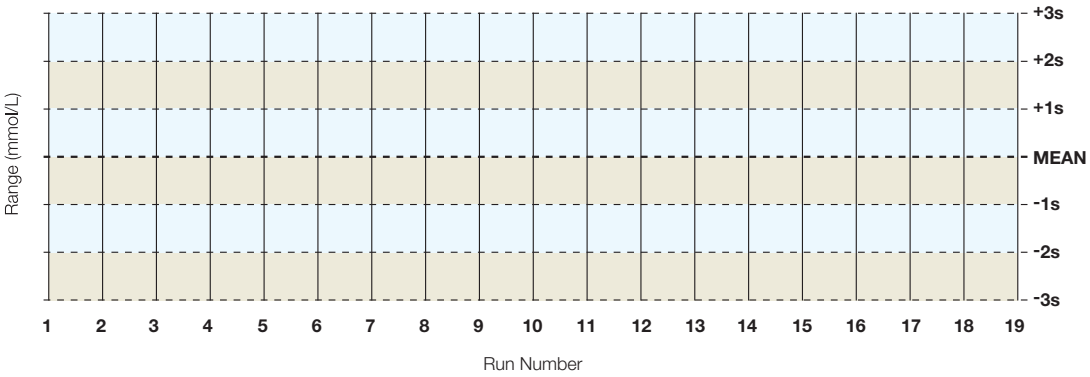
9 The combination of patient and quality control specimens analyzed together is referred to as an "analytical run" or "run" for short.

Self Test #4
Create a Levey-Jennings Chart

1. Create a Levey-Jennings chart for the Level I control reported for Laboratory A in Self Test #2 using a mean of 90 U/L and a standard deviation of 9 U/L. Assume that each data point was obtained on separate days. Are there any points outside the ±2s limits?



2. Create a Levey-Jennings chart for the Level II control reported for Laboratory A in Self Test #2 using a mean of 350 U/L and a standard deviation of 25 U/L. Assume that each data point was obtained on separate days. Are there any points outside the ±2s limits?



Answers to Self Test on Page 54

Using a Levey-Jennings Chart to Evaluate Run Quality

The laboratory needs to document that quality control materials are assayed and that the quality control results have been inspected to assure the quality of the analytical run. This documentation is accomplished by maintaining a QC Log and using the Levey-Jennings chart on a regular basis. The QC Log can be maintained on a computer or on paper. The log should identify the name of the test, the instrument, units, the date the test is performed, the initials of the person performing the test, and the results for each level of control assayed. Optional items for the log include: method and the assay temperature (usually included for enzymes). There should be room to write in actions taken to resolve any situation which is identified as "out-of-control" or unacceptable and a place for documentation of supervisory review.

Once the QC results are entered into the QC log, they should be plotted on the Levey-Jennings chart. When the results are plotted, an assessment can be made about the quality of the run. The technologist/technician performing the test should look for systematic error and random error.

Systematic Error

Systematic error is evidenced by a change in the mean of the control values. The change in the mean may be gradual and demonstrated as a **trend** in control values or it may be abrupt and demonstrated as a **shift** in control values.

Trend

A trend indicates a gradual loss of reliability in the test system. Trends are usually subtle. Causes of trending may include:

- Deterioration of the instrument light source
- Gradual accumulation of debris in sample/reagent tubing
- Gradual accumulation of debris on electrode surfaces
- Aging of reagents
- Gradual deterioration of control materials
- Gradual deterioration of incubation chamber temperature (enzymes only)
- Gradual deterioration of light filter integrity
- Gradual deterioration of calibration

An example of trending on a Levey-Jennings chart is provided in Figure 5.

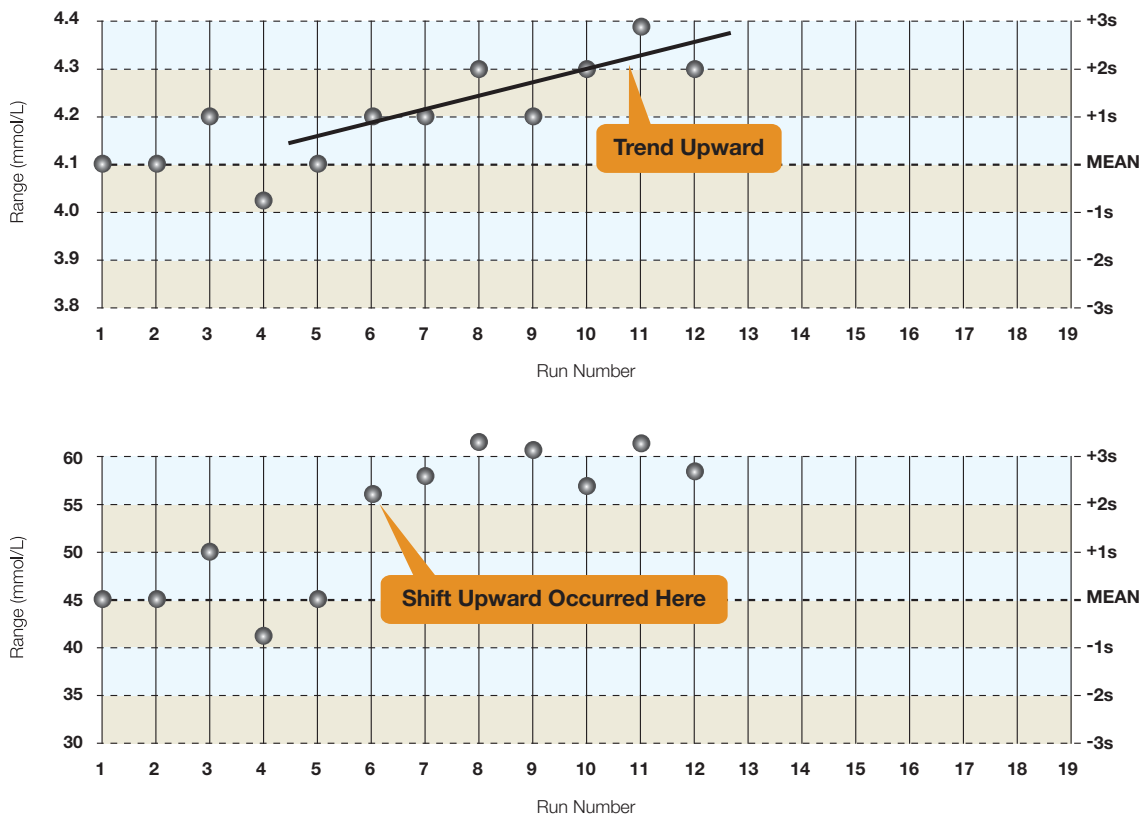
Shift

Abrupt changes in the control mean are defined as shifts. Shifts in QC data represent a sudden and dramatic positive or negative change in test system performance. Shifts may be caused by:

- Sudden failure or change in the light source
- Change in reagent formulation
- Change of reagent lot
- Major instrument maintenance
- Sudden change in incubation temperature (enzymes only)
- Change in room temperature or humidity
- Failure in the sampling system
- Failure in reagent dispense system
- Inaccurate calibration/recalibration

An example of a shift in test system performance is provided in Figure 5.

Figure 5: Trend Upward and Shift Upward



Random Error

Technically, random error is any deviation away from an expected result. For QC results, any positive or negative deviation away from the calculated mean is defined as random error. There is acceptable (or expected) random error as defined and quantified by standard deviation. There is unacceptable (unexpected) random error that is any data point outside the expected population of data (e.g., a data point outside the ±3s limits).

Westgard Rules

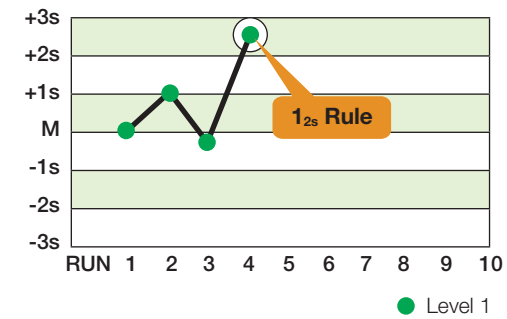
In 1981, Dr. James Westgard of the University of Wisconsin published an article on laboratory quality control that set the basis for evaluating analytical run quality for medical laboratories. The elements of the Westgard system are based on principles of statistical process control used in industry nationwide since the 1950s.[10] There are six basic rules in the Westgard scheme. These rules are used individually or in combination to evaluate the quality of analytical runs.

Westgard devised a shorthand notation for expressing quality control rules. Most of the quality control rules can be expressed as N_L where N represents the number of control observations to be evaluated and L represents the statistical limit for evaluating the control observations. Thus 1_{3s} represents a control rule that is violated when one control observation exceeds the ±3s control limits.

RULE 1_{2s}

This is a warning rule that is violated when a single control observation is outside the ±2s limits. Remember that in the absence of added analytical error, about 4.5% of all quality control results will fall between the 2s and 3s limits. This rule merely warns that random error or systematic error may be present in the test system. The relationship between this value and other control results within the current and previous analytical runs must be examined. If no relationship can be found and no source of error can be identified, it must be assumed that a single control value outside the ±2s limits is an acceptable random error. Patient results can be reported.

