Practical Tips to Manage Laboratory QC Data

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Objectives

- Review QC data for shifts and trends
- Critically assess laboratory performance against peers
- Identify the danger of making frequent QC adjustments

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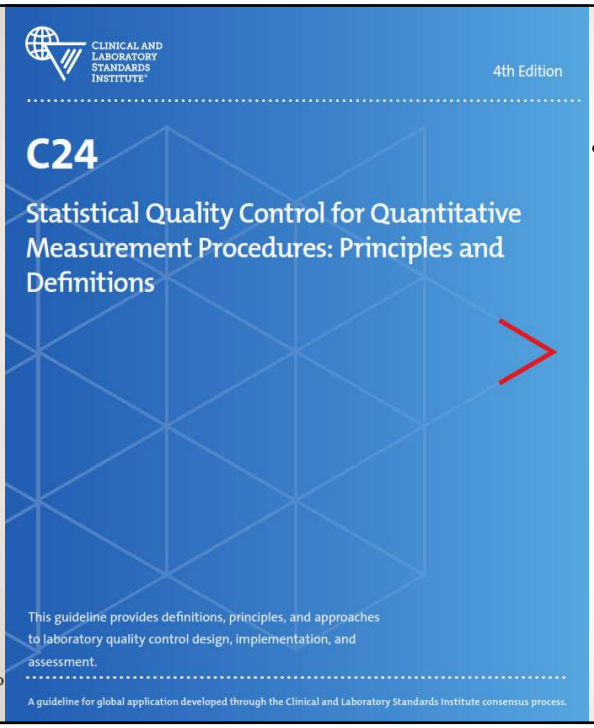

- Revision published 2016 by CLSI

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Definitions

- *Quality assurance* in pathology and laboratory medicine is the practice of assessing performance in all steps of the laboratory testing cycle including pre-analytic, analytic, and post-analytic phases to promote excellent outcomes in medical care.
- *Quality control* (QC) is an integral component of quality assurance and is the aggregate of processes and techniques to detect, reduce, and correct deficiencies in an analytical process.
- *Quality improvement* is the practice of continuously assessing and adjusting performance using statistically and scientifically accepted procedures.

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College of American Pathologists 4

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QC Recommendations

- ISO 15189 – 5.6.2.1 The laboratory shall design internal control systems that verify the attainment of the intended quality of results. Special attention should be paid to elimination of mistakes in the process of handling samples, requests, examinations, reports, etc.
- Documentation should include quality control procedures based on manufacturer instructions for use.
- Internal Quality Control (internal to the laboratory) is defined as a set of procedures undertaken by laboratory staff for the continuous monitoring of operation and the results of measurements in order to decide whether results are reliable enough to be released.
- The regular analysis of QC materials can serve as an essential component of a laboratory's internal control system.

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The Modern Lab is a Factory

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Historical Quality Control

- Born from the 1900's industrial (factory) model of quality in the analytical process
- Periodically inspect product on factory line for quality – does product meet specifications?
- Quality control is a stabilized surrogate sample analyzed like a patient sample containing known amount of measured analyte.
- If the analytical system can achieve the desired result using the QC sample, then the system is stable and quality patient results are being produced.

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Definitions

- Accuracy or "trueness" are descriptions of the extent to which measurements approach the "true value"
  - Bias or difference is a parameter of accuracy
- Precision = reproducibility, the values obtained on repetitive measurement
  - Standard deviation is a parameter of precision

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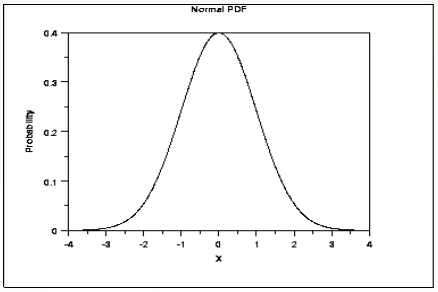
Gaussian Distribution Curve



