Quality Control in the Coagulation Laboratory

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Werfen Group | Instrumentation Laboratory

Objectives

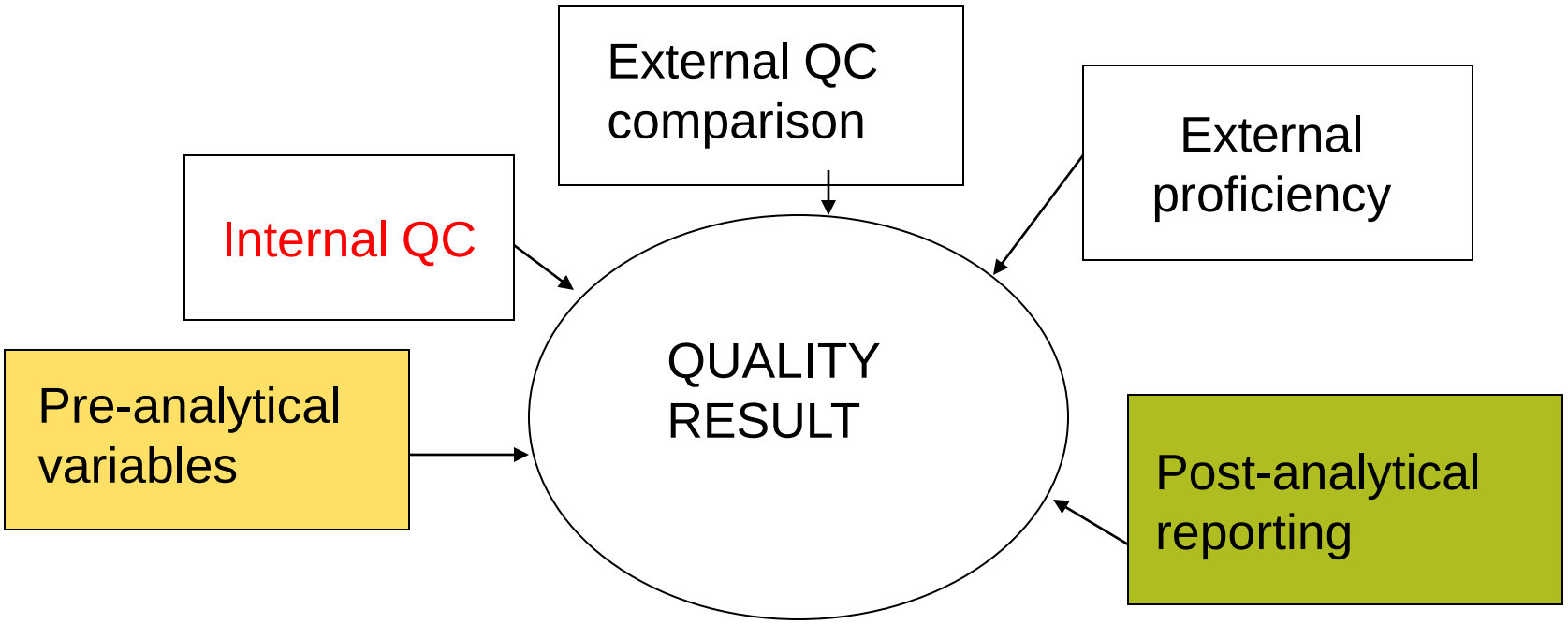
- Define Quality
- Understand how to Establish a QC range
- Review examples of QC errors
- Learn how to use the Levey-Jennings chart to guide troubleshooting of the system
- Review commonly used Westgard rules
- Review how to determine data to be submitted to Accutrak

Responsibilities

- It is the responsibility of the Medical Director of the Laboratory or their designee to determine each laboratory's quality control policy.

What is a Quality Result?

- **Accurate -** shows the “true” answer; on target
- Reflects the ***in vivo*** state of the patient
- Provided in a **timeframe** that is useful to the clinician



Goal of Quality Control

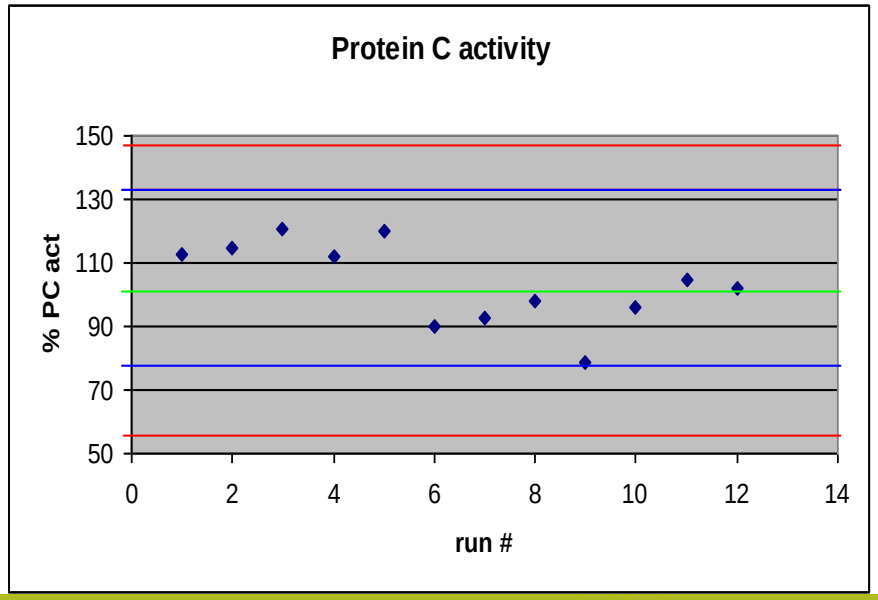
Catch ***all*** significant errors without repeating tests unnecessarily

Significant Error: A wrong answer that causes a change in the diagnosis or treatment of a patient; or a proficiency testing failure

Levey-Jennings Plot

- 1950 - Levey and Jennings proposed that quality could be monitored in a quantitative, statistical way