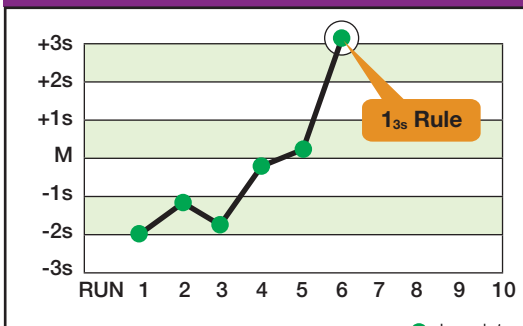
Figure 6: 1_{2s} Rule



RULE 1_{3s}

This rule identifies unacceptable random error or possibly the beginning of a large systematic error. Any QC result outside ±3s violates this rule.

Figure 7: 1_{3s} Rule



10 There are several laboratory QC software packages that use the Westgard scheme. Unity Real Time™ software from Bio-Rad Laboratories is one such package. It not only uses the basic six rules, but unlike other laboratory QC software packages, it also uses additional applications for evaluation of run quality. The Westgard rules can be used manually in concert with Levey-Jennings charts, but manual application is less efficient.

RULE 2_{2s}

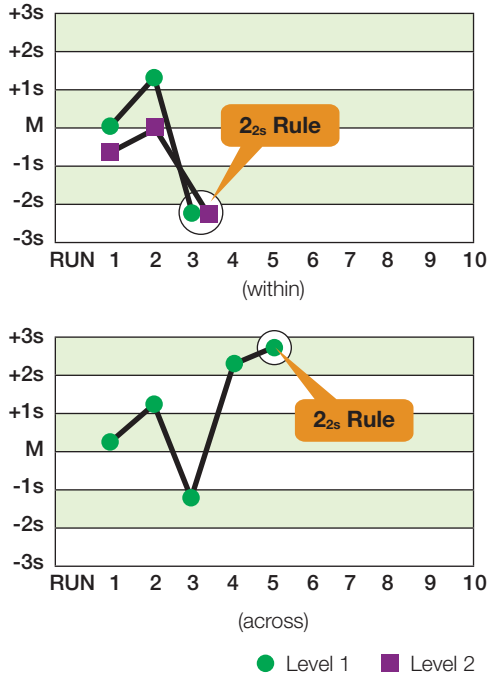
This rule identifies systematic error only. The criteria for violation of this rule are:

- Two consecutive QC results
- Greater than 2s
- On the same side of the mean

There are two applications to this rule: within-run and across runs. The within-run application affects all control results obtained for the current analytical run. For example, if a normal (Level I) and abnormal (Level II) control are assayed in this run and both levels of control are greater than 2s on the same side of the mean, this run violates the within-run application for systematic error. If however, Level I is -1s and Level II is +2.5s (a violation of the 1_{2s} rule), the Level II result from the previous run must be examined. If Level II in the previous run was at +2.0s or greater, then the across run application for systematic error is violated.

Violation of the within-run application indicates that systematic error is present and that it affects potentially the entire analytical curve. Violation of the across run application indicates that only a single portion of the analytical curve is affected by the error.[11]

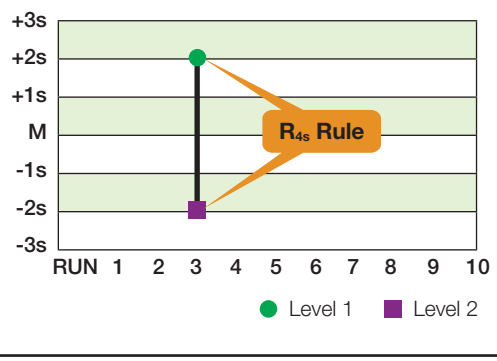
Figure 8: 2_{2s} Rule



RULE R_{4s}

This rule identifies random error only, and is applied only within the current run. If there is at least a 4s difference between control values within a single run, the rule is violated for random error. For example, assume both Level I and Level II have been assayed within the current run. Level I is +2.8s above the mean and Level II is -1.3s below the mean. The total difference between the two control levels is greater than 4s (e.g. [+2.8s – (-1.3s)] = 4.1s).

Figure 9: R_{4s} Rule



11 This rule also applies to trilevel (three level) controls. Whenever any two of the three levels violate the criteria for this rule within the run, unacceptable systematic error may be present and must be resolved.

Violation of any of the following rules does not necessarily require rejection of the analytical run. These violations typically identify smaller systematic error or analytical bias that is not often clinically significant or relevant. Analytical bias may be eliminated by performing calibration or instrument maintenance.

RULE 3_{1s}

The criteria which must be met to violate this rule are:

- Three consecutive results
- Greater than 1s
- On the same side of the mean

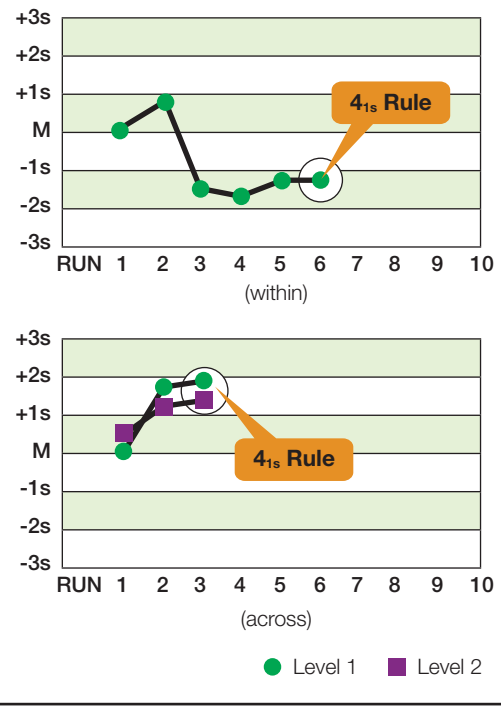
RULE 4_{1s}

The criteria which must be met to violate this rule are:

- Four consecutive results
- Greater than 1s
- On the same side of the mean

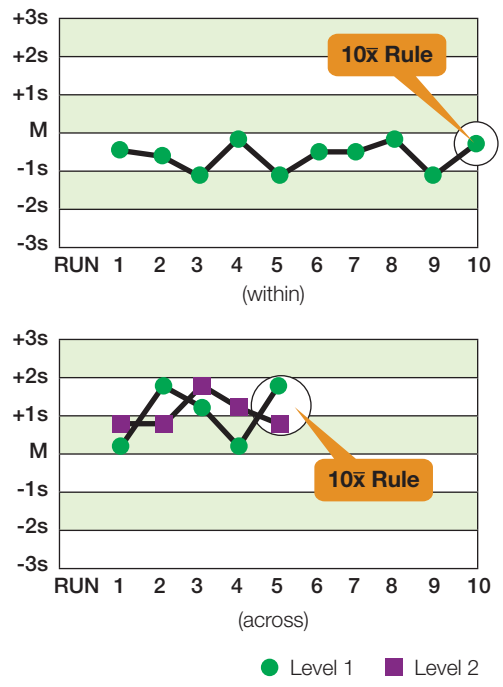
There are two applications to the 3_{1s} and 4_{1s} rule. These are within control material (e.g. all Level I control results) or across control materials (e.g., Level I, II, and III control results in combination). Within control material violations indicate systematic bias in a single area of the method curve while violation of the across control materials application indicates systematic error over a broader concentration.[12]

Figure 10: 4_{1s} Rule



12 Use of 3_{1s} detects smaller analytical bias than 4_{1s} and is said to be more sensitive to analytical bias.

Figure 11: 10$\bar{x}$ Rule



RULES

7$\bar{x}$ | 8$\bar{x}$ | 9$\bar{x}$ | 10$\bar{x}$ | 12$\bar{x}$

These rules are violated when there are:

- 7 or 8, or 9, or 10, or 12 control results
- On the same side of the mean regardless of the specific standard deviation in which they are located.

Each of these rules also has two applications: within control material (e.g., all Level I control results) or across control materials (e.g. Level I, II, and III control results in combination). Within control material violations indicate systematic bias in a single area of the method curve while violation of the across control materials application indicates systematic bias over a broader concentration.[13,14]

[13] The 7$\bar{x}$ control rule is far more sensitive to analytical bias than the 12$\bar{x}$ and the chances of finding seven consecutive control observations on one side of the mean are much higher than finding twelve. It is extremely important that each individual laboratory be aware of highly sensitive rules like 7$\bar{x}$, 8$\bar{x}$ and 9$\bar{x}$ and apply them sparingly, if at all.

[14] When evaluating different laboratory QC software packages be sure that all applications of the Westgard rules are included. Be careful of instrument QC packages. These may be deficient. Some do not check all six of the Westgard rules or perform both within and between run checking. Refer to the instrument manual or ask the manufacturer about control rule applications for specific instrument models.

Self Test #5
Evaluate Levey-Jennings Charts

Study the following Levey-Jennings charts. Evaluate the last run (Run No.12) on each chart. Identify the control rule violated (if any), and the type of error most likely associated with the control rule violation (i.e., systematic or random error).