± 1 SD = 68.3% data

± 2 SD = 95.5% data

± 3 SD = 99.7 % data

± 4 SD = 99.9% data

QC ranges set to +/- 2SD

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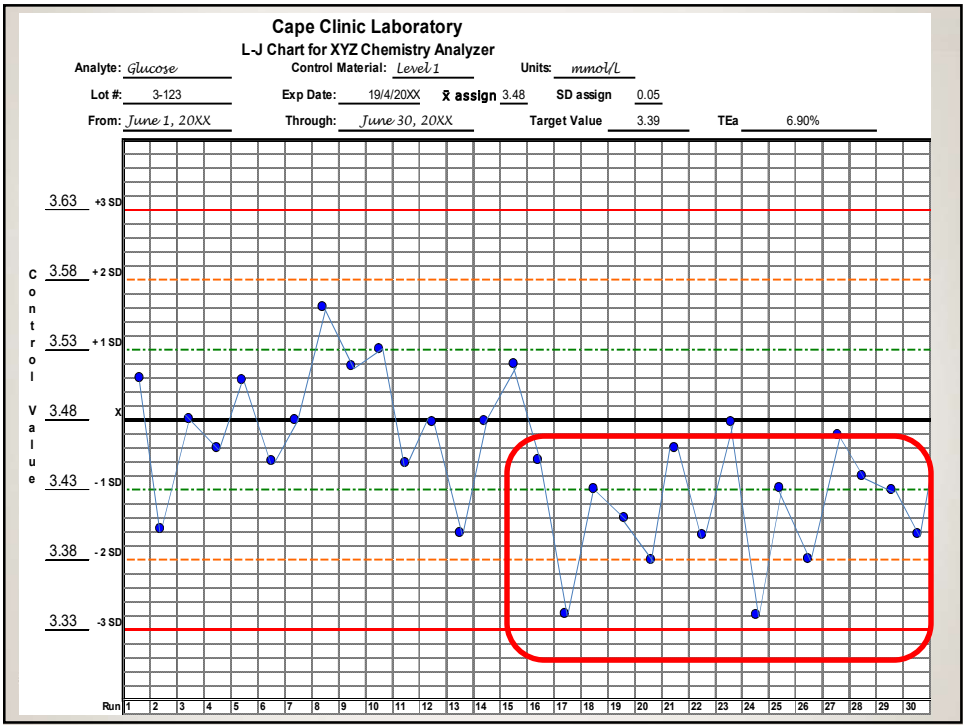

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Traditional QC Multi-rules

- Historically, QC practices are based on test performance, by setting the mean +/- 2SD as the QC target range and utilizing one or more rules:

1_{2S} - 1 point outside 2 SD - warning only

1_{3S} - 1 point outside 3 SD (inaccuracy/imprecision)

2_{2S} - 2 consecutive points outside 2 SD on the same side of the centre line (bias)

R_{4S} - Range of 2 points greater than 4 SD (imprecision)

4_{1S} - 4 consecutive points exceeding 1 SD on the same side of centre line (bias)

10_{X} - 10 consecutive points above or below the mean (bias)

- The selection of rules will depend on the Quality goal desired and the level of method performance

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Quality Control

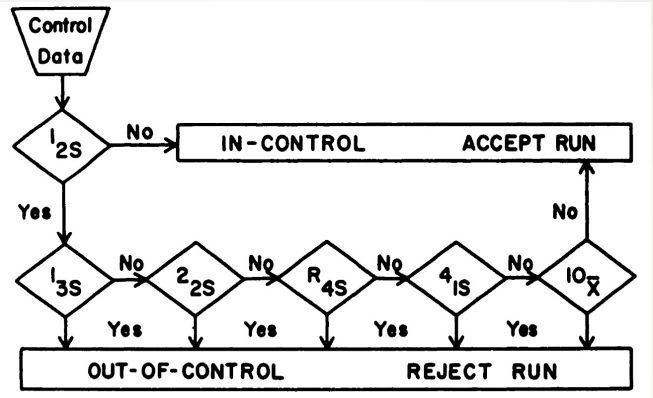

Fig. 1. Logic diagram for applying a series of decision criteria (control rules) in the multi-rule Shewhart procedure

Westgard JO, Berry PL, Hunt MR, Groth T. A Multi-Rule Shewart Chart for Quality Control in Clinical Chemistry. Clin Chem 1981;27;493-501.

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Quality Control Review

- Continuous/daily review – Bench tech at the time of analysis
  - Verify QC is recorded in Bio-Rad Unity program (check all tests/QC levels)
  - Stop patient testing
  - Troubleshoot any failed QC, **document** corrective actions
  - Perform patient look-back (to prior acceptable QC) if necessary
  - Check for ongoing shifts/trends in QC data
- Weekly/monthly review – Lead techs and manager
  - QC failures, investigation, and patient look-backs are documented
  - Assay bias, precision, trends/shifts are addressed and compared to peers
- Monthly review – Medical director
  - Review QC charts, corrective action documented for QC failures
  - Assess QC performance against peers and adjust QC ranges as needed

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QC Troubleshooting Table

In the event of a failed QC run, begin troubleshooting as follows.
Document the steps taken on the Instrument QC Log

1	Repeat all QC levels with fresh QC material ↓ QC out	QC within limit →	STOP
2	Check QC on a fresh reagent pack (same lot number) ↓ QC out	QC within limit →	STOP
3	Check calibration – verify that you're not at the end or that this is part of a post calibration shift trend. ↓ QC out	QC within limit →	STOP
4	Re-calibrate same reagent and calibrator lot ↓ QC out	QC within limit →	STOP
5	New calibrators & re-calibrate ↓ QC out	QC within limit →	STOP
6	Check reagent lots—try new lot ↓ QC out	QC within limit →	STOP
7	Instrument troubleshooting/Maintenance ↓ QC out	QC within limit →	STOP
8	HOTLINE		