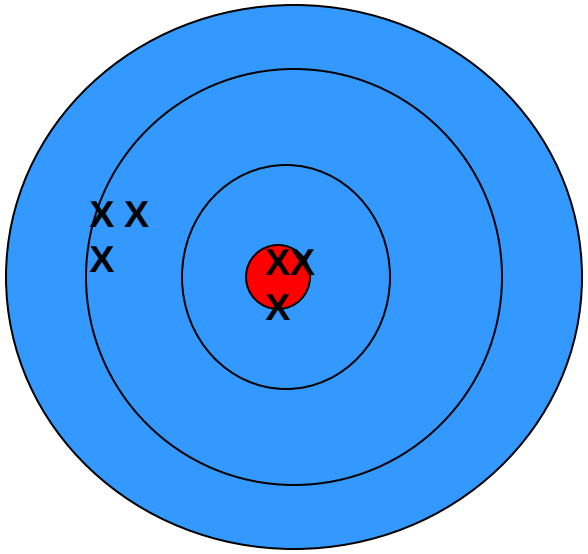
- Recommended that labs use the mean of a set of repetitive values, with acceptable limits set at +/- 3SD



Statistical Definitions

- Mean - average of a series of measurements
- SD - standard deviation; A measure of the imprecision; variability of results over time
- %CV = SD/mean x 100
- Bias - a measure of inaccuracy; How far a series of measurement is from the “true” value

Precision (%CV) and Accuracy (bias)



Precision: How closely multiple values match each other

Accuracy: How close values are to the “true” value

Establishing QC Ranges

- **New Method** : Determine method precision and bias.
- A minimum of 20 values over 20 days optimal, run at various times of the day, by various operators, with various bottles of reagent and controls.
- Screen for outliers and exclude from statistics.
- Calculate mean and SD

New Method QC Range

QC Level 1	PT									
1	11.8									
2	11.2									
3	11.9									
4	11.7									
5	11.9									
6	11.5		Mean	=Average(B2:B21)			11.7			
7	11.9									
8	11.7		SD	=stdev(B2:B21)			0.20			
9	11.6		2SD				0.40			
10	11.4									
11	11.6		Calculate mean +/- 2SD				11.3 - 12.1			
12	11.9									
13	11.8		Exclude outiers >3SD and recalculate if necessary							
14	12									
15	11.7		%CV	=(H9/H7)*100			1.7			
16	11.8		Compare %CV to package insert value and Accutrak							
17	11.6									
18	11.8									
19	11.5									
20	11.6									

Establishing QC Ranges

New lot numbers for existing method:

- Minimum of 20 values over 20 days optimal
- If not possible, 4 values over 5 days
- Tested with various vials of reagent, times of day, operators
- Calculate mean
- SD – if a well-established method, and mean is similar to the previous, can use the historical SD/CV

Historical SD or %CV

Advantage: takes into account slight variation in instrumentation and reagents over time.

- Cumulative data from at least 6 months
- Requires stable performance
  - No drifts or shifts due to reagent deterioration

Example:

- Old lot PT Level 1 mean = 11.5, SD 0.3, %CV 2.6
- New lot PT Level 1 mean = 12.0
  - Calculate historical SD based on CV
  - 0.026 x 12.0 = 0.3

Historical CV Example

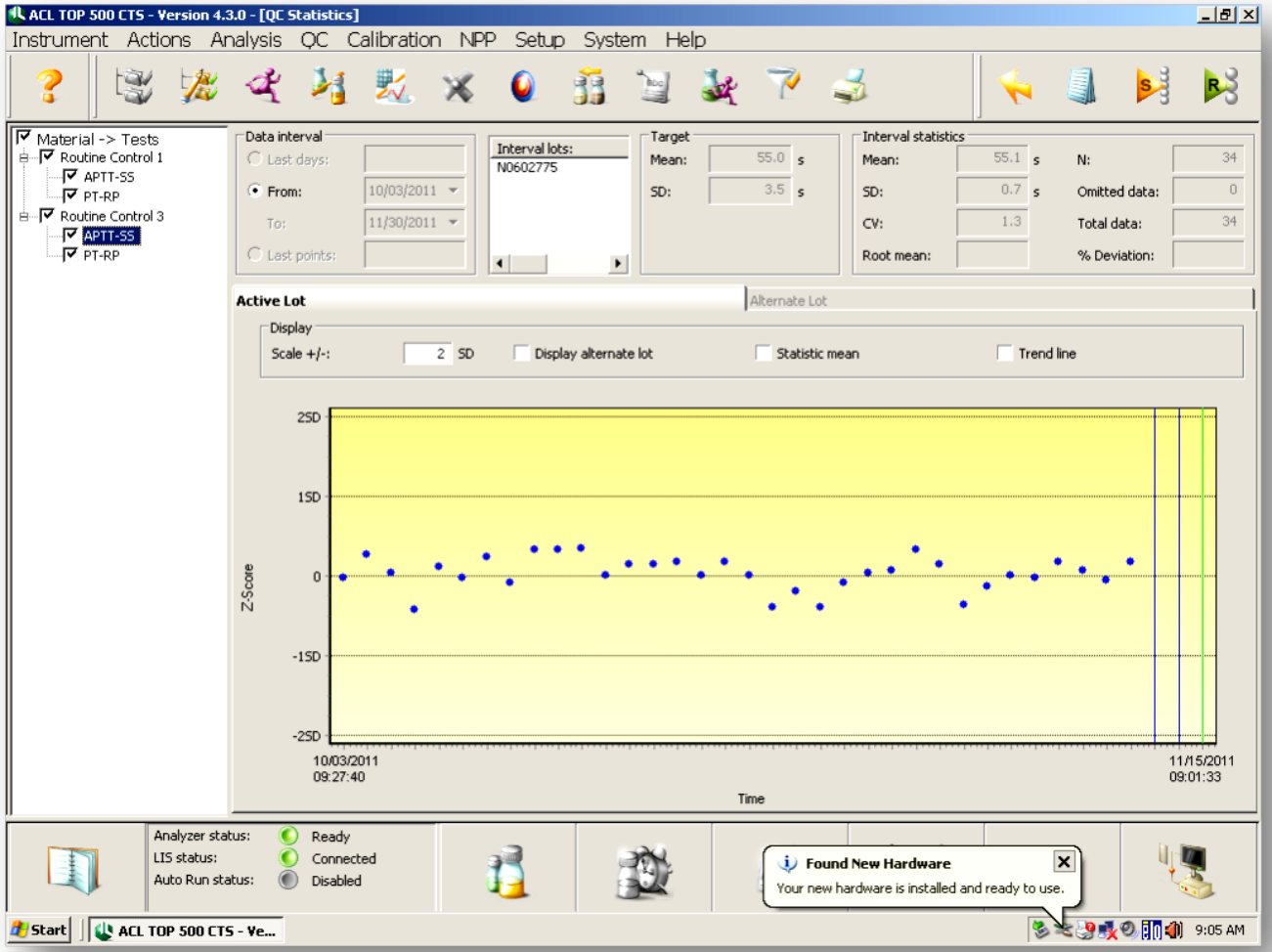
	Normal control			
	%CV			
Jan	5.2			
Feb	3.6		Control's	
March	4.8		mean value = 95%	
Apr	5.0			
May	5.5		SD = 95 x (4.6/100)	
June	4.8			
July	4.2		SD = 4.37	
Aug	4.0			
Sept	5.3		2SD range = 86 - 104	
Oct	4.5			
Nov	3.7			
Dec	5.0			
Average	**4.6**			