Charts 1-6: Single Levels of Control **Charts 7-9: Bilevel Controls (two control levels)**

Chart 1

Rule Violated: **Error:**

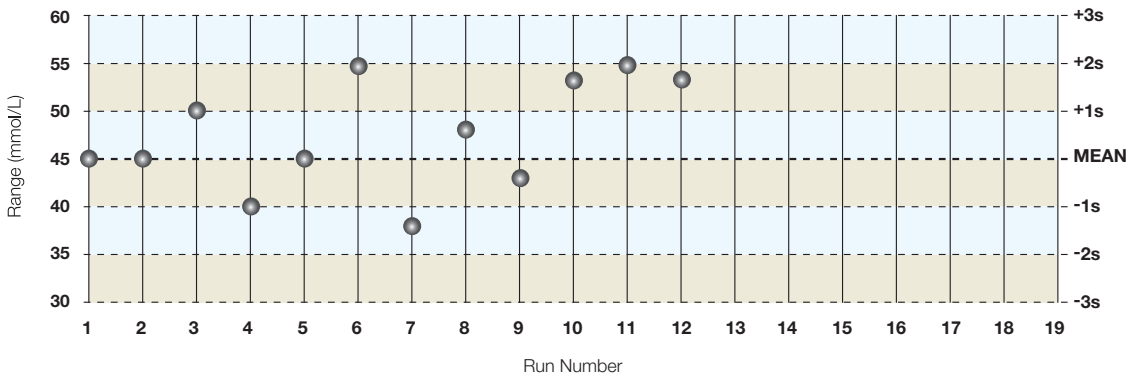
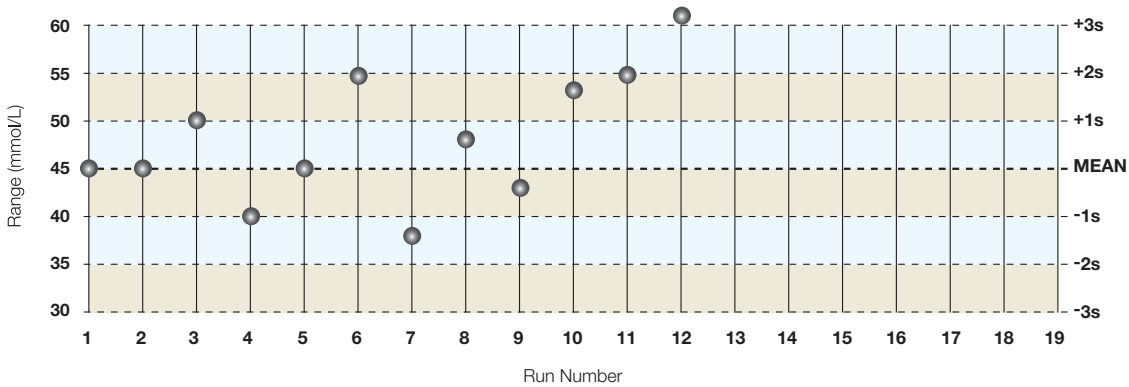


Chart 2

Rule Violated: **Error:**



Answers to Self Test on Page 55

Self Test #5 Continued

Chart 3

Rule Violated: **Error:**

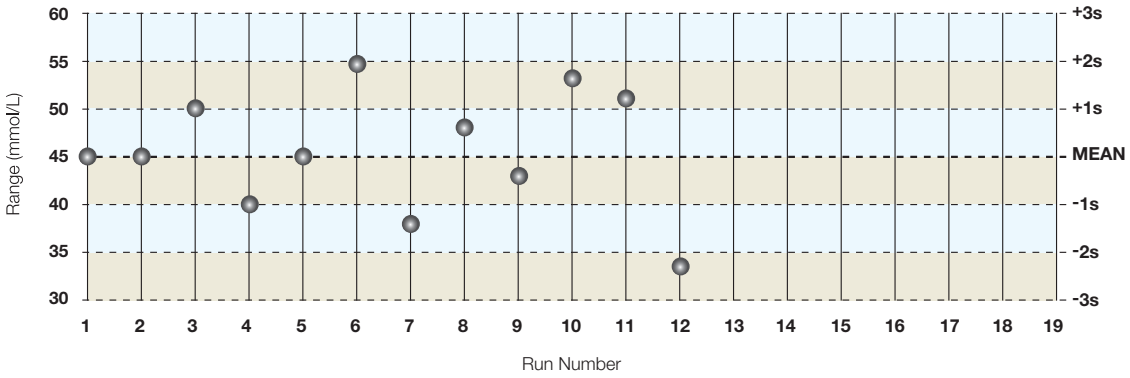


Chart 4

Rule Violated: **Error:**

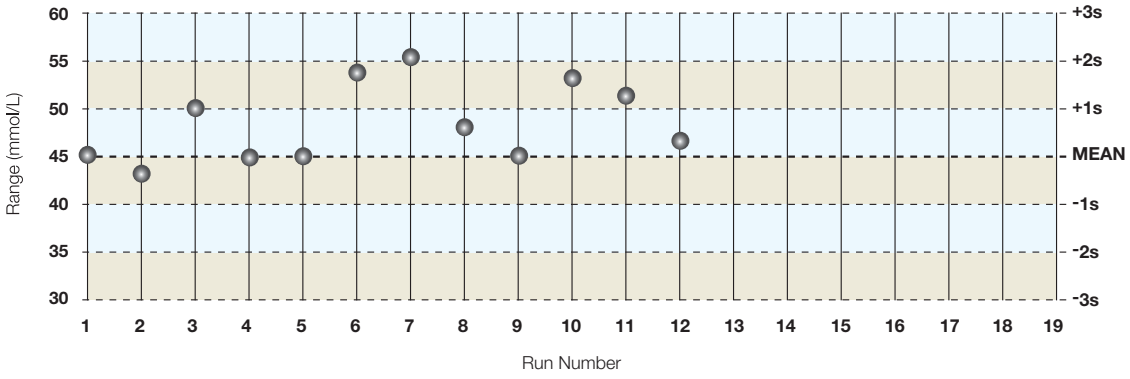
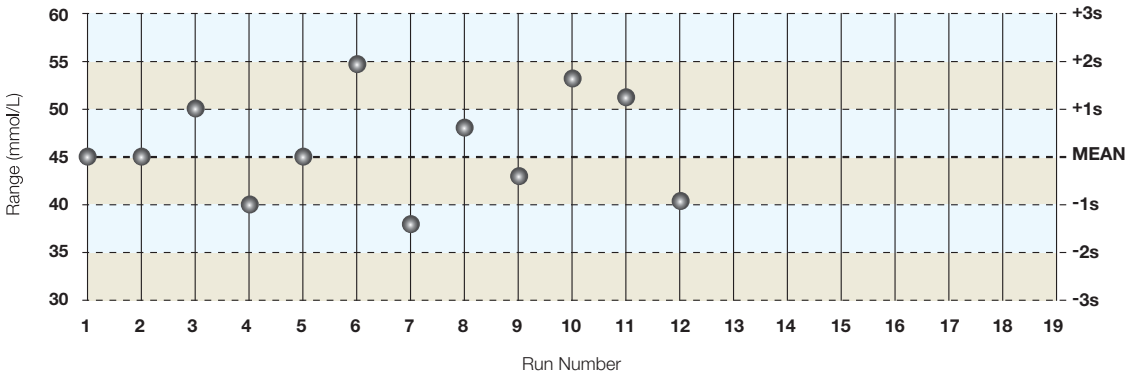