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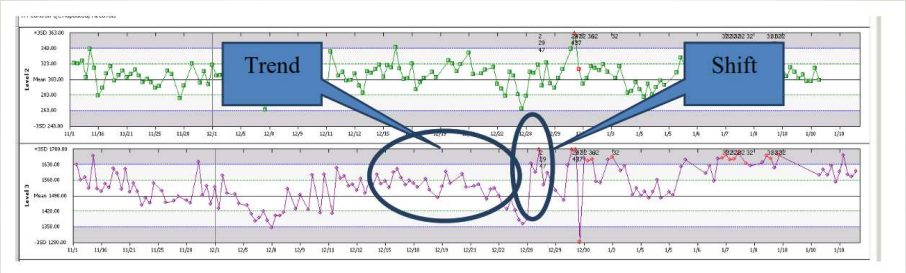
Troubleshooting Out of Control QC



- Out of control QC detects unstable performance – possibility for erroneous patient results
- First step - STOP PATIENT TESTING!
- Trends occur gradually over time – reagent or control degradation
- Shifts occur suddenly – calibration or reagent lot change

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Impact on Laboratory Quality

- Many factors can cause errors in test results
  - Reagent degradation – exposure to temperature, light, humidity
  - Calibrator and control storage
  - Instrumentation –maintenance frequency, part failure, drift
  - Personnel – incorrect operation, calibration, inadvertent mistakes

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Laboratory Errors

- Systematic Errors lead to bias from one point forward for a period of time. (problem with calibration, standards, reagents, blanks, controls)
- Random Errors occur with a single sample and are not persistent (clot, bubbles, drugs, hemolysis)
- Easier to detect systematic than random errors when using QC solutions (ie persistent errors)

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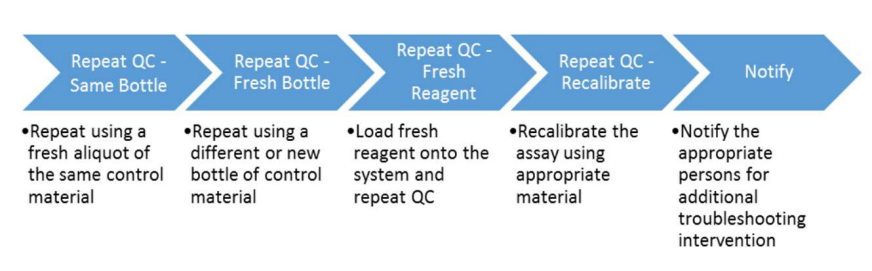
Corrective Actions for Unacceptable QC



- Methodically address key sources of analytical performance – QC, reagent, calibration, then analyzer breakdown or operator error, one at a time
- Once source discovered and issue resolved, must go back, since last successful QC and reanalyze specimens (patient look-back), correcting results if needed

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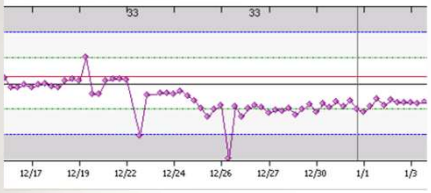
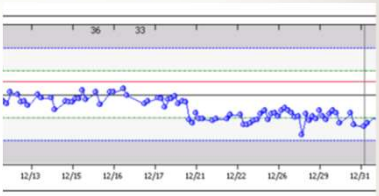
QC Review – Shifts and Trends

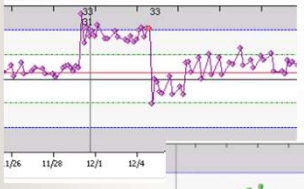
Shift in a single level of QC

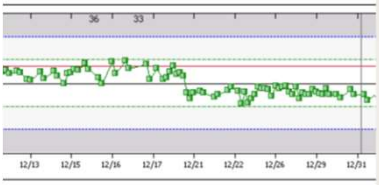


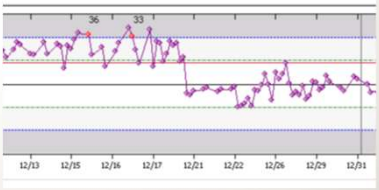
Shift in all 3 levels of QC



Step Behavior







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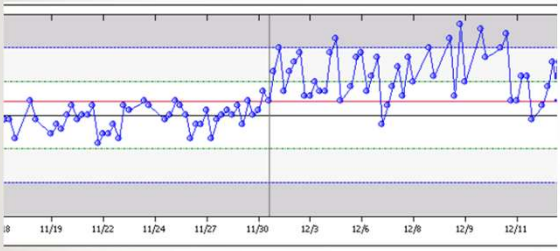
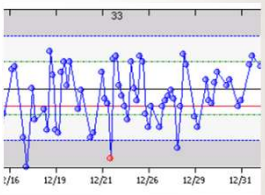
QC Review – Change in Precision