Assayed QC - Expected Values

"The reported ranges were determined over multiple runs on IL Coagulation ...Systems using specific lots of reagents. **The mean of the control range determined in your laboratory may vary due to the lot of reagent used."**

"Due to differences in reagents and instrumentation, each laboratory should establish its own Target Value and Acceptance Range (mean and standard deviation). However, any properly functioning coagulation system should yield ***mean*** values within the Acceptance Range on the package insert."

Is This Excellent QC Performance?

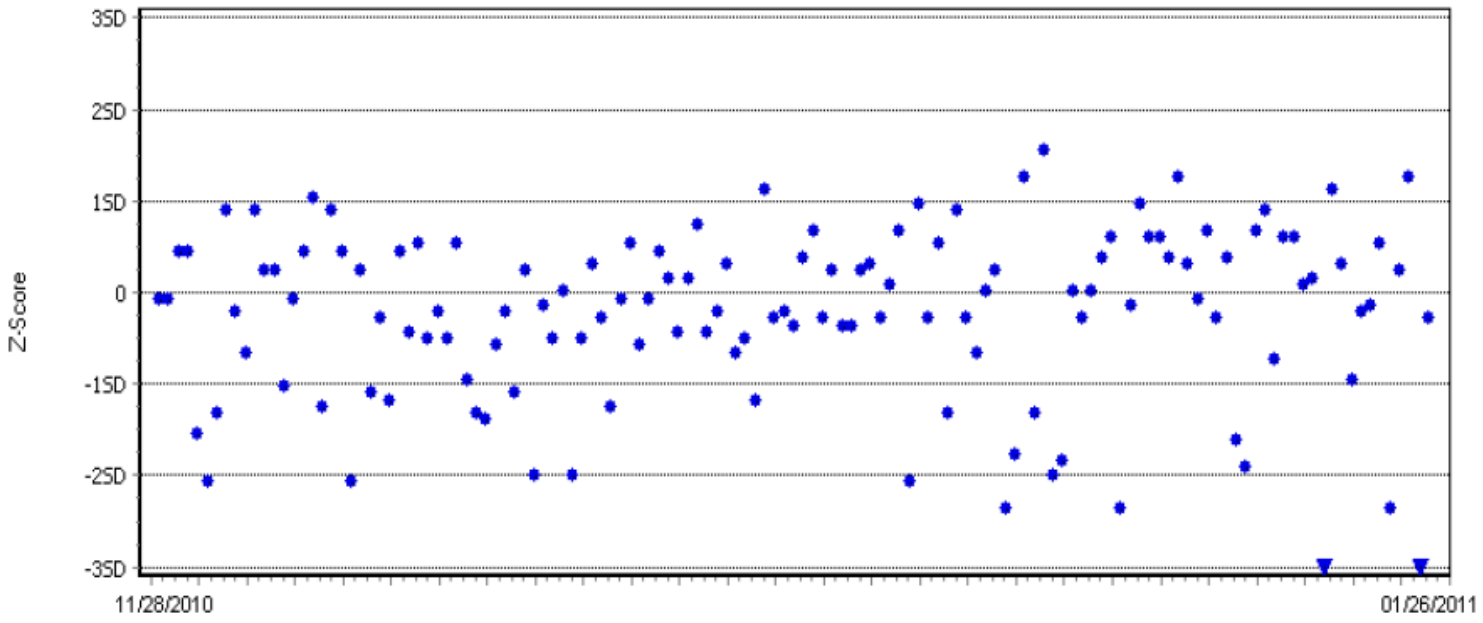


Is This Acceptable QC performance?

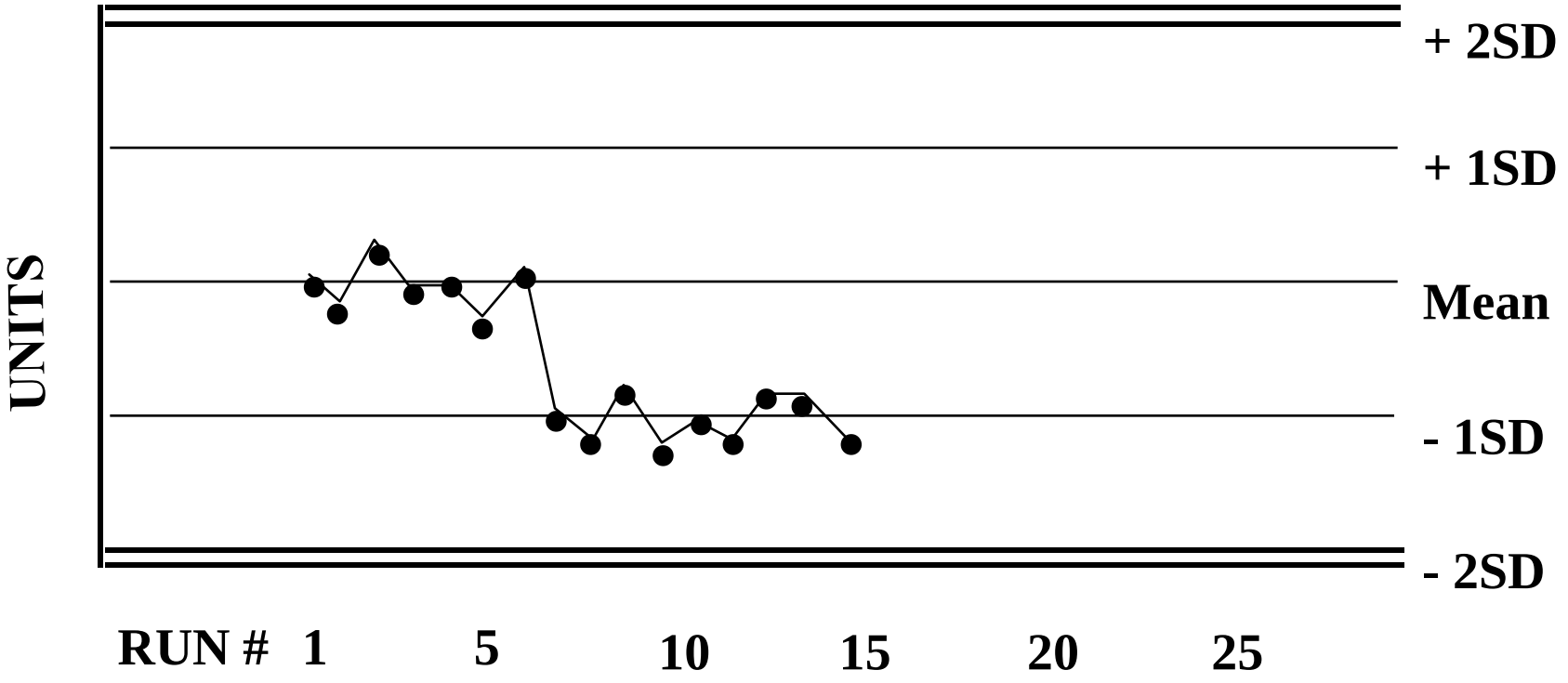
Test Code:	APTT-SS		
QC Material:	Normal C. Unassayed	**Data Interval:**	60 Days