Chart 5

Rule Violated: **Error:**



Self Test #5 Continued

Chart 6

Rule Violated: **Error:**

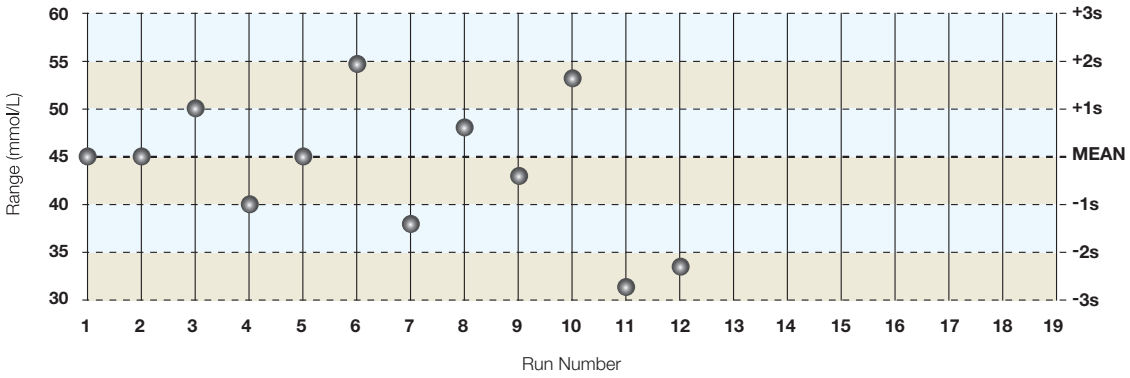


Chart 7

Rule Violated: **Error:**

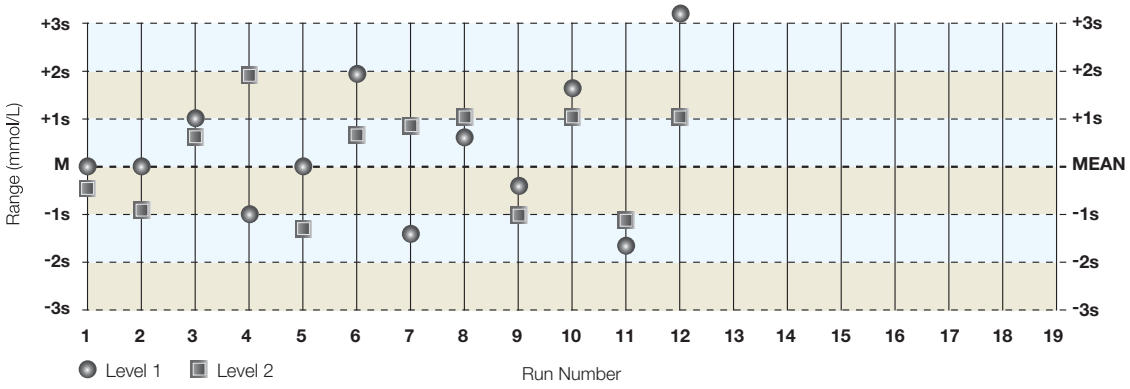
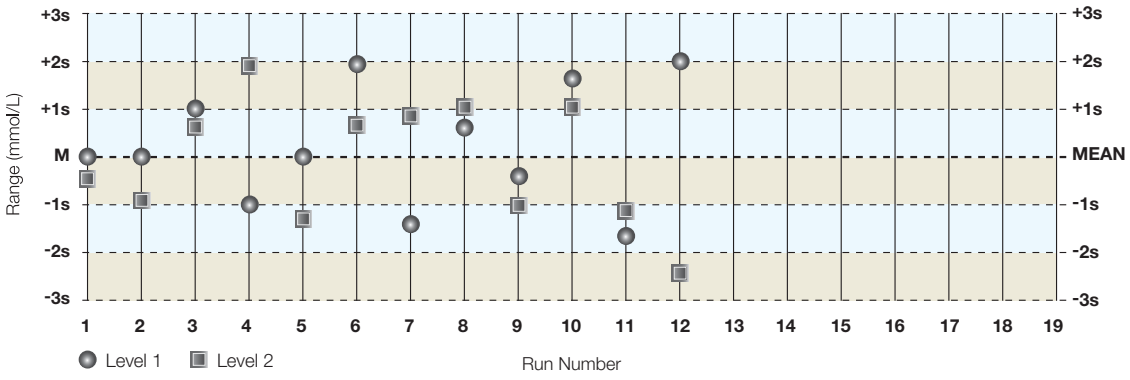


Chart 8

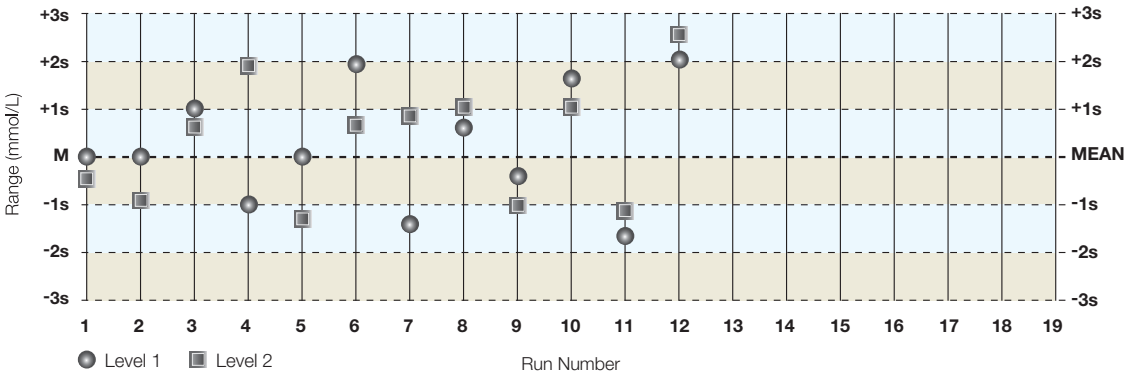
Rule Violated: **Error:**



Self Test #5 Continued

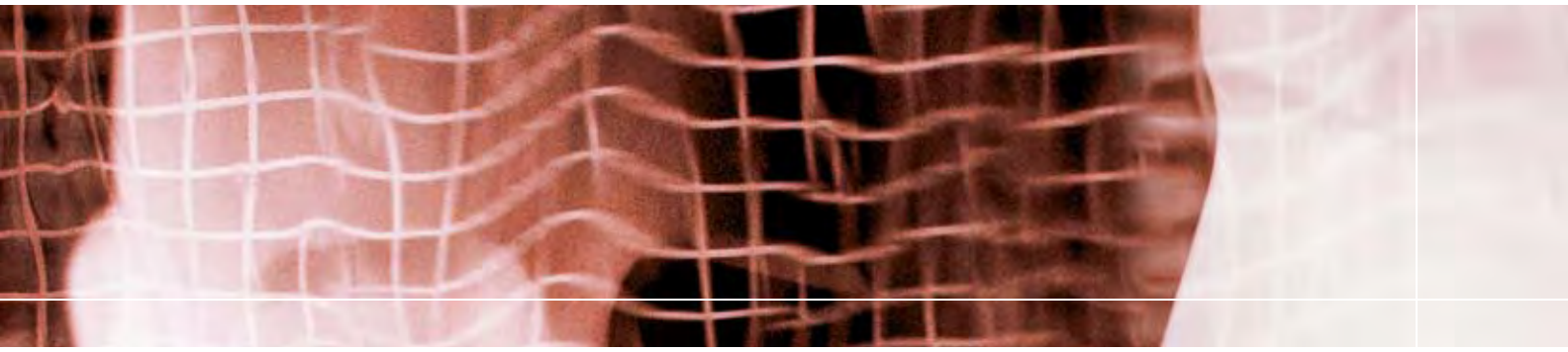
Chart 9

Rule Violated: **Error:**



Answers to Self Test on Page 55

CHAPTER 4



Additional Quality Control Statistics

Coefficient of Variation [CV]

The Coefficient of Variation [CV] is the ratio of the standard deviation to the mean and is expressed as a percentage.

The CV allows the technologist to make easier comparisons of the overall precision. Since standard deviation typically increases as the concentration of the analyte increases, the CV can be regarded as a statistical equalizer. If the technologist/technician is comparing precision for two different methods and uses only standard deviation, he or she can be easily misled. For example, a comparison between hexokinase and glucose oxidase (two methods for assaying glucose) is required. The standard deviation for the hexokinase method is 4.8 and it is 4.0 for glucose oxidase. If the comparison only uses standard deviation, it can be incorrectly assumed that the glucose oxidase method is more precise that the hexokinase method. If, however, a CV is calculated, it might show that both methods are equally precise. Assume the mean for the hexokinase method is 120 and the glucose oxidase mean is 100. The CV then, for both methods, is 4%. They are equally precise.

Formula 4: Calculating the Coefficient of Variation [CV]

$$CV = (s \div \bar{x})\,100$$

Where:

s = standard deviation

$\bar{x}$ = mean

The Coefficient of Variation can also be used when comparing instrument performance. Consider the data in Table 2.

Table 2: Imprecision Differences Due to Instrument or Reagent

	Level I (Normal Control) Chemistry Control Lot No. 12345	Level I (Normal Control) Chemistry Control Lot No. 12345
	Instrument #1 / Reagent #1 ▾ CV	Instrument #2 / Reagent #2 ▾ CV
Calcium	6.1%	5.9%
Phosphorus	5.2%	9.9%
Glucose	4.4%	4.2%

In the example shown in Table 2, Instrument #1 and Instrument #2 have similar precision for calcium and glucose, but Instrument #1 demonstrates much better precision than Instrument #2 for phosphorus. Because the precision was calculated from data for the same lot number and level of control, the differences in precision are likely due to the instrument or reagent.

In Table 3, the difference in performance is probably due to the change from Reagent #1 to Reagent #2. However, it could also be due to lack of regular maintenance or some other cause.

Table 3: Imprecision Differences Due to Instrument or Reagent or Lack of Regular Maintenance

	Level I (Normal Control) Chemistry Control Lot No. 12345	Level I (Normal Control) Chemistry Control Lot No. 12345
	Instrument #1 / Reagent #1 ▾ CV	Instrument #1 / Reagent #2 ▾ CV
Calcium	4.2%	6.8%

The data in Table 4 is for three different kits for testing ß-hCG. Kits #1, #2 and #3 exhibit similar performance in the normal range (mid-range) and at the high end of the method curve. However, Kit #3 has a much higher CV at the low end of the curve. This lack of precision at the low end of the method curve for ß-hCG provides justification to use either Kit #1 or #2, rather than Kit #3 for testing. Imprecision and inaccuracy are most important at the clinical decision levels. For ß-hCG, the clinical decision levels are at low concentrations (corresponding to the early pregnant state in the female and early testicular cancer in the male) or at moderate concentrations (to diagnose the progression of pregnancy).