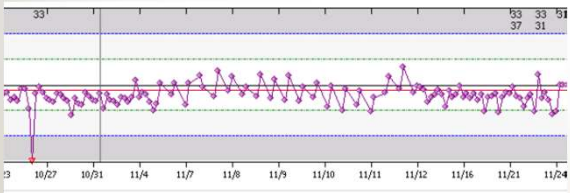
Abrupt change in precision



Generally poor precision



Seesaw pattern



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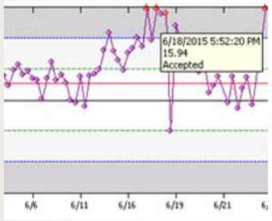
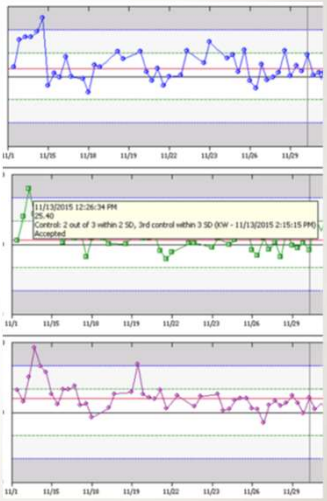
QC Review – Inappropriate Comments

Accepted a 1-2s as warning, but follows a 1-3s failure – should be fail not a warning



Level 2 QC, 1-2s warning, next QC level 3 also 1-2s, accepted, should have failed as 2-2s



Frequent 1-2s warnings with no action taken

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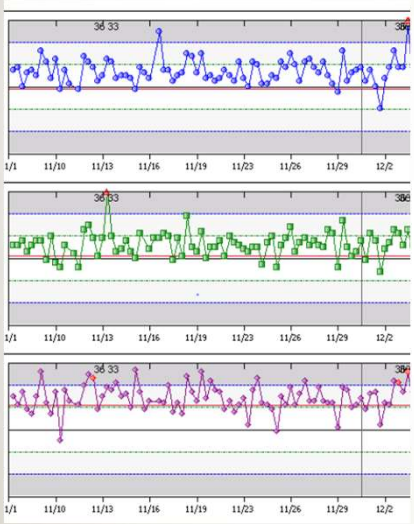
QC Review – Bias



Bias to mean – all 3 levels of QC

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Patient Look-Back

- Retest patients back to previous successful QC
- Start every 10th patient to locate problem, then test every sample to determine if clinically significant change
- Required when "chemistry" of analyzer changed as part of troubleshooting
  - Assay recalibrated as part of troubleshooting
  - Reagent changes as part of troubleshooting
  - Maintenance or other analyzer adjustments made
  - Whenever last group of patients not bracketed by successful QC
- May require clinical correlation and result correction or comment as "Results in question; clinical review recommended"
- If samples not available - Clinical contact as – "In reviewing the quality control parameters associated with the tests below, the laboratory has discovered a performance failure that calls these results into question. The results have been commented as questionable in the patient record and the patient's account credited. Specimens are not available for retesting. We recommend that the clinical impact of this result be reassessed."

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Quality Control

- Part of a quality management system focused on fulfilling the quality requirements
- Quality requirements specify the characteristics necessary for a product or service to be fit for its intended use, for laboratory measurements, the total allowable error (TEa) . If the measurement error in a patient result exceeds the TEa, the result fails to meet its quality requirement.
- QC of the testing process ensures that analytical variability meets the accuracy and precision requirements established for that test, appropriate for patient care.

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Total Allowable Error versus Total Analytical Error

- Total allowable error TEa > Total analytical error TAE
  (medical usefulness) (method)
- Medical usefulness (TEa) requirement must be greater than analytical error (TAE)
- TAE = bias (%) + 2.0 CV (analytical performance)
- TEa or ATE (allowable total error) is determined from medical decision points/biologic variability

Note TAE first publication used 1.65 CV, 2.0 CV is close approximation, but push to move to 4.0 CV, 5.0 CV and even 6.0 CV with six sigma

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Biological Variability and TEa

	Analyte	Number of papers	Biological Variation		Desirable specification		
			CVw	CVg	I(%)	B(%)	TE(%)
S-	Albumin	24	3.2	4.75	1.6	1.43	4.07
U-	Albumin, concentration, first morning	3	36.0	55.0	18.0	16.4	46.1
U-	Albumin, output, night urine	3	29.5	58.0	14.8	16.3	40.6
S-	Albumin, glycated	3	5.2	10.3	2.6	2.9	7.2
S-	Aldosterone	2	29.4	40.1	14.7	12.4	36.7
U-	Aldosterone	1	39.4	40.1	19.7	14.05	46.56
S-	Alkaline phosphatase	22	6.45	26.1	3.23	6.72	12.04
S-	Alkaline phosphatase, bone	4	6.2	37.4	3.1	9.5	14.6
S-	Alkaline phosphatase, liver	1	10.0	27.0	5.0	7.2	15.4
S-	Alkaline phosphatase, placental	1	19.1	---	9.6	---	---
U-	Ammonia, output, 24h	1	24.7	27.3	12.4	9.2	29.6
S-	Amyloid A	1	25.0	61.0	12.5	16.5	37.1

Note on abbreviations:
CVw = within-subject biologic variation
CVg = between-subject biologic variation
I = desirable specification for imprecision
B = desirable specification for inaccuracy
TE = desirable specification for allowable total error

This most recent and extensive listing of biologic goals has been provided by Ricos C, Alvarez V, Cava F, Garcia-Lario JV, Hernandez A, Jimenez CV, Minchinela J, Perich C, Simon M. "Current databases on biologic variation: pros, cons and progress." Scand J Clin Lab Invest 1999;59:491-500. *This database was most recently updated in 2014.*