Target:	
Mean:	30.0
SD:	1.4
Unit:	s

Statistic:			
Mean:	29.7	**N:**	133
SD:	1.3	**Omitted:**	0
CV:	4.4	**Total Data:**	133



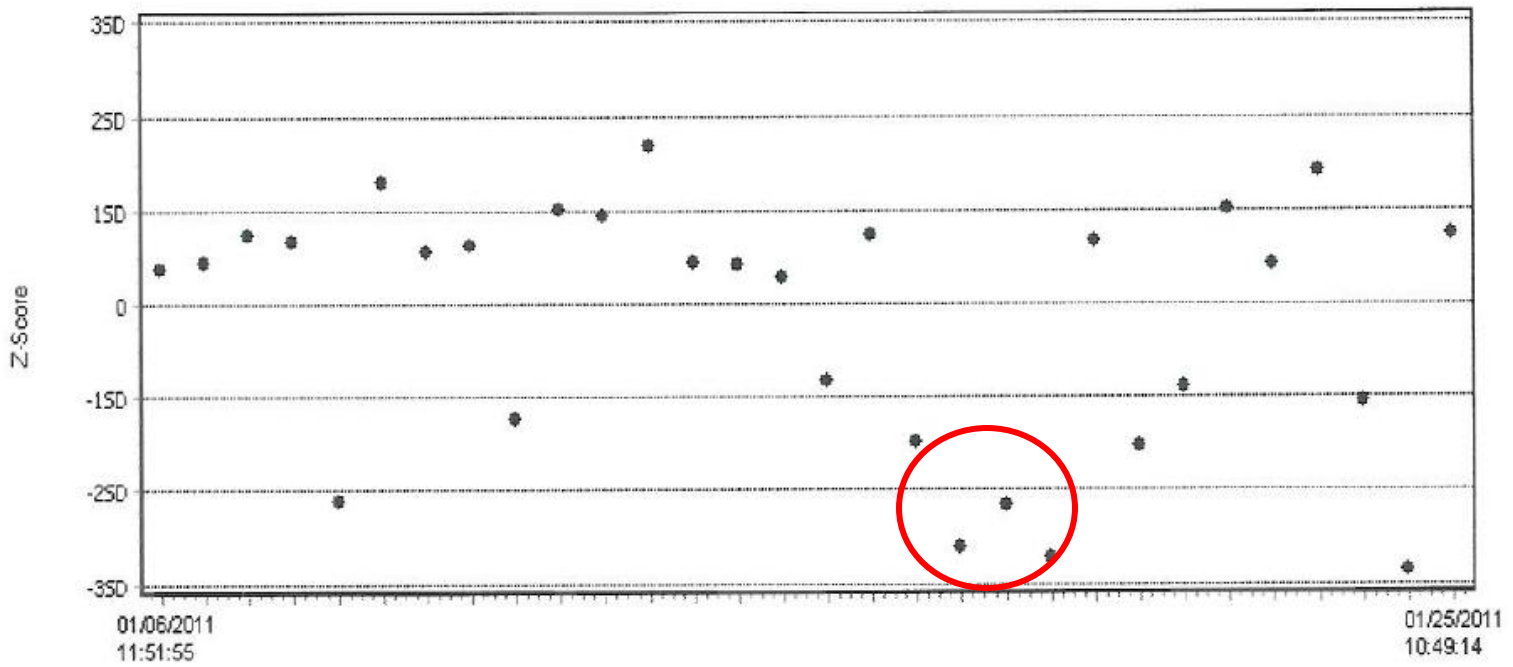
Levey-Jennings Graph Showing Abrupt Shift