Table 4: Imprecision Differences Along the Method Curve

	Level I (Low) Immunoassay Control Lot No. 12345	Level II (Normal) Immunoassay Control Lot No. 12345	Level III (High) Immunoassay Control Lot No. 12345
	Test: ß-hCG ▾ CV	Test: ß-hCG ▾ CV	Test: ß-hCG ▾ CV
Kit #1	6.0%	4.5%	12%
Kit #2	5.7%	5.0%	10%
Kit #3	15.0%	4.7%	11%

The previous examples have shown how CV can be used to compare and evaluate instruments or reagents. So, what is an acceptable CV?

There are several sources which may be referenced to determine expected levels of precision. These include:

- Precision information provided in the product insert or instrument manual
- Interlaboratory comparison programs
- Proficiency surveys[15]
- Evaluations of instruments and methods published in professional journals
- CLIA proficiency limits (US)

15 When comparing the Coefficient of Variation always be sure to compare normal levels to normal levels, abnormal highs to abnormal highs, abnormal lows to abnormal lows.

Comparative Evaluations

There are several sources that provide performance expectations to which the laboratory can compare its standard deviation. These include the instrument manual or test method description, proficiency surveys and interlaboratory QC programs.

Instrument Manuals & Test Method Descriptions

Instrument manuals and test method descriptions publish expectations for between-run and within-run precision. These expectations are determined by the manufacturer through repetitive testing and may reflect ideal conditions. If the method description defines a between-run precision of 0.1 mmol/L for potassium, then the laboratory performance in the example meets manufacturer specifications. If however, the between-run specification is 0.05 mmol/L, then the standard deviation calculated for the example indicates that the laboratory is less precise than the manufacturer's expectation. This may indicate a possible problem exists. However, before any final assessment is made, the laboratory should compare its results to proficiency and/or interlaboratory QC reports which are more indicative of "real world" experience.

Proficiency Surveys

Laboratories participating in a proficiency testing program[16] receive a set of "unknown" liquid or lyophilized samples. The samples are assayed by the laboratory for each test performed. Results are obtained and reported to the proficiency agency. The agency collects the data and, using various statistical models, determines what the consensus value of the unknown sample should be for each test. Then, the test result reported by each laboratory is compared to this consensus value and the laboratory is graded for accuracy. The proficiency agency provides a summary report that contains summary data of all the participating laboratories along with an accuracy grading report. The summary report identifies, among other statistics, the standard deviation of all values submitted by participating laboratories for each test. This statistic can be used to compare and assess day-to-day laboratory precision. The same type of information can be obtained from interlaboratory comparison reports supplied by most control manufacturers.

Interlaboratory QC Programs

In an interlaboratory comparison program, laboratories submit monthly data collected for each control product tested. These data are combined with data from other laboratories which use the same instrument.[17] The benefit of an interlaboratory program over a proficiency program is that the interlaboratory program provides statistics collected from repeated daily testing whereas the proficiency program provides statistics collected from single events that occur only 3 times a year in the United States and somewhat more frequently in other countries.

16 Proficiency regulations vary widely from country to country. In the United States, all laboratories performing non-waived testing as defined by CLIA must participate in a proficiency program.

17 A few interlaboratory comparison programs (i.e. Unity™ Interlaboratory Program from Bio-Rad) group data by method.

CLIA Proficiency Limits

There are a number of published performance limits for commonly tested analytes in the United States CLIA regulation. These limits can be accessed on the internet at the following web address.

http://wwwn.cdc.gov/clia/regs/subpart_k.aspx

Self Test #6
Calculating the Coefficient of Variation

Calculate the CV for Laboratory A and Laboratory C data sets in Self Test #2.

Answers to Self Test on Page 55

Coefficient of Variation Ratio [CVR]

Although accuracy of test results is paramount in the clinical laboratory, precision is just as important. One way a laboratory can determine whether the precision of a specific test is acceptable is to compare its precision to that of another laboratory performing the same test on the same instrument using the same reagents (laboratory peer group).

Formula 5: Calculating the Coefficient of Variation Rate [CVR]

$$CVR = \frac{\text{Within Laboratory CV}}{\text{Peer Group CV}}$$

An easy way to make this comparison is to divide the laboratory CV by the laboratory peer group CV obtained from an interlaboratory comparison report.

For example, if the CV for potassium on a particular instrument is 4% and the potassium for all other laboratories using the same instrument is 4.2%, then the coefficient of variation ratio [CVR] is 4/4.2 or 0.95. Any ratio less than 1.0 indicates that precision is better than the peer group. Any score greater than 1.0 indicates that imprecision is larger. Ratios greater than 1.5 indicate a need to investigate the cause of imprecision and any ratio of 2.0 or greater usually indicates need for troubleshooting and corrective action. Something in the test system is causing the increased imprecision and patient test results may not be entirely reliable. Certainly, repeated tests such as glucose for diabetic patients or prothrombin times for patients taking coumadin will not be reliable when the imprecision is high.

Standard Deviation Index [SDI]

The standard deviation index [SDI] is a peer-based estimate of reliability. If the peer group mean is defined as $\bar{x}_{Group}$, the standard deviation is defined as s_{Group} and the laboratory's mean is defined as $\bar{x}_{Lab}$ (See Formula 6).

Formula 6: Calculating the Standard Deviation Index [SDI]

$$SDI = \frac{(\bar{x}_{Lab} - \bar{x}_{Group})}{S_{Group}}$$

The target SDI is 0.0 which indicates a perfect comparison with the peer group. The following guidelines may be used with SDI. A value of:

- 1.25 or less is considered acceptable.
- 1.25 – 1.49 is considered acceptable to marginal performance. Some investigation of the test system may be required.
- 1.5 – 1.99 is considered marginal performance and investigation of the test system is recommended.
- 2.0 or greater is generally considered to be unacceptable performance and remedial action is usually required.

Self Test #7
Calculating the Coefficient of Variation Ratio

Calculate the CVR for Laboratory A and Laboratory C data sets in Self Test #2. Assume that the peer group CV is 2.5% for Level I and 3.0% for Level II.

Answers to Self Test on Page 55

Self Test #8
Calculating the Standard Deviation Index

Calculate the SDI for Laboratory A and Laboratory C data sets in Self Test #2. Provide an evaluation of instrument performance. Assume the peer group mean for the Level I control is 80 U/L and the peer group standard deviation is 13.5 U/L. The peer group mean for the Level 2 control is 350 U/L and the peer group standard deviation is 8.0 U/L.

Answers to Self Test on Page 55

What Do You Want to Learn?

CHAPTER 5

Choosing a Quality Control Product

Selecting a Control Product

Many different quality control products are available for laboratories. Choosing the right quality control product requires careful consideration. Sometimes laboratory decision makers yield to the temptation of purchasing the most inexpensive product. Unfortunately, the cheaper alternative often exhibits significant limitations such as a short shelf life after opening. A reduced shelf life can result in unnecessary waste if the laboratory cannot use all the material. Other products are not sufficiently similar to patient specimens (serum urine, spinal fluid, or plasma). This can cause some problems with certain test systems because these products do not interact with the test system in the same manner as a patient sample.

Some inexpensive quality control products don't have all analytes at medically relevant decision levels. In some cases, laboratory administrators are misled by "box" pricing (This "Box Pricing" topic is described more thoroughly in this chapter).

Shelf Life

When purchasing a quality control product, it is necessary to know the approximate volume of control to be used each day. For example, general chemistry control products are usually sold in 10 mL vials. Laboratories that use 10 mL or more per day, generally are not concerned with stability. But for those laboratories that use a low volume of control (1 mL/day for example), shelf life becomes an important issue.

Your quality control shelf life should match or exceed the laboratory's normal usage rate or money will be wasted. For example, a laboratory that purchases a quality control product that offers only a 5 day stability, when their usage rate would require 10 days to fully use the product, will waste 50% of the product. Consequently, if the laboratory paid $0.18/mL for the product, their actual cost based on usage is $0.36/mL. A better purchase choice would have been a more expensive quality control product ($0.28/mL) that offered a 10 day shelf life stability for all analytes.

Box Pricing

Box pricing is a misleading quoting practice that many laboratories fall into at one time or another. Assume a laboratory is negotiating prices with two vendors for an expensive quality control product. One vendor offers the product at $8.00 per mL or $144 per box, and the other vendor offers the product at $120 per box without quoting a per mL price. The first vendor provides 18 mL for $144, while the second vendor only provides 12 mL for $120. The product cost per mL from the second vendor is equal to $10 per mL, or $2 per mL more than the box quoted at $144.

Always ask for quality control product quotes on a per mL basis and not box price.

Clinical Relevant Decision Levels

This aspect of quality control products is important. It requires the laboratory to compare the relevant clinical levels for each test to those provided in the quality control product. For example, the laboratory objective is to purchase a trilevel (three level) quality control that will allow the lab to "control" (evaluate) the method curve for low TSHs (<3 µIU/mL), normal TSHs (between 3.0 µIU/mL and 10 µIU/mL) and abnormal high TSHs (>10 µIU/mL). The instrument is linear to 50 µIU/mL.