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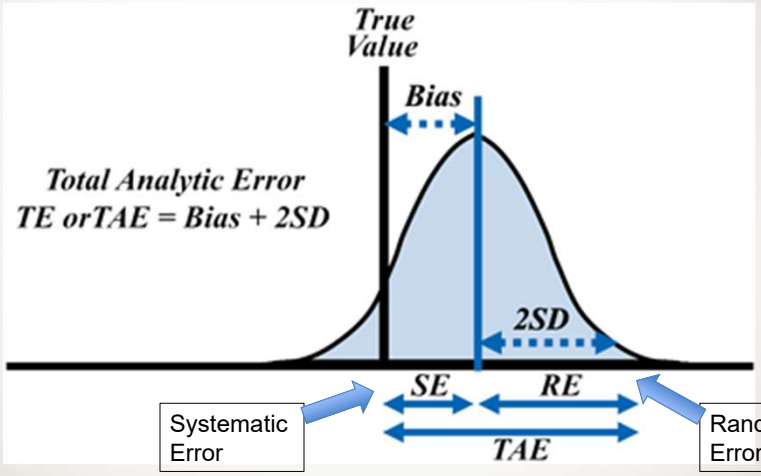
Total Analytical Error



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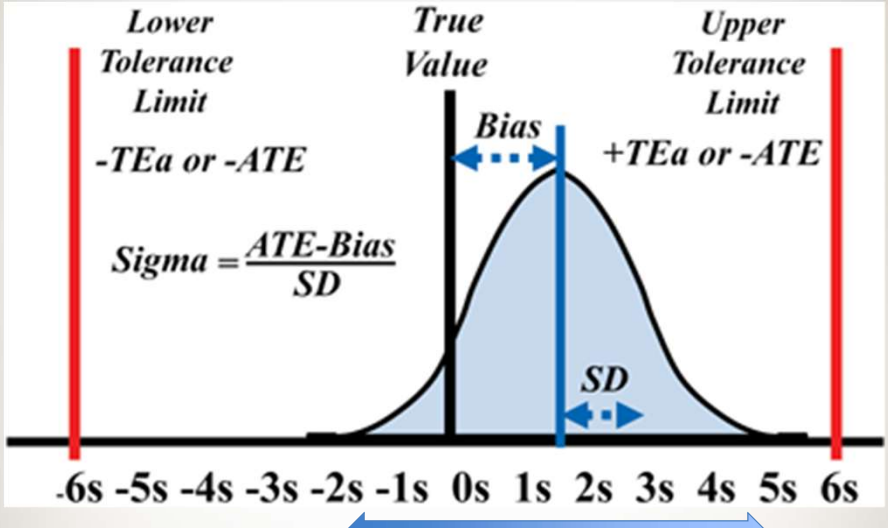

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QC Ranges

- Quality control ranges should be based on observed instrument variability rather than manufacturer recommendations (too wide)
- Glucose normal control in manufacturer package insert.
  (target value = 50–150 mg/dL or 2,78–8,33 mmol/L)
- Analyzer has 1.5% CV (imprecision)
  - TAE (total analytical error) = bias + 2 CV
  - TAE = 0% + 2 (1.5%) = +/- 3% (assuming no bias)
- If mean of QC run over several days= 100 mg/dL (5,5 mmol/L)
  - 100 +/- 3% = 97 – 103 mg/dL QC Range (mean +/- 2SD)
  - (5,5 +/- 0.17 = 5,33 – 5,67 mmol/L)
- Biologic variability TEa for glucose
  - 100 mg/dL (5,5 mmol/L) = 7%.
- Analyzer TAE (3%) is < total allowable error TEa (7%)
  - QC ranges set to detect errors within the medical allowable limits

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Quality Control Commutability

- QC materials contain stabilizers and preservatives to extend shelf life
- Alters the matrix of the QC sample
- Behaves differently on different analyzers, so results may not match between manufacturers
- CLSI recommends analyzing new QC lots, once a day for 10 days (min 10 data points)
  - However, CLSI EP05 notes that 20 days may be required to estimate all contributions from periodic and occasional sources of variability that contribute to a measurement procedure's long-term performance

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Sources of QC Shifts

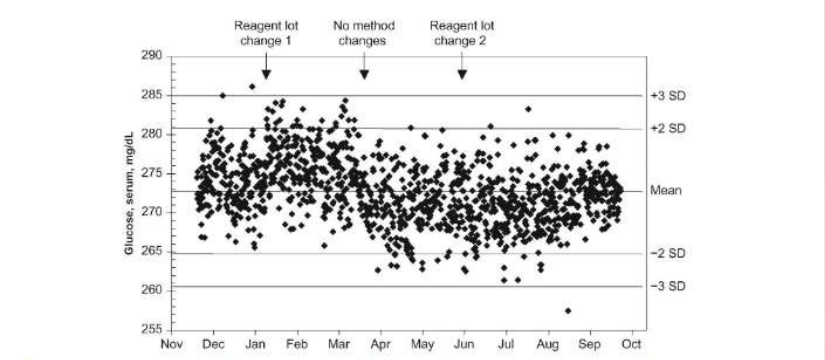

Figure 5-2 Levey–Jennings plot of QC results (n = 1,232) for a single lot of QC material used for a 10-month period. The mean and SD are cumulative values from all data.