Levey-Jennings Showing a Shift

QC Material:	High Abn C Unassayed	Data Interval:	30 Points

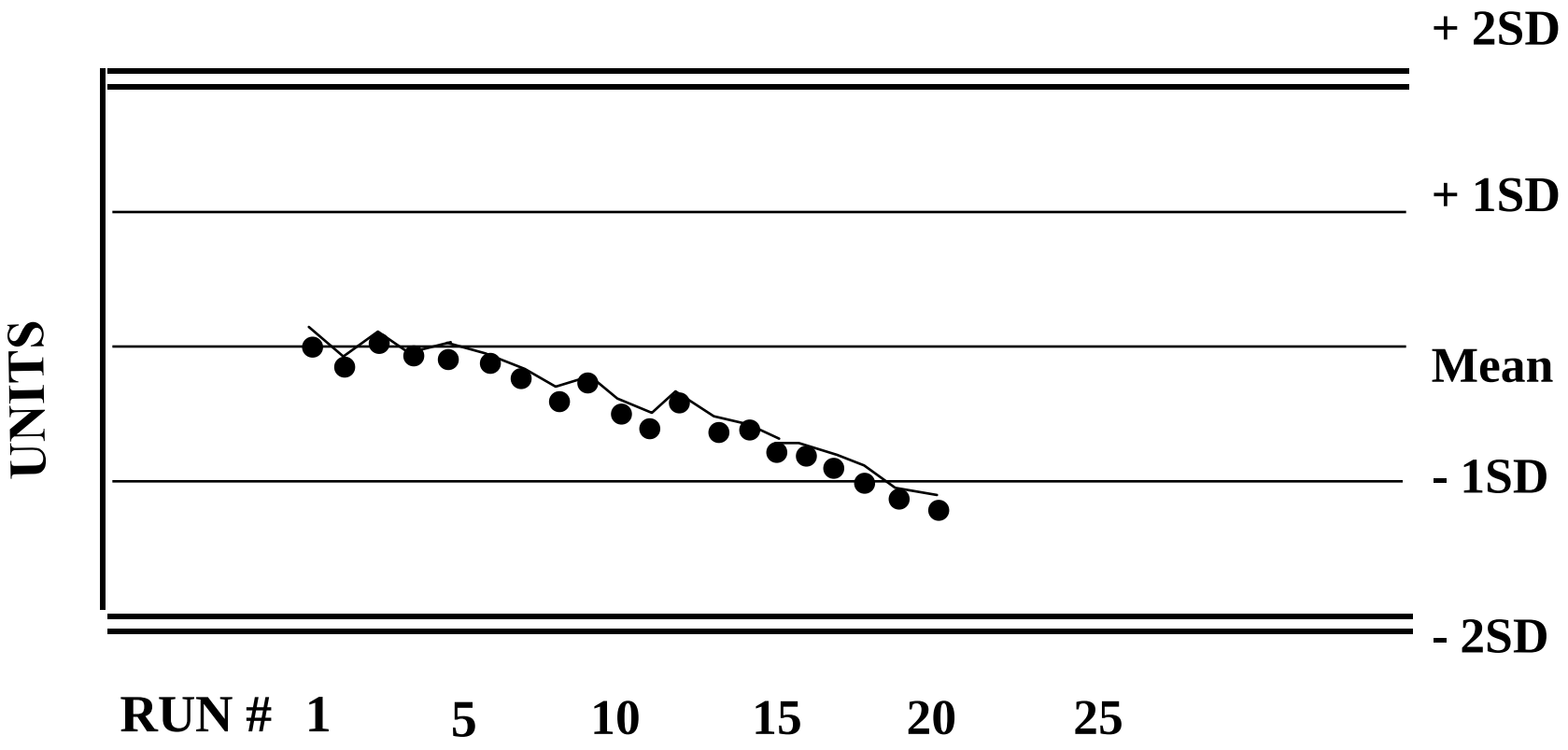
Target:		Statistic:			
Mean:	54.0	Mean:	53.5	N:	30
SD:	3.0	SD:	4.1	Omitted:	0
Unit:	s	CV:	7.6	Total Data:	30



Common Causes of QC shifts

- Change in reagent preparation, e.g. incorrect reconstitution volume
- New calibration curve
- Change in analyzer, e.g. new syringes, PM done
- Incorrect lot number on board

Levey-Jennings with a Trend



Common Causes of Trends

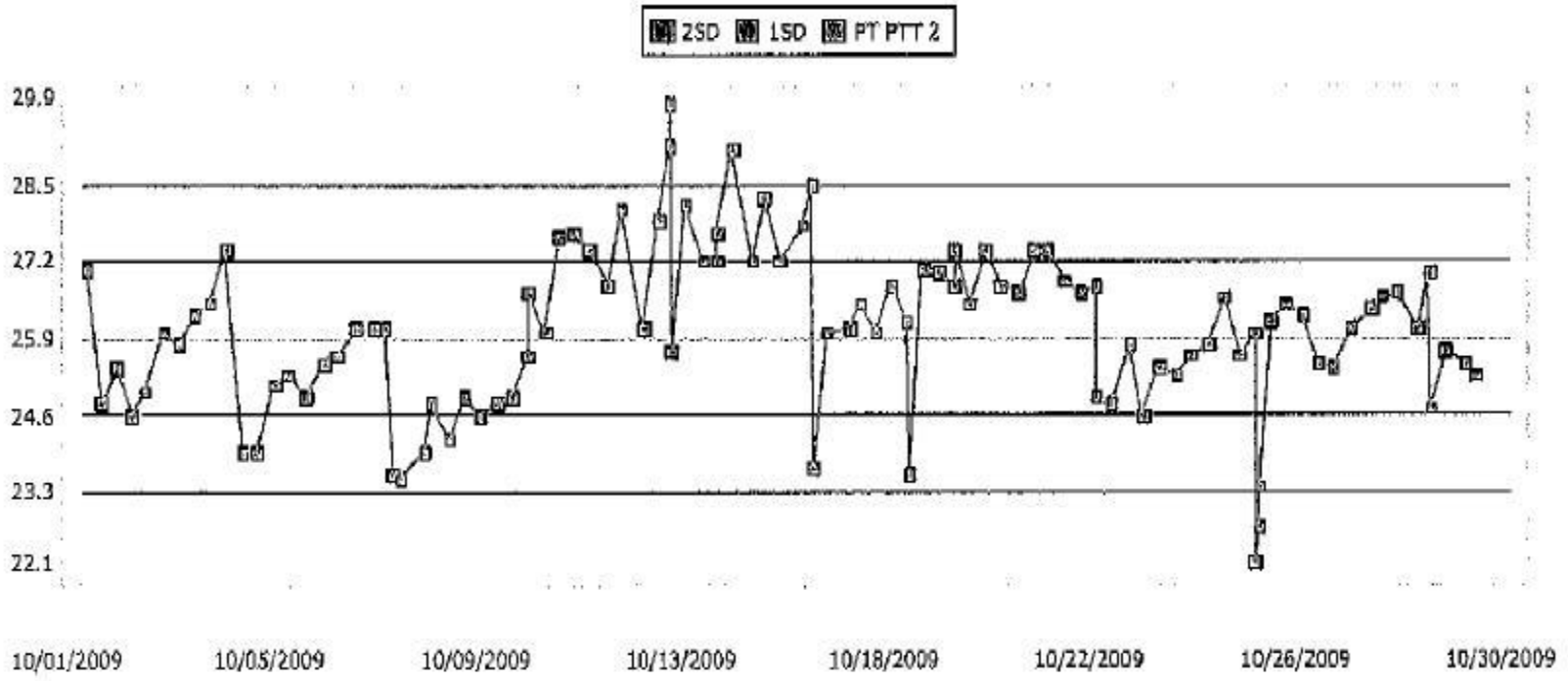
- Changes in a reagent or control, e.g. deterioration
- Contamination of the analyzer
- Minor trends in control or reagent are expected over the stability of the materials.
- Gradual wear of an instrument part, e.g. syringes seals.