A quality control vendor offers an immunoassay control with three levels:

- Low Level (1.03 – 1.23 µIU/mL)
- Normal Level (7.5 – 9.6 µIU/mL)
- High Abnormal Level (27.9 – 34.5 µIU/mL)

This product meets the laboratory's diagnostic criteria. It contains three distinct levels at the decision limits used by the laboratory and adequately challenges the upper limit of linearity of the instrument.

A second vendor also offers a trilevel product for a reduced price:

- Low Level (3.0 – 5.0 µIU/mL)
- Normal Level (8.0 – 10.0 µIU/mL)
- High Abnormal Level (45 – 55 µIU/mL)

In this case, the cheaper product does not "control" low TSH because the level is higher than the laboratory decision limit. Furthermore, it does not provide adequate control on the high end of the curve because the level for the high control is too near the instrument linearity limit and may often exceed the limit. The price is lower but the product provides less or no value.

CAUTION: It is often impossible to find a perfect quality control product for every instrument, kit or method available. When deciding on a quality control vendor, assess the entire test menu of the instrument or department. For example, the immunoassay instrument used in the laboratory has a test menu that includes about 50 different hormones and therapeutic drugs. One quality control product which may be more expensive provides trilevel diagnostic utility for 45 analytes. A less expensive product may provide true trilevel utility for only 30 of the 50 analytes or 60% of the test menu.

Whenever a test result cannot be adequately verified, the laboratory runs the risk of reporting a result which may be incorrect. Incorrect laboratory results can damage laboratory reputation, but more importantly they may harm patients. Whenever possible, a laboratory should select the quality control product that provides the best trilevel diagnostic utility.

Interlaboratory Comparison Programs

Participation in an Interlaboratory Quality Control Comparison Program is highly recommended. Without such programs the laboratory becomes a statistical island and has no means to regularly verify the reliability of its work. One of the easiest methods to assess reliability and imprecision is to compare the within-laboratory method means and standard deviations to other laboratories using the same instrument and method (peer group).

Over 9,000 laboratories worldwide benefit from their participation in the Unity™ Interlaboratory Program from Bio-Rad. Find out more at www.QCNet.com.

Other Considerations When Choosing a Quality Control

While pricing and the appropriateness of analyte concentrations is important, the quality control product purchase decision should also take into consideration the value of other services provided by the manufacturer.

The quality control purchaser should have the following in mind when evaluating a quality control product. Check each box as it applies to you.

Yes	No	
☐	☐	Does the manufacturer provide an interlaboratory comparison program?
☐	☐	Is the interlaboratory program professionally staffed in order to provide the optimal technical advice or help?
☐	☐	How many laboratories use the program?
☐	☐	What kind of comparative statistical reports are provided and are they easily readable and understandable?
☐	☐	Are comparative reports returned quickly?
☐	☐	Does the manufacturer provide a QC software package?
☐	☐	Can the software package import QC data from instruments or LIS systems?
☐	☐	Does the vendor provide any educational support?
☐	☐	Are the product and services reliable?
☐	☐	Is the vendor ISO certified?
☐	☐	Does the vendor provide a high quality product at a good value?

CHAPTER 6

Final Examination & Evaluation

Final Examination

First Name | Last Name | Position / Title

Laboratory / Company Name | Lab Area / Department

Street Address

City | State | Zip Code

Use the following data set for Questions 1 – 3

{4.23, 4.23, 4.23, 4.23, 4.27, 4.31, 4.36, 4.36, 4.36, 4.40, 4.44, 4.48, 4.48, 4.53, 4.57, 4.57, 4.61, 4.61, 4.66, 4.70, 4.83}

1. What is the mean for the data set?

a. 4.45
b. 4.32
c. 4.41
d. None of the above

2. What is the standard deviation of the data set?

a. .32
b. .28
c. .18
d. None of the above

3. What is the CV for the data set?

a. 3.1%
b. 6.3%
c. 3.6%
d. None of the above

4. What is the SDI for a glucose test that has a mean of 125 mmol/L and a standard deviation of 4.2 mmol/L when the peer group mean is 117 mmol/L and the standard deviation is 4.9 mmol/L?

a. 1.63
b. -1.63
c. 1.90
d. -1.90

5. Based on good laboratory practice, how frequently should quality control materials be tested for any one test?

a. Once each work shift
b. Each day of testing
c. More than once per day if the test is not stable
d. a and b
e. b and c
d. All of the above

Final Examination Continued

6. Which of the following statements is true?

a. Good laboratory practice allows the laboratory to control a test run with a single level of control
b. At minimum two levels of control should be tested daily for each test run in the laboratory
c. Good laboratory practice allows the laboratory to control a test run with a single level of control as long as the laboratory is participating in proficiency testing
d. All of the above

7. When comparing an instrument to its peer group, which statistic provides the most useful information regarding its accuracy?

a. Mean
b. Standard deviation
c. CVR
d. SDI

8. When comparing an instrument to its peer group, which statistic provides the most useful description of overall imprecision?

a. Mean
b. Standard deviation
c. CVR
d. SDI

9. Which of the following Westgard Rules primarily detect systematic error?

a. 1_{2s}
b. 2_{2s}
c. 1_{3s}
d. All of the above

10. Which of the following Westgard Rules primarily detect random error?

a. R_{4s}
b. 2_{2s}
c. 1_{3s}
d. a and c
e. None of the above

Final Examination **Continued**

11. Study the control charts 11a through 11c. Please provide the control rule violated (if any) and the type of error most likely associated with the control rule violation (i.e., systematic or random error) and how the control rules were applied (e.g., across/within control materials, across/within runs) at run number 12.

Chart 11a

Rule Violated: **Error:**

Application:

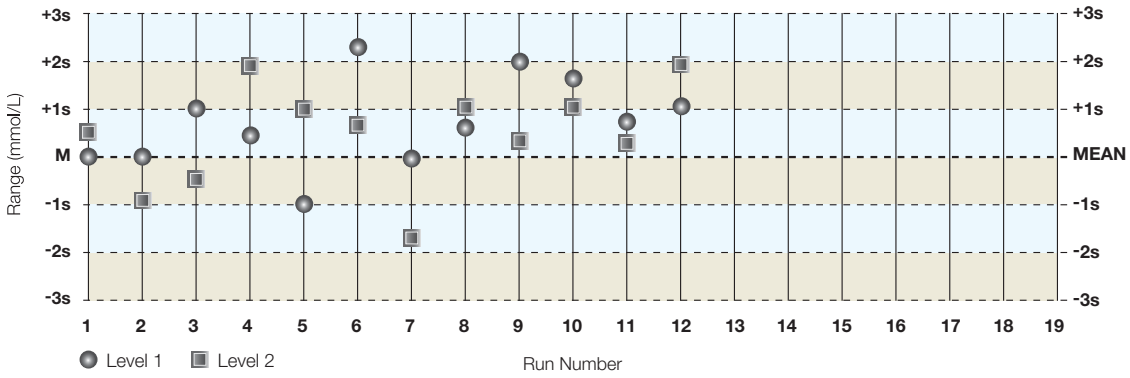
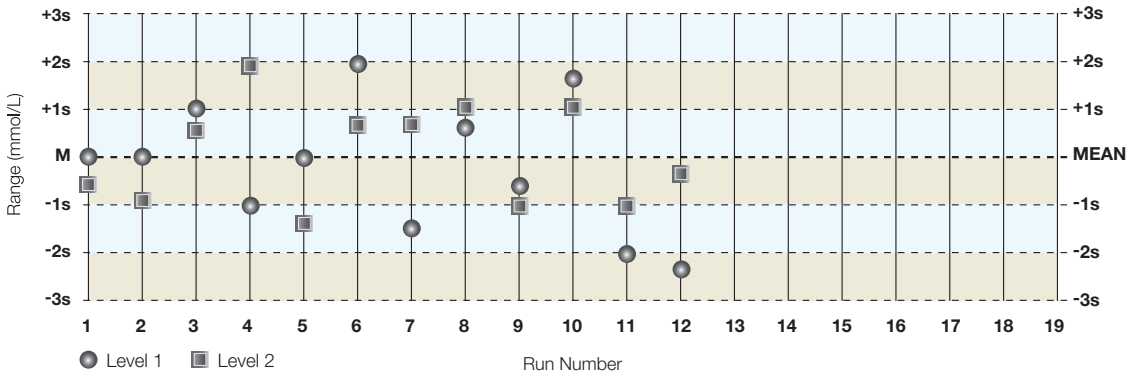


Chart 11b

Rule Violated: **Error:**

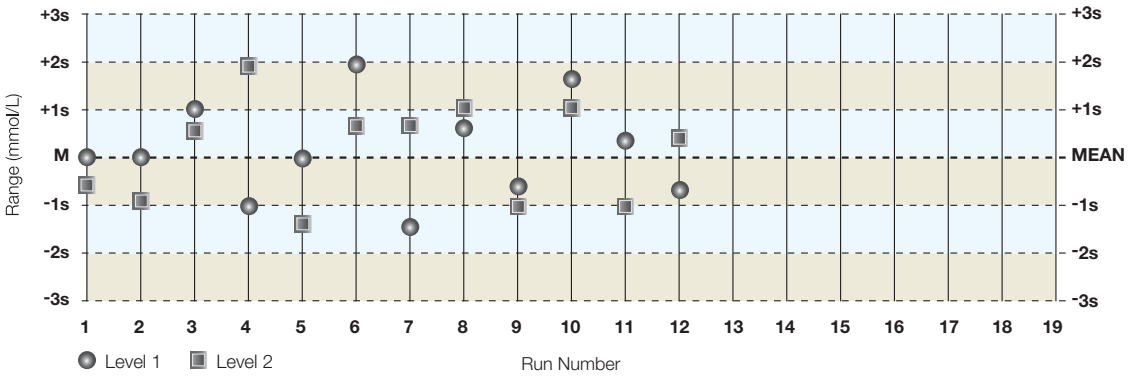
Application:



Final Examination Continued

Chart 11c

Rule Violated:	Error:
Application:	



12. If the light source on an instrument is gradually weakening, it could contribute to what type of error?

a. Random error
b. Systematic error
c. Both a and b
d. None of the above

13. If you change a reagent on the instrument and your control results demonstrate a sudden and consistent increase in value, this phenomena can best be described as:

a. A shift in performance due to systematic error.
b. A trend in performance due to systematic error.
c. A shift in performance due to random error.
d. A trend in performance due to random error.