- QC supply should last long enough to judge method stability over multiple calibrations, reagent lot changes, environment, maintenance and any other factor that could impact QC.

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QC Range Adjustment Case

- *Medical director took over laboratory where Lead tech during monthly review would update all chemistry QC means to previous month averages from Bio-Rad Unity*
- Frequent range adjustments are **bad practice**!
- Defeats the purpose of analyzing QC
- Laboratory wants to establish a historical performance over several months, calibrations reagent changes to detect performance issues like shifts and biases that affect patient results

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- New homocysteine QC lot
- Need to set new ranges
- Package insert ranges are
  +/- 30% @ 7.56
  +/- 27% @ 13.66
  +/- 29% @ 27.15
- Lab analyzes an aliquot of QC once a day for next 20 days - long enough to estimate operator, instrument, calibration and environmental variability

ARCHITECT
Homocysteine Controls

Read Highlighted Changes: Revised October 2014.

INTENDED USE

The ARCHITECT Homocysteine Controls are for the estimation of test precision and the detection of systematic analytical deviations of the ARCHITECT iSystem (reagents, calibrators and instrument), when used for the quantitative determination of total L-homocysteine in human serum or plasma.

Refer to the ARCHITECT Homocysteine reagent package insert and the ARCHITECT System Operations Manual for additional information.

CONTENTS

3 Bottles (7.7 mL each) of ARCHITECT Homocysteine Controls contain L-homocysteine in processed human serum and phosphate buffer.

Preservative: sodium azide.

The controls yield the following homocysteine concentrations (µmol/L):

Bottle	Homocysteine Concentration (µmol/L)	Range (µmol/L)
CONTROL L	7.56	5.36 - 9.76
CONTROL M	13.66	9.97 - 17.35
CONTROL H	27.15	19.26 - 35.04

Each laboratory should establish its own concentration ranges for new control lots at each control level. This can be accomplished by assaying a minimum of 20 replicates over several (3-5) days. Sources of variation that can be expected should be included in this study in order to be representative of future system performance. These may include:

- Multiple stored calibrations
- Multiple reagent lots
- Multiple calibrator lots
- Multiple processing modules
- Data points collected at different times of the day

These results should be applied to your laboratory's quality control practices.

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Start Date: 08.17.2017 End Date: 09.16.2017

Control Name: HOMOCYST Module: 1

Control Lot Number: 802911530 Module Serial Number: iSR51335

Assay	Level	N	Actual Mean	SD	%CV
Total HCY2	Level 1	80	7.17462	0.53356	7.43679
Total HCY2	Level 2	81	13.13210	0.78258	5.95926
Total HCY2	Level 3	81	26.12728	1.38373	5.29613

Current QC:

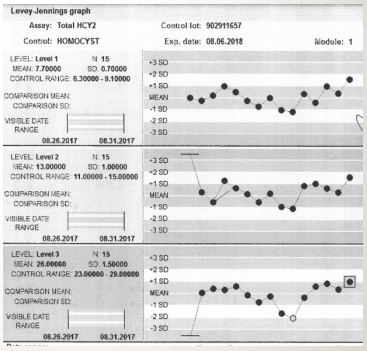
7.7 +/- 0.7 (9.0% CV)
13.0 +/- 1.0 (7.7% CV)
25.0 +/- 1.5 (6.0% CV)

TEa = 15.5% biologic

- New lot ranges take into account instrument performance to set mean and adopt historic precision (CV) unless mean close to current (then can use SD)

CV same Level 1 = 7.2 +/- 0.65 (9.0% CV)
No change Level 2 = 13.0 +/- 1.0 (7.7% CV)
SD same Level 3 = 26.0 +/- 1.5 (5.8 % CV)

- What about a new lot of reagent?



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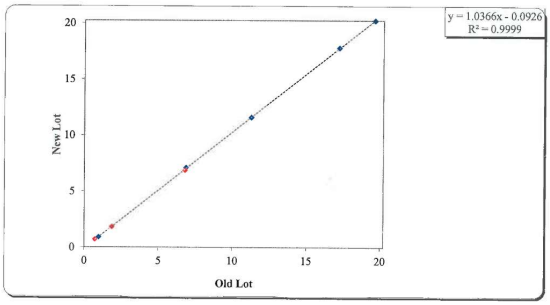
CREATININE

Lot-to-Lot Comparison (AMR Check)

Patients / Controls	Old Lot	New Lot	Bias	% Bias
1	0.97	0.91	0	-6
2	6.88	7.11	0	3
3	11.28	11.60	0	3
4	17.23	17.81	1	3
5	19.63	20.23	1	3
6				
7				
8				
9				
Control 1 (0.66-0.78)	0.72	0.69	0	-4
Control 2 (1.74-2.06)	1.87	1.83	0	-2
Control 3 (6.50-7.30)	6.81	6.86	0	1
			Mean % Bias:	**0**

5 patients old vs new reagent lot

Controls old vs new



Reagent lot changes shouldn't shift controls, unless matrix effects!