Trends alert us to possible future failures

Random Error - Imprecision

Instrument Coag	**File ID** PT PTT 2	**Level** 2	**Lot Opened** 09/13/2009
Lot Number NO987358	**Location** PMH Main Lab	**Lot Expires** 09/30/2010	**Lot Closed** 00/00/00

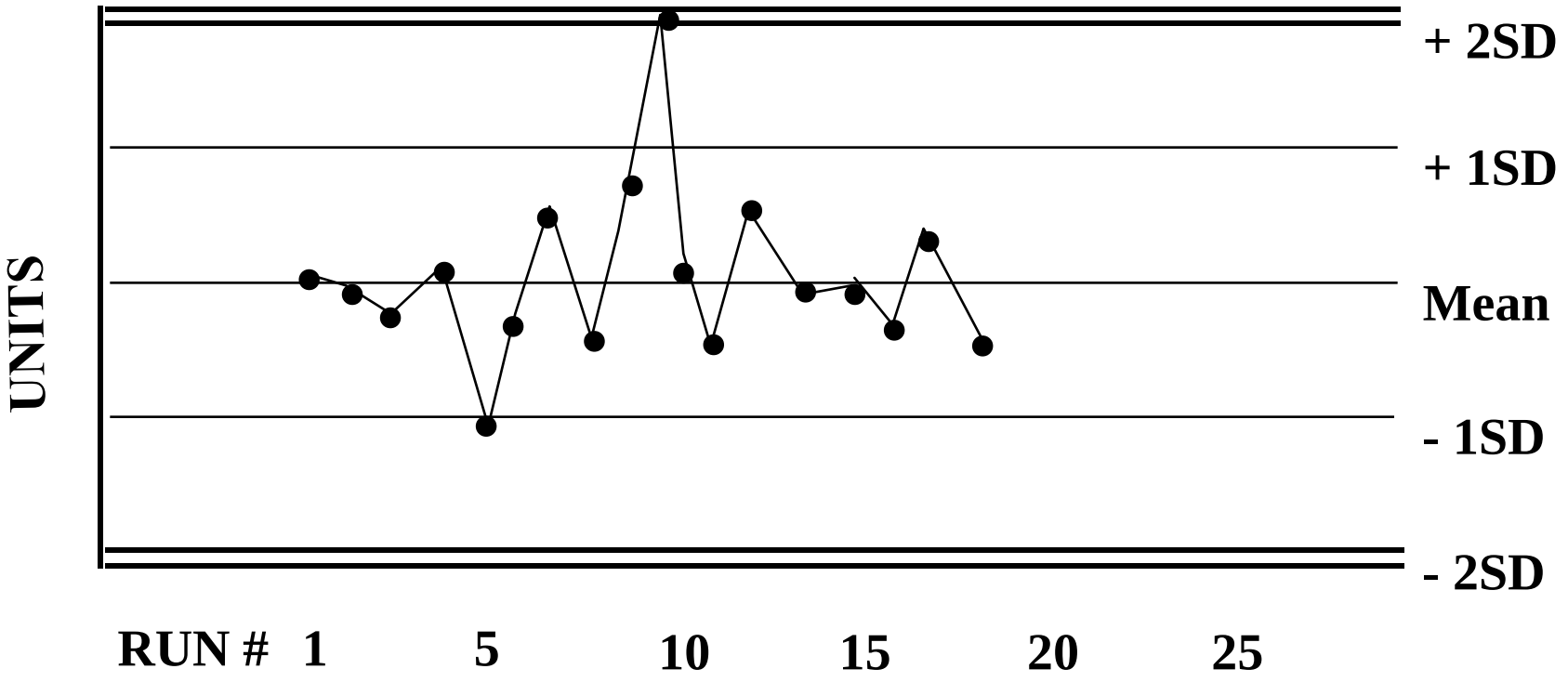
Protime QC (10/01/09 - 10/30/09) *102 points*



File Test Comment: [09/13/09 11:22 1007T] Exp Mean modified. [31.1]->[25.9], Exp Stdev modified. [1.137]->[1.3], Reason: incorrect mean and sd entered

File/Dates	M(E)	SD(E)	CV(E)	Range(E)	M(O)	SD(O)	CV(O)	Range(O)
PT PTT 2 Current	25.90	1.30	5.01	23.3-28.5	26.06	1.38	5.32	23.29-28.84

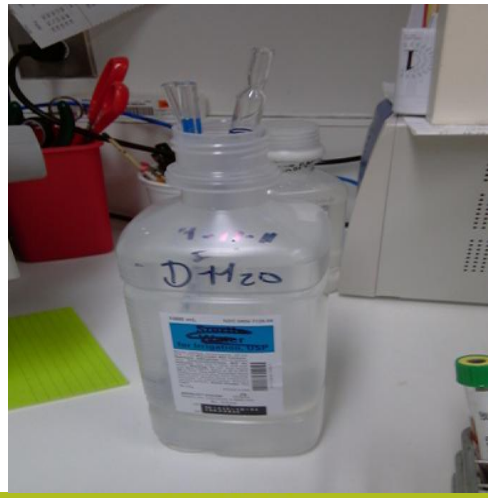
Levey-Jennings Graph Showing a Statistical Outlier



