Concepts in Quality Control Data Management

Bio-Rad Laboratories
Quality System Specialist – Thomasine Newby

Objectives

At the conclusion, the participant should be able to:

- Describe how laboratory quality is achieved
- Identify common causes of random and systematic error
- List the steps used to plan a statistical QC procedure
- Evaluate QC using Westgard rules and graphs

Reference Material Clinical and Laboratory Standards Institute

Statistical Quality Control for Quantitative Measurement Procedures: Principles and Definitions; Approved Guideline – Third Edition (C24-A3, Vol.26 No. 25)

Quality control is one of the most important and least often appreciated activities in the clinical lab.

- Quality control decisions are based on:

Cost

Laboratory Credibility

Patient Care

Errors

- Laboratory quality is achieved through the reporting of accurate patient results by controlling:

Pre-Analytical

Analytical

Post-Analytical

Errors

Pre-Analytical

- Incorrect or incomplete patient instruction & preparation
- Patient sample not properly collected
- Sample taken from wrong patient
- Patient sample not properly preserved

Errors

- Wrong result reported or charted – transcription errors
- Computer error – LIS integrity
- Incorrect interpretation of test results provided to clinician
- Incorrect patient normal ranges
- Results reported from an instrument not used to establish the normal range

Post-Analytical

Errors

Analytical

- Instrument malfunction
- Lack of maintenance
- Inadequate environmental control
- Inadequate electrical supply
- Inadequate water supply
- Inadequate operator training
- Incorrect calibration
- Use of compromised reagents and/or calibrators

QC Strategy

QC Strategy

1. Define QC material
2. Decide the number of measurements and the location of QC
3. Set the control limits
4. Define Error – random/systematic
5. Decide on the QC rules for acceptable run
6. Outline the response to the data acceptance decision (out-of-control)

Select Control Materials

- Menu
- Shelf life/open-vial stability
- Vial to vial variability
- Medical relevant levels
- Challenge range of instrument
- Matrix/preservatives
- QC material different from calibrator material
- Number of levels and concentration
  - Sufficient to determine proper method performance over the measuring range of interest

Frequency and Sequence

- Frequency of QC
  - QC must be analyzed once during a run
  - Run is defined as interval that the method is considered stable
- Sequence of QC
  - QC results evaluated before reported patients
  - Placement immediately after calibration may give false low imprecision and shift during run

Set Control Limits

Parallel Testing vs. Product Inserts

CLIA Regulations

"The stated values of an assayed control material may be used as the target values provided the stated values correspond to the methodology and instrumentation employed by the laboratory and are verified by the laboratory."

CLIA 88, Final Rule
Federal Register, February 2, 1992
Standard 493.1218

CLSI Recommendations

"If assayed controls are used, the values stated on the assay sheets provided by the manufacturer should be used as guides in setting the initial control limits for testing new materials. Actual values for the mean and standard deviation must be established by serial testing in the laboratory. The observed mean should fall within the range published by the manufacturer."

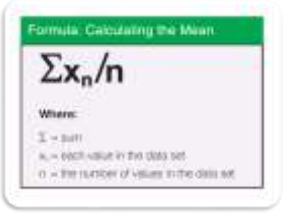
Clinical and Laboratory Standards Institute
C24-A3 Volume 26 Number 25
2006

QC Statistics

- The first step in defining decision limits

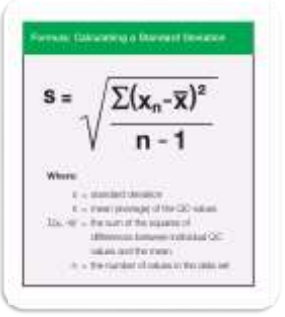
[$\bar{x}$]	[s]	[cv]
Mean	Standard Deviation	Coefficient of Variation

Mean



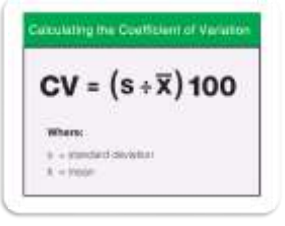
- Arithmetic average of a set of data points
- Sum of values divided by the number of values

Standard Deviation



- A measure of variability of the data points
- The degree of dispersion around the mean

Coefficient of Variation



- Measure of variability
- Expressed as a percent

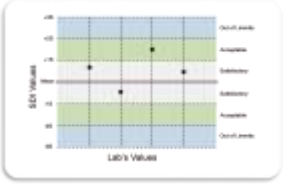
Calculation a Mean/Standard Deviation

- CLSI Recommendations
  - Standard
  - Provisional

Things to Remember When Calculating QC Statistics

- Do I have a sufficient number of data points for the calculation?
- Have I used a sufficient number of analytical runs to account for random variables?
  - Multiple calibrations
  - Multiple reagent lots
  - Maintenance
  - Technologists
  - Environmental conditions
- Did I follow “NORMAL” procedure on each analytical run?
- Have I appropriately excluded outliers?