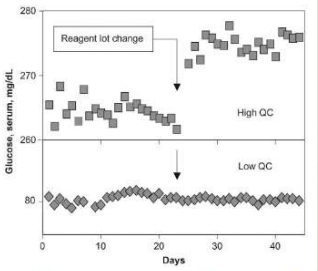


Figure 5-4 Levey–Jennings graph showing impact of a reagent lot change on matrix interaction with QC materials.

Performed by: R Walls Date: 04-02-2018

Old kit #: 34990UN17 New kit #: 06815UN17

Cal lot #: 45091FD01 Cal lot #: 45091FD01

QC lot #: 47960 QC lot #: 47960

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FORM - Chemistry Reagent Validation

Instructions: Complete all green squares with required data

Assay: IgE

Analyzer: Immulite 2000xpi

Prepared By: Sabah Ghazi

Date: 3/16/2021

Old Lot Information: Reagent Lot Number 516, Expiration Date 4/30/2021; Calibrator Lot Number 135, Expiration Date 4/30/2021; QC Lot Number 403080, Expiration Date 8/31/2022

New Lot Information: Reagent Lot Number 518, Expiration Date 7/31/2021; Reagent Lot Number 518, Expiration Date 7/31/2021; Calibrator Lot Number 135, Expiration Date 7/31/2021; QC Lot Number 403080, Expiration Date 8/31/2022

Patients / Controls	Old Lot	New Lot	Bias	% Bias
1	59.3	67.1	8	13
2	31.9	33.2	1	4
3	2.47	2.39	0	-3
4	19.3	19.4	0	1
5	66.8	71.9	5	8
6	8.94	8.64	0	-3
7	197	194	-3	-2
8				
9				
10				
QC Data	**Old Lot**	**New Lot**	**Bias**	**% Bias**
Level 1	36.1	145	-13	-4
Level 2	147	143	-4	-3
Level 3	82.7	89.1	6	8
			Mean % Bias:	1
Current Control Mean	**Mean**	**SD**	**2 SD**	**Range**
Control Level 1	425	39	78	347.00-503.00
Control Level 2	142.5	12	24	118.5-166.50
Control Level 3	90	8	16	74.00-106.00
Control Level 4				

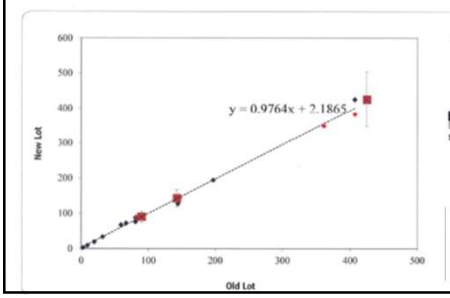
Level 1 QC new lot close to lower limit – Matrix effect or random imprecision?

Lead recommended adjusting QC range for new reagent, but we've been same QC lot for several months and reagent lots

Requested to repeat QC

Then recalibrate and repeat QC – much improved!

No QC adjustment necessary at this time, watch for now!



Patient/Control Line

Slope = 0.9764

Intercept = 2.1865

R² = 0.9945

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Multiple Analyzers

- How to set QC ranges with multiple same analyzers in the lab?
- Set QC range for each analyzer separately, OR
- Set QC range for a group of analyzers (adjust CV wider to account for multiple analyzers) – easier to maintain one mean/SD!
- 5 chemistry analyzers – albumin control run once/day for 20 days

  analyzer 1 = 2.44 +/- 0.01

  analyzer 2 = 2.41 +/- 0.02

  analyzer 3 = 2.40 +/- 0.02

  analyzer 4 = 2.46 +/- 0.02

  analyzer 5 = 2.42 +/- 0.02

Mean = 2.43 +/- 0.05 (2.1% CV) current setpoint = 2.5 +/- 0.05 (2%)

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Ongoing Assessment of QC Program

- Periodically review mean, SD, CV to ensure appropriate ranges – identify changes in method performance requiring corrective action
- Investigate measurement procedures with frequent QC failures, determine root cause of failures and identify corrective action
- Monitor rate of QC rule rejections, number of patient specimens needing retesting compared to number of patient results requiring correction
- Review analytical errors not detected using statistical QC to determine whether QC strategy can be modified to better detect errors
- Supplement QC strategy with Proficiency testing/EQA
- Participate in an Interlaboratory QC program

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Benefits of Interlaboratory QC Comparison

- Receive QC data from actual performance to establish better QC ranges for new lots
  - Package insert QC ranges often static, wide, and cover many lots and test methods/instruments
  - QC comparison provides peer group data to establish QC ranges for new lots based on other laboratory performance using your methods
- Helps patients by assuring quality of results across different methods and labs world-wide