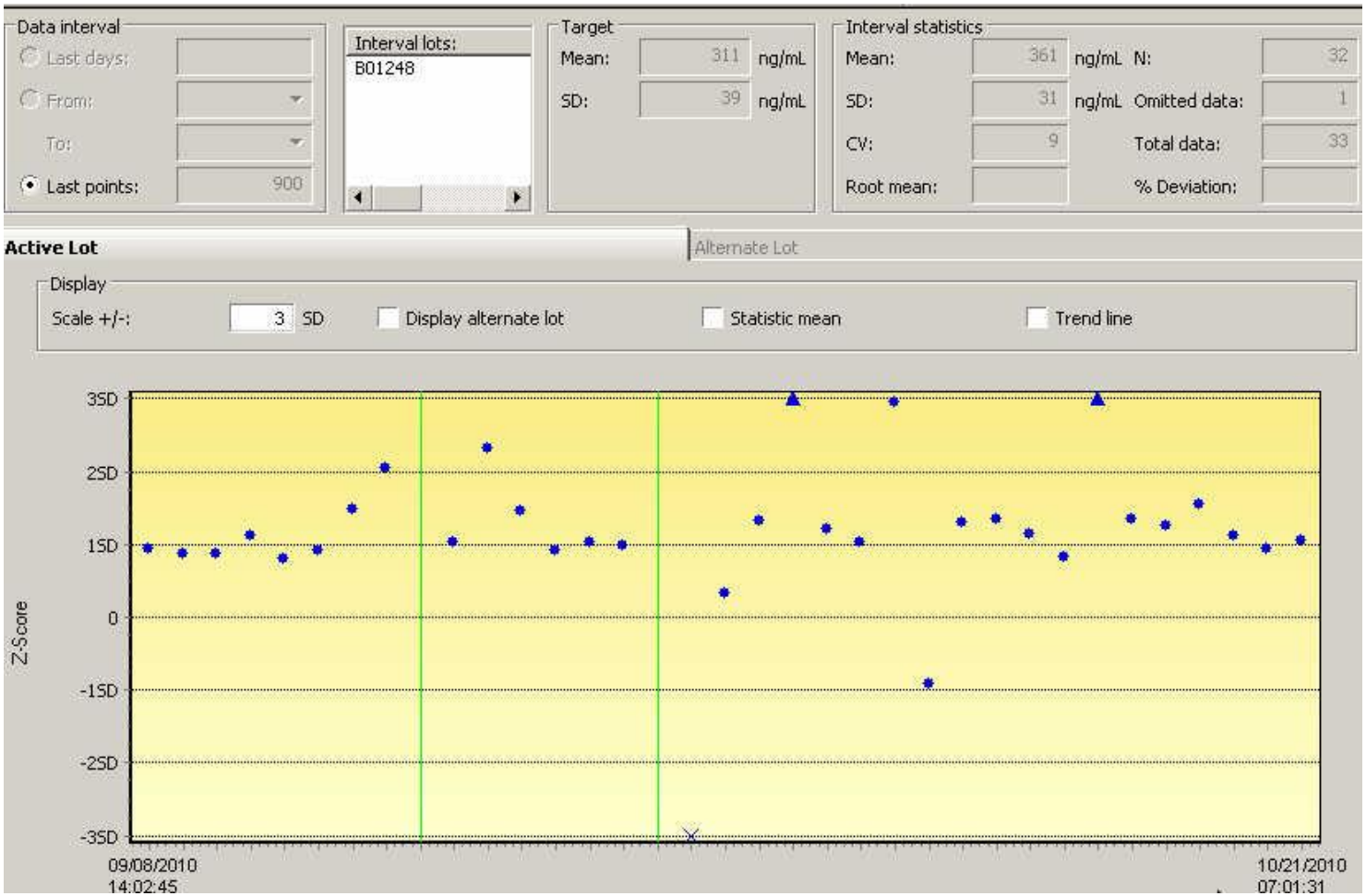
Causes of QC Failures

Mistakes in Reagent or QC preparation

- Storage or shipping temperature failures
- Reconstitution errors:
  - Pipetting
  - Water
  - Mixing
  - TIMING