14. If one of two control values within a single test run is between 2s and 3s on the positive side of the mean, you should:

a. Reject the entire run and repeat the patient samples
b. Suspect that either random or systematic error may be present
c. Accept the run if no error can be detected
d. b and c

15. Two control vendors are trying to sell you a general chemistry control product. One vendor is much cheaper than the other. List four items you should consider carefully before making a decision about which product to buy.

a. _____ **c.** _____

b. _____ **d.** _____

Final Examination **Continued**

Please check your answer as True or False

		True	False
16.	**Performance limits for commonly tested analytes may be found in the CLIA regulation.**	☐	☐
17.	**A box price of $100 for a control product that is configured as 50 x 10 mL is better than a quote for a control product configured as 25 x 5 mL at $42.50 per box.**	☐	☐
18.	**A CVR of 0.8 indicates that laboratory imprecision needs improvement.**	☐	☐
19.	**The CV is a good statistic to use when comparing the performance of different instruments or methods.**	☐	☐
20.	**The R 4s Westgard Rule detects random error only.**	☐	☐

Send your completed final examination to:

Bio-Rad Laboratories
ATTN: Marketing Department
9500 Jeronimo Road
Irvine, CA 92618-2017

Bio-Rad Laboratories is approved as a provider for Category 1 Continuing Education by the PACE Program through the American Society of Clinical Laboratory Science. This basic to intermediate self instructional course is approved for 2.5 contact hours. This course is also approved for California clinical licensees under the PACE California Accrediting Agency License No. 0001.

A certificate of completion will be awarded to anyone who scores 70% or higher.

PACE Program Evaluation

Directions

Please use both sides of this form to evaluate this workbook. Fill in the numbered circle to indicate your ratings of this program's objectives using one response per line, completely erasing errors.

Please send your completed survey to:

Bio-Rad Laboratories
ATTN: Marketing Department
9500 Jeronimo Road
Irvine, CA 92618-2017

Phone: (949) 598-1200
Fax: (949) 598-1550

Program / Workbook Title: Basic Lessons in Quality Control

Program No: 226-201

Date: ____/____/____ (Mo / Day / Yr)

Workbook Rating	Poor				Excellent	No Answer
1. To what extent was the workbook organized and effective?	1	2	3	4	5	N/A
2. To what extent did the workbook clarify and focus on stated objectives?	1	2	3	4	5	N/A
3. To what extent were the graphics and tables applicable and effective?	1	2	3	4	5	N/A

Workbook Content Rating	Poor				Excellent	No Answer
1. To what extent did the workbook content relate to the stated objectives?	1	2	3	4	5	N/A
2. Rate your level of expertise on this subject matter prior to using this workbook.	1	2	3	4	5	N/A
3. Rate the level of contribution this workbook made to your overall knowledge on this subject matter.	1	2	3	4	5	N/A
4. Rate your overall satisfaction with this workbook.	1	2	3	4	5	N/A

Please continue on the next page ▸

PACE Program Evaluation **Continued**

Objectives Rating Rate your level of achievement	Poor				Excellent	No Answer
1. Be able to define, apply the basic elements of quality control and implement a quality control program.	1	2	3	4	5	N/A
2. Be able to define, calculate and apply the following statistics: mean, standard deviation, coefficient of variation, coefficient of variation ratio, and standard deviation index.	1	2	3	4	5	N/A
3. Be able to choose, describe and apply each of the Westgard rules.	1	2	3	4	5	N/A
4. Be able to determine which Westgard rules identify random error and which rules identify systematic error.	1	2	3	4	5	N/A
5. Be able to identify and differentiate shift and trend.	1	2	3	4	5	N/A
6. Be able to identify and differentiate random error and systematic error.	1	2	3	4	5	N/A
7. Be able to construct a Levey-Jennings chart and evaluate graphed data for out-of-control events.	1	2	3	4	5	N/A
8. Be able to assess instruments, reagents and control products using the coefficient of variation.	1	2	3	4	5	N/A
9. Be able to evaluate within lab using the coefficient of variation ratio.	1	2	3	4	5	N/A
10. Be able to evaluate laboratory accuracy using the standard deviation index.	1	2	3	4	5	N/A
11. Be able to choose/recommend control materials based on shelf life, box pricing, clinically relevant decision levels, matrix effects and interlaboratory comparison programs.	1	2	3	4	5	N/A

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Self Test Answers & Solutions

Self Test #1

1. Quality Control is a statistical process used to monitor and evaluate the analytical process.
2. a. Regular testing of quality control products.
   b. Comparison of quality control results to specified statistical limits or ranges.
3. A unit of measure.
4. Good laboratory practice suggests that controls be tested for each analyte at least once each day the test is performed. If the test is unstable or if a change has occurred which could alter test stability, controls should be run more frequently.
5. False

Self Test #2

Laboratory A Level I: $\bar{x}$ = 97.2 U/L
Level II: $\bar{x}$ = 318.2 U/L

Laboratory B Level II: $\bar{x}$ = 181.6 U/L

Laboratory C Level I: $\bar{x}$ = 95.9 U/L
Level II: $\bar{x}$ = 318.7 U/L

Self Test #3

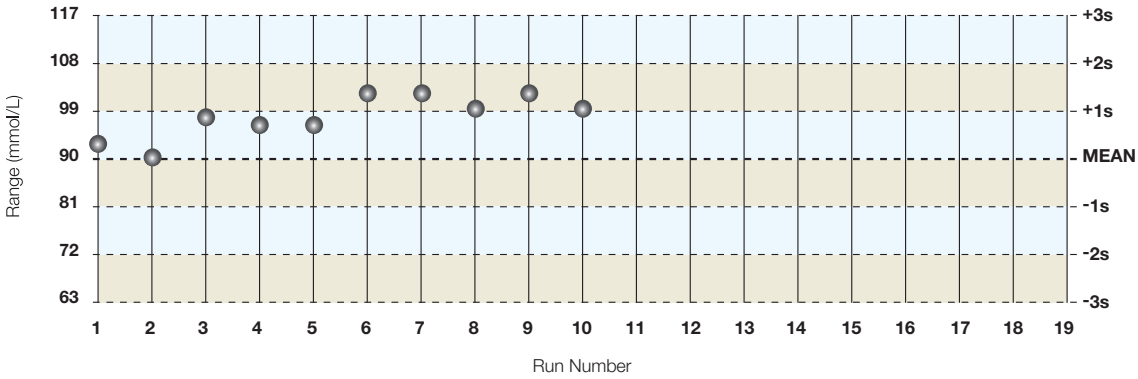
Laboratory A Level I: s = 2.7
Level II: s = 11.57

Laboratory B Level II: s = 1.65

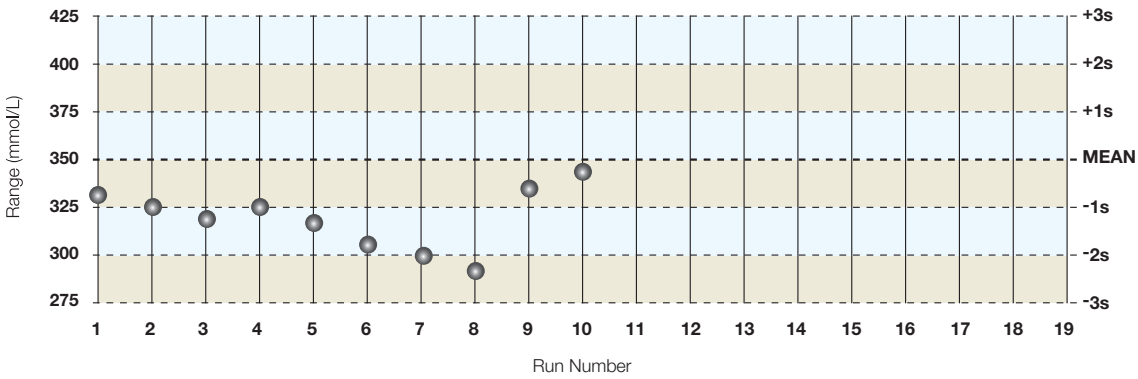
Laboratory C Level I: s = 5.78
Level II: s = 19.63

Self Test #4

Level 1: There are no points outside the ±2s limits.