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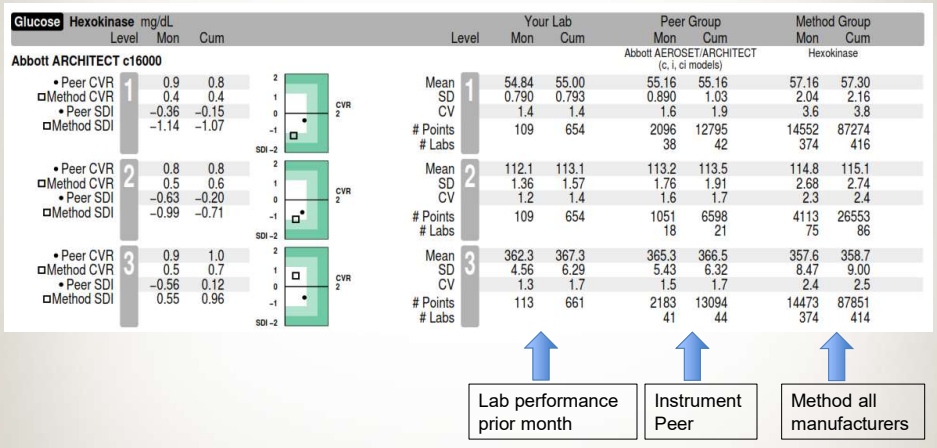
Interlaboratory QC Comparison Program



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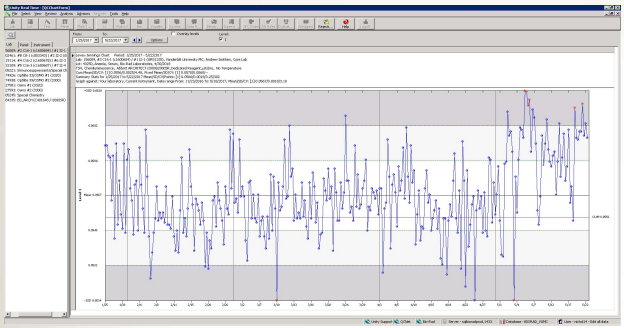
QC Troubleshooting



Month 0.0585 +/- 0.0018 (3.11%)

Cum = 0.0556 +/- 0.0025 (4.49%)

Setpoint = 0.055 +/- 0.003 (5.45%)

Peer = 0.0545 +/- 0.0065 (11.99%)

- Recent QC shift noted for low TSH control. After troubleshooting, recalibration and maintenance, QC still high.
- What are next steps to consider?

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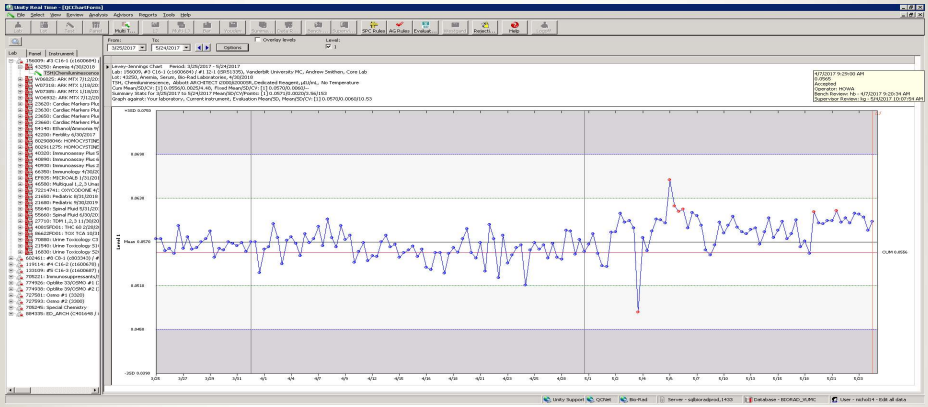
After QC Adjustment



New set point = 0.057 +/- 0.006 (10.5%)

Adjusted mean to summary lab stats of 0.0571 +/- 0.002 (3.56%)

Peer = 0.0545 +/- 0.0065 (11.99%)

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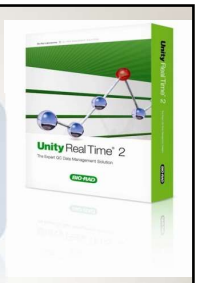
Quality Control Data



- ***ISO 15189: The laboratory shall have a procedure to prevent the release of patient results in the event of quality control failure.***
  - Bidirectional communication with LIS and/or Middleware allows the lab to prevent the instrument from releasing 'suspicious' results.
  - Samples can be placed 'on hold' until error condition has been corrected.
  - Traceability in URT2.0 or LIS/Middleware can indicate when last valid QC was analyzed.
- ***The laboratory shall also evaluate the results from patients that were examined after the last successful quality control event.***

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Managing QC Take Home Messages

- DO calculate control limits from your lab data (DON'T use package insert QC ranges)
- DO use computer and statistics to analyse and interpret QC data
- DO select QC procedures to detect medically important errors
- DO define the TEa and error budget for each test
- DO hold patient samples and troubleshoot root-cause of out-of-control conditions (don't just repeat the controls until "in range")
- DO review QC regularly and comment corrective actions
- DO monitor ongoing performance by interlaboratory QC program
- DO NOT adjust QC ranges unless scientific reason for change

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