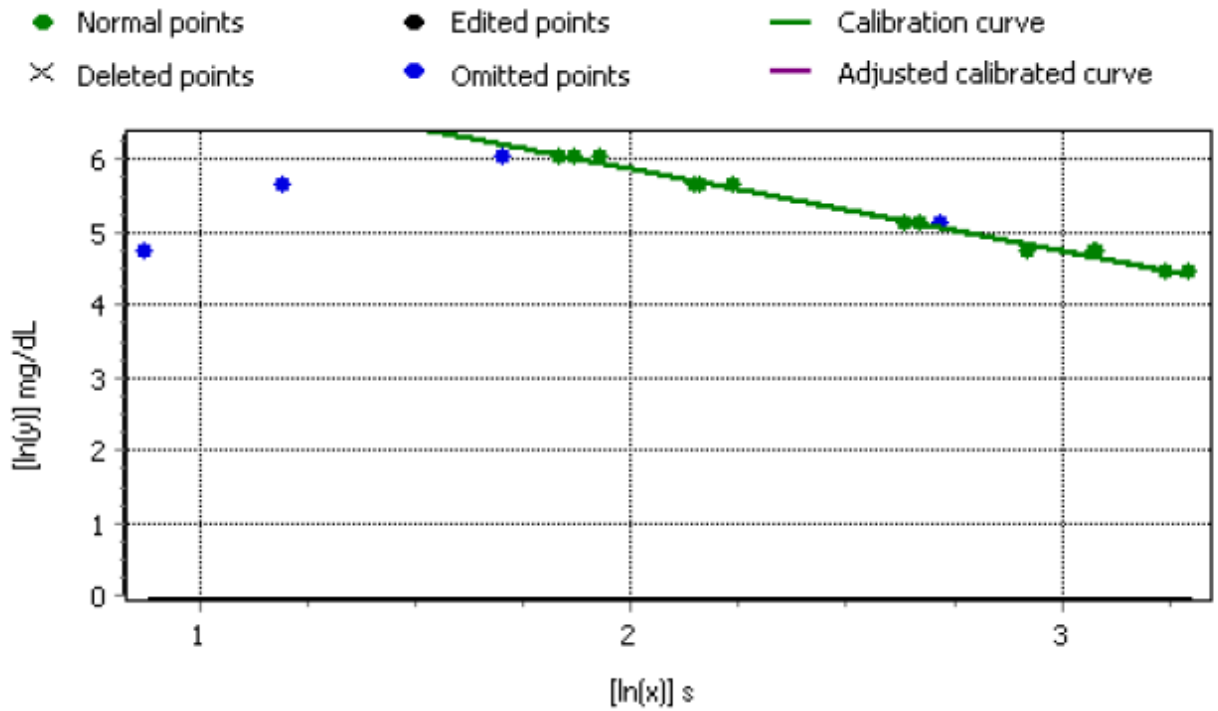


Incorrect Mean

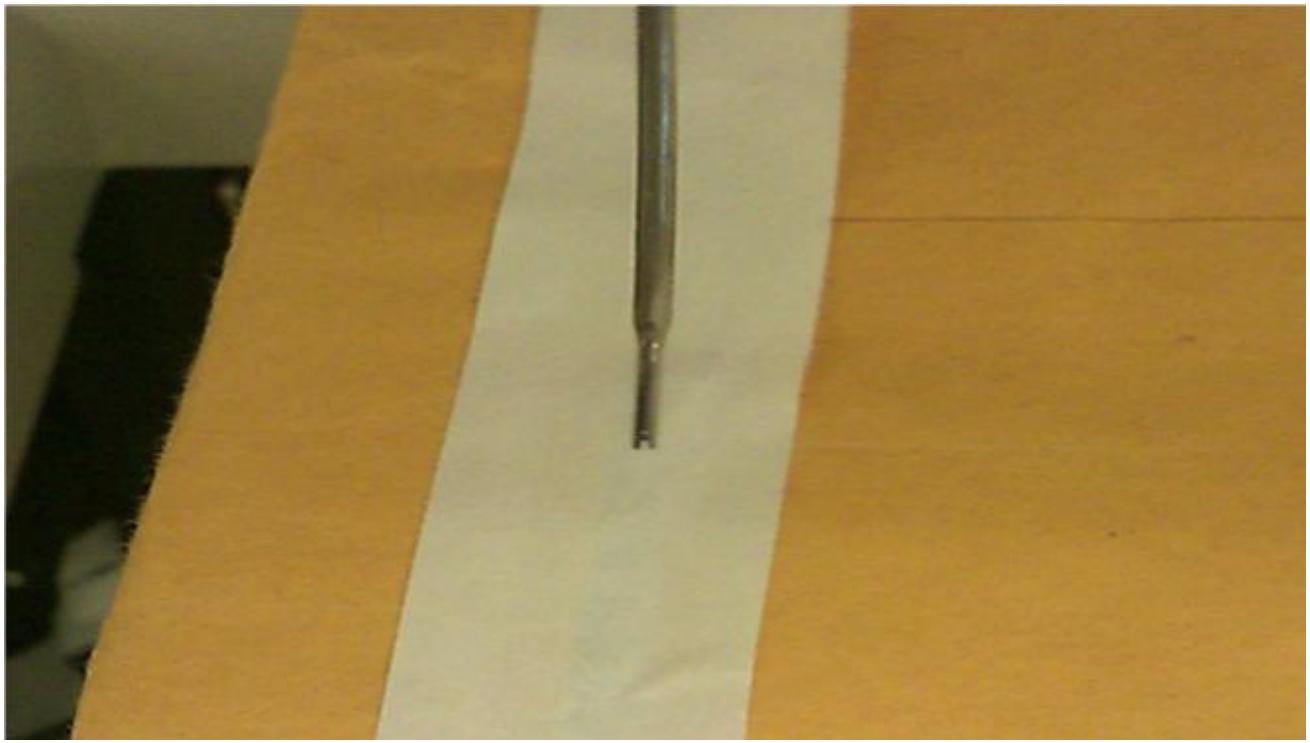


Incorrect Calibration Curve

Regression Type:	Linear regression		
X - Transformation:	ln(x)		
Y - Transformation:	ln(y)		
Y-Intercept:	8.118E+00	**Adjusted Y:**	
Slope:	-1.130E+00	**NPP:**	
r2:	0.991	**NPP Value:**	



Mechanical Failures



Improperly Performed Maintenance

- Or…maintenance not performed
- Incorrect solution used for cleaning or rinsing
- Syringes not correctly seated after replacement
- Incorrect probe/needle alignment

Bubbles!

QC Failure Classification and Management

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Corrective Actions

- Rerun – if using 2SD rule only
- Make fresh reagent – both levels out?
- Make fresh control material – one level out?
- Perform maintenance – clean, avoid contamination
- Look for trends/shifts
- Other considerations (Calibration, H_2O, pipettes)
- Consider instrument malfunction
- Consider instrument failure

How to Handle an Outlier (within the +/- 3 SD Range)

If using Westgard multi-rules – not an automatic failure

If using only a 2SD range:

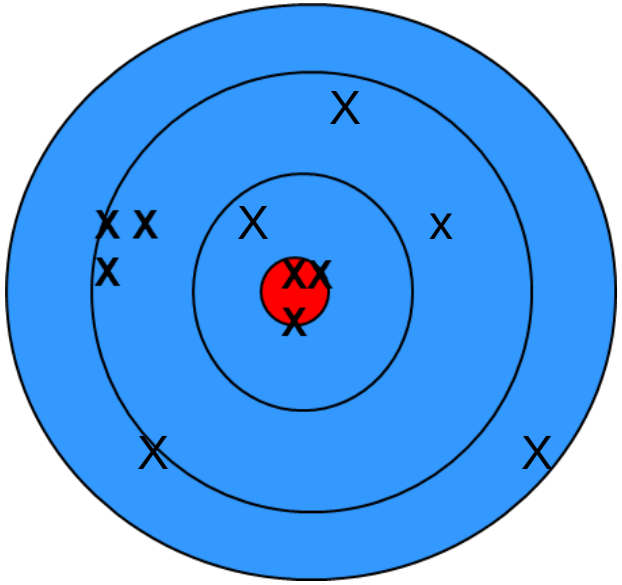
- If the numeric results for the outlier is between 2 SD and 3 SD, this is very likely a statistical outlier. If the graphical display does not show a 3 SD range, the operator must run the control again.
- If the result of the rerun is now “in control” (falls within 2 SD) the analytic run is accepted and both QC runs (the statistical outlier and the acceptable rerun) are to be included in the control data base.

How to Handle an Outlier (within the +/- 3 SD Range)…cont'd

- If the rerun of the control reflects the same parameter as still being out of control between the 2 SD and 3 SD limits, (fails 2-2s) this reflects systematic error and the operator should troubleshoot
- Look for shifts or trends, are the mean and SD correct?

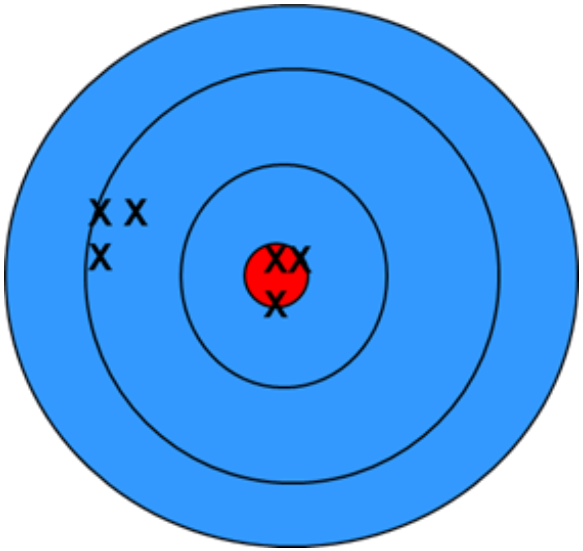
Error Classification

- Random – spuriously occurs, not consistent. Indicates imprecision. – high CV



Error Classification

- Systematic – an ongoing error such as a shift or drift in results. Indicates inaccuracy



Westgard Rules Overview