Standard Deviation Index (SDI)

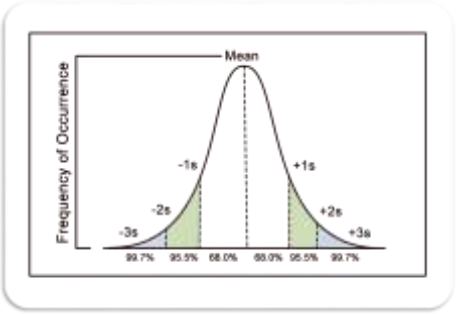


- Target SDI is 0.0, indicating that the lab’s mean value is the same as the peer’s

Coefficient of Variation Ratio (CVR)

- Ideally, CVR ≤ 1.0, since your values are from a single lab
- While the peer CV is from several
- If CVR = 1.5 to 2.0, the lab is 50-100% less precise than its peer group, usually requiring investigation

Arriving at Decision Limits



Types of Analytical Errors

Random

- Precision
- Inherent to the test system
- Always present
- Minimize any increase

Systematic

- Accuracy
- Shifts
- Trends

Set Quality Control Rules

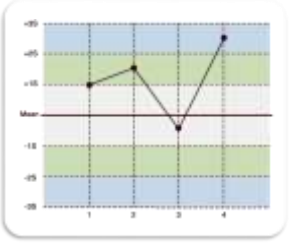
Westgard Rules

Westgard Rules Basics

- Error Detection
  - Random
  - Systematic
- False Rejection
- Multi-rule improves error detection with a low probability of false rejection
- Minimum of 2 controls per run
- Not all rules are necessary for all tests

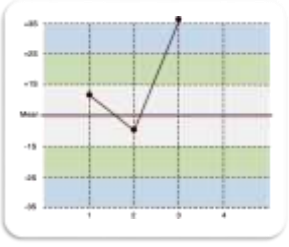
1 - 2s Rule

- Violated when a single control value is outside ±2 standard deviations from the mean
- Usually a warning rule
- Applied in a single run
- Does not usually require run rejection



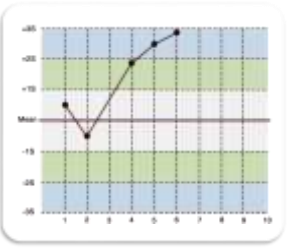
1 - 3s Rule

- Violated when a single control value is outside ±3 standard deviations from the mean
- Detects principally random error, but may indicated the beginning of a large systematic error
- Applied within a single run
- May be cause for run rejection



2- 2s Rule

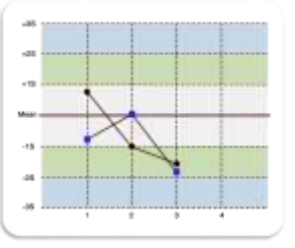
- Violated when two consecutive control values are:
  - Greater than ±2 standard deviations from the mean
  - On the same side of the mean
- Indicates systematic error potentially affecting only a single portion of the analytical curve
- May be cause for run rejection



Across Run

2- 2s Rule

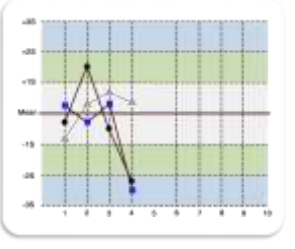
- Violated when two consecutive control values are:
  - Greater than ±2 standard deviations from the mean
  - On the same side of the mean
- Indicates systematic error potentially affecting the entire analytical curve
- May be cause for run rejection



Within Control Material

2 of 3-2s Rule

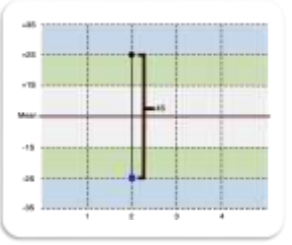
- Violated when any two of all three levels of control in a run are greater than ±2 standard deviations on the same side of the mean



Within Run

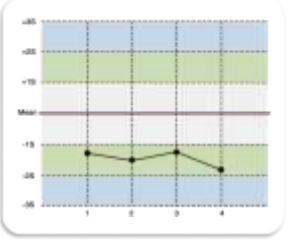
R - 4s Rule

- Violated when there is a 4 standard deviation difference between two control values within the same run
- Indicates random error
- Applied within a single run
- May be cause for run rejection



4 - 1s Rule

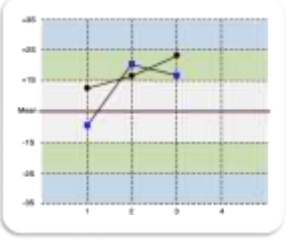
- Violated when 4 consecutive QC values are:
  - Greater than ±1 standard deviation from the mean
  - On the same side of the mean
- Indicates systemic bias in a single area of the method curve
- Usually not clinically significant bias
- Run rejection is not usually required



Within Control Materials

4 - 1s Rule

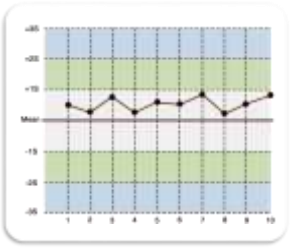
- Violated when 4 consecutive QC values are:
  - Greater than ±1 standard deviation away from the mean
  - On the same side of the mean
- Indicates systematic error over a broader range of concentrations
- Usually not clinically significant bias
- Run rejection is not usually required



Across Control Material

10$\bar{x}$ Rule

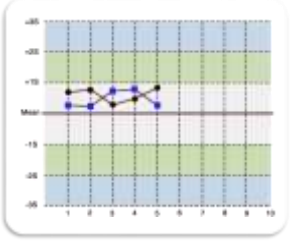
- Violated when 10 consecutive control values within one level are on the same side of the mean
- Indicates systematic error in a single area of the method curve
- Usually not clinically significant bias
- Run rejection is not usually required



Within Control Material

10$\bar{x}$ Rule

- Violated when 10 consecutive control values across levels are on the same side of the mean
- Indicates systematic error over a broader range of concentrations
- Usually not clinically significant bias
- Run rejection is not usually required



Across Control Material

Troubleshooting
Out of Control Situations

Troubleshooting Random Error

- Was there a deviation from procedure?
- Was the correct equipment used?
- Is there potential for random malfunction in the test system?
- Is the test sensitive to technique?
- Is this error a manifestation of pre-analytical error?
- Is the test system vulnerable to electrical power fluctuations?
- Is this truly random error or the initial stages of systematic error?

Sources of Random Error

- Power supply
- Double pipetting of control sample
- Misplacement of control sample within the run
- Air bubbles in water supply
- Random air bubbles in reagent or sample pipette system

Sources of Systematic Error

- Improper alignment of sample or reagent pipettes
- Drift or shift in incubator chamber temperature
- Inappropriate temperature/humidity levels in the testing area
- Change of reagent or calibrator lot
- Deterioration of reagent while in use, storage or shipment

Sources of Systematic Error

- Deterioration of the control product while in use, storage or shipment
- Incorrect handling of the control product (e.g., freezing when not recommended)
- Inappropriate storage of control products in frost-free freezers
- Dirty filter wheel
- Failing light source
- Use of non-reagent grade water in the test system
- Recent calibration
- Change in test operator

Troubleshooting the Control Product

- Is the product being aliquoted and frozen?
- Is the product being properly stored before and after reconstitution?
- Is the reagent being reconstituted with volumetric pipettes?
- Is reagent-grade water used for reconstitution?

Troubleshooting with Graphics

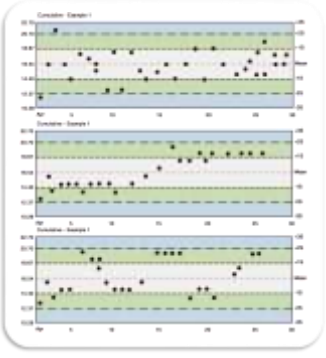
Troubleshooting Using Graphical Techniques

Levey-Jennings Charts

Frequency Histograms

Youden Plots

All 3 charts have same mean, SD, & CV



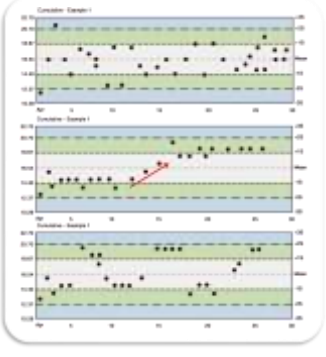
Levey-Jennings Chart

Look For a Pattern

Expected

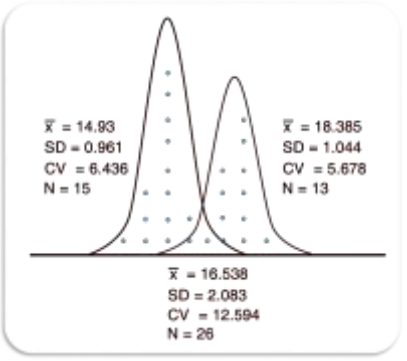
Shift Up

Cyclical



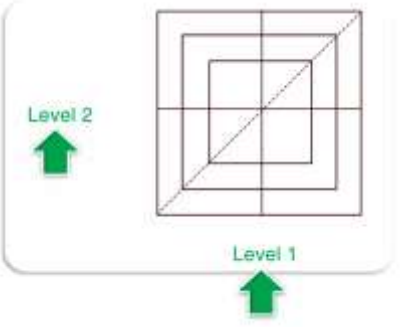
Levey-Jennings Chart

Dual Population



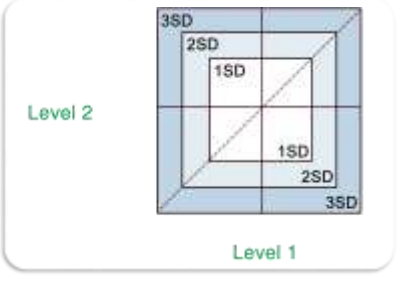
Frequency Histogram

Accuracy and Precision



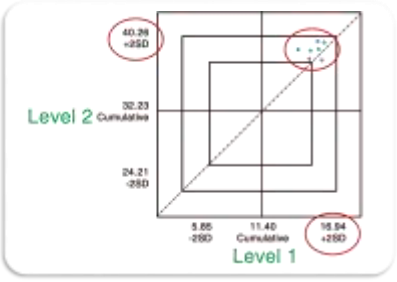
Youden Plot

Accuracy and Precision



Youden Plot

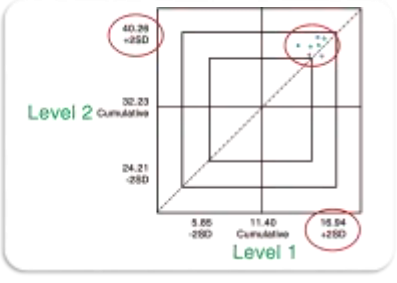
Accuracy and Precision



Youden Plot

- Both levels have positive bias
- If random error, where would points be?

Accuracy and Precision



Youden Plot

- Both levels have positive bias
- If random error, where would points be?

Action Plan for Rule Violations

1. Review last 10 points (both levels)
2. Consult troubleshooting guides
3. Consult procedure manual
4. Evaluate the test system
5. Check maintenance records
6. Correct problem

Good Laboratory Habits

- Check rule violations to determine the type of error
- Relate the type of error to possible causes
- Consider factors in common on multi-test systems
- Relate the problem to recent changes
- Verify the solution and document the remedy
- Perform a regular review of the Quality System to assess effectiveness

Keys to Productive Review of Lab Quality System

- Consider these questions
  - Statistical out-of-control events
  - Frequency of outliers
  - Amount of bias present
  - Are the rules in effect specific to the methodology or technology and TEa?
  - Would more stringent single rule or more multi-rule improve error detection?
  - Should the mean be adjusted?
  - How much imprecision is present?
  - How much bias is present?

Keys to Productive Review of Lab Quality System (Continued)

- Consider these questions
  - Are you using the appropriate peer group to estimate the lab's comparative bias?
  - Are the performance goals for the test, imprecision and bias, set appropriately?
  - How frequently do Westgard errors occur?
  - How frequently is the test recalibrated?

One last Question to Ask Yourself

As you are running QC and find you have something out of control, What changed?

Questions?