Level 2: There is one point outside the -2s limits.



Self Test Answers & Solutions

Self Test #5

Chart 1
Rule Violated: 3_{1s}
Error: Systematic Bias

Chart 2
Rule Violated: 1_{3s}
Error: Random or Large Systematic

Chart 3
Rule Violated: 1_{2s} Warning
Error: Warning, None Found

Chart 4
Rule Violated: $10\bar{x}$
Error: Systematic Bias

Chart 5
Rule Violated: None
Error: None

Chart 6
Rule Violated: 2_{2s}
Error: Systematic

Chart 7
Rule Violated: 1_{3s}
Error: Random or Large Systematic
Application: None

Chart 8
Rule Violated: R_{4s}
Error: Random
Application: None

Chart 9
Rule Violated: 2_{2s}
Error: Systematic
Application: Within Run

Self Test #6

Laboratory A Level I: CV = 2.8%
Level II: CV = 3.6%

Laboratory C Level I: CV = 6.0%
Level II: CV = 6.15%

Self Test #7

Laboratory A Level I: CVR = 1.12
Level II: CVR = 1.20

Laboratory C Level I: CVR = 2.4
Level II: CVR = 2.0

Self Test #8

Laboratory A Level I: SDI = +1.3
Acceptable to marginal performance

Level II: SDI = – 4.0
Unacceptable performance, remedial action required

Laboratory C Level I: SDI = 1.18
Acceptable performance

Level II: SDI = – 3.9
Unacceptable performance, remedial action required

Suggested Reading

Bio-Rad Laboratories would like to offer some suggestions for additional reading to help further your knowledge in Quality Control and to assist you in your efforts towards continuous improvement.

1. National Committee for Clinical Laboratory Standards. *Internal Quality Control: Principles and Definitions;* C-24A.
2. Cembrowski, G.S.; Carey, R.N. *Laboratory Quality Management: QC & QA,* ASCP Press (1989).
3. Westgard, J.O.; Barry, P. L.; Hunt M.R.; Groth, T. *A Multi-Rule Shewhart Chart For Quality Control In Clinical Chemistry;* CLIN. CHEM. 27/3 493-501 (1981).
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5. Weisbrot, M.D. *Statistics For The Clinical Laboratory;* J.B. Lippincott Company, Philadelphia (1985).
6. Davies, O.L. Goldsmith, P.L. *Statistical Methods In Research and Production,* New York (1984).
7. Westgard, J.O.; Koch, D.D.; Oryall, J.J.; Quam, E. F.; Feldbruegge, D. H.; Dowd, D. E.; Barry, P.L. *Selection Of Medically Useful Quality Control Procedures For Individual Tests Done In A Multi-Test System;* CLIN. CHEM. 36, 230 (1990).
8. Howanitz, Peter J and Joan H. *Laboratory Quality Assurance,* McGraw-Hill Book Company (1987).
9. Cooper, Greg, and Gillions, Trudy. *Producing Reliable Test Results in the Medical Laboratory* (2007).

List of Tables

List of Figures

List of Formulas

Definition of Terms

A

Abnormal control n.
a control product which contains a physiologically high or low concentration of a particular analyte.

Analyte n.
a substance or constituent for which the laboratory conducts testing.

Analytical method n.
the means by which an analyte is measured.

Analytical process n.
a series of steps taken in the analysis or testing of patient specimens or samples.

Assay* n.
1. a quantitative determination or measurement of the amount, activity, or potency of a constituent; a quantitative assessment of an analyte.
2. Assay, vt., to analyze or measure a sample of a specimen to determine the amount, activity, or potency of a specific analyte or substance.

Assay range n.
the upper and lower limits of the amount, activity, potency of a specific analyte between which measurement is possible.

Average n.
see Mean.

B

Between run precision n.
precision calculated from data collected from separate runs.

Bias n.
the systematic, signed deviation of the test results from the accepted reference value.

C

Coefficient of variation* [CV] n.
1. a measure of relative precision.
2. for a non-negative characteristic, the ratio of the standard deviation to the average.

Coefficient of variation ratio [CVR] n.
1. for purposes of this manual, the ratio obtained by dividing the laboratory monthly coefficient of variation by the peer group monthly coefficient of variation.
2. a peer based estimate of precision.

Concentration* n.
a measure of the amount of dissolved substance per unit of volume.

Constituent n.
1. component of a sample.
2. analyte.

D

Decision level* n.
(clinically relevant decision level)
(decision point/cut-off level) a test value or statistic that marks the upper (or lower) boundary between a negative (normal) or acceptable result and a positive (abnormal) or unacceptable result.

I

Imprecision n.
lack of precision.

In control adj.
indicates that the test system is operating within pre-determined specifications.

Interlaboratory QC program n.
1. a program which accepts laboratory QC data at regular intervals for statistical analysis and comparison to other laboratories.
2. QC program.

ISO n.
1. International Organization for Standardization.
2. an international body of experts that sets general standards of performance.

L

Levey-Jennings Chart n.
a graph that identifies the mean, the working range and other limits for a control sample and shows results of control tests over a period of time.

Lyophilized* adj.
the characteristic describing the result of the process of vacuum-freeze-drying a liquid material to make its components more stable.

M

Matrix n.
for the purposes of this manual, all the components of a control product except the analyte.

Matrix effect n.
the influence of a sample property, other than the analyte, on the measurement, and thereby on the value of the analyte.

Definition of Terms

Mean n.
1. for quality control products, the best estimate of an analyte's true value.
2. the sum of values divided by the number of values[1].

Method n.
see Analytical method.

Method Curve n.
1. a mathematically derived linear or non-linear curve specific to a particular analytical method.
2. used to quantify the measurement of an analyte by comparison to a standard of known concentration.

N

Normal control n.
a control product that contains a physiologically normal concentration of a particular analyte.

O

Open-vial stability n.
the amount of time expressed in hours or days a control product or analyte contained in a control product is considered stable and reliable after the control vial is opened or reconstituted.

Out of control adj.
indicates that the test system is operating outside pre-determined specifications.

P

Peer group n.
1. for the purposes of this manual, a group that uses the same instrument, analytical method, reagent and use the same lot of control.
2. a group that shares the same characteristics.

Precision* n.
the closeness of agreement between independent test results obtained under prescribed conditions.

Proficiency testing/external quality assessment n.
a program in which multiple specimens are periodically sent to members of a group of laboratories for analysis and/or identification; in which each laboratory's results are compared with those of the other laboratories in the group and/or with an assigned value, and reported to the participating laboratory and others[1].

Q

QC Log n.
a written or computerized listing of successive quality control results.

Quality Control Product(s) n.
liquid or freeze-dried materials of human, animal, or chemical origin that are used to monitor the quality and consistency of the analytical process.

Quality Control* n.
1. the operational techniques and activities that are used to fulfill requirements for quality.
2. in healthcare testing, the set of procedures designed to monitor the test method and the results to assure test system performance; Note: QC includes testing control materials, charting the results and analyzing them to identify sources of error, and evaluating and documenting any remedial action taken as a result of this analysis.

R

Random error n.
any random deviation from the laboratory mean.

Range* n.
a measure of dispersion which is the difference between the largest and the smallest observed value of a quantitative characteristic in a given sample.

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

Run[1] n.
1. an interval within which the accuracy and precision of a testing system is expected to be stable but cannot be greater than 24 hours or less than the frequency recommended by the manufacturer.
2. analytical run.

S

Shelf life n.
the amount of time an unopened control product is considered reliable when stored properly.

Shift n.
1. a sudden and eventually stable change in control values and possibly patient values.
2. a type of systematic error.

Standard Deviation [s] n.
1. a statistic which quantifies the dispersion of values within a specified set of values.
2. precision.

Standard Deviation Index [SDI] n.
a peer-based estimate of accuracy.

* Reproduced with permission, CLSI Harmonized Terminology Database (www.CLSI.org)

Definition of Terms

Statistic(s) n.
for the purposes of this manual, a mean, standard deviation, standard deviation index [SDI], coefficient of variation [CV], or coefficient of variation ratio [CVR] calculated from data collected through regular testing of quality control products.

Statistical Limits n.
for the purposes of this manual

1. a defined range of data calculated from quality control data using the mean and standard deviation.
2. used to differentiate an analytical process that is in control from one that is not in control.

Statistical Process n.
a series of steps that results in production of one or more statistics.

Statistical Process Control n.
a set of rules that use statistics to monitor and evaluate a process.

Systematic error n.
a trend or shift away from the laboratory mean.

T

Trend n.
1. a gradual, often subtle, increase or decrease in control values and possibly patient values.
2. a type of systematic error.

W

Westgard Rules n.
a set of 6 statistical rules with multiple applications when used separately or in concert with each other that are used to verify the reliability or lack of reliability for patient test results.

Within run precision n.
precision calculated from data collected from a single run.

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For further information, please contact your local Bio-Rad office or learn more online at www.bio-rad.com/qualitycontrol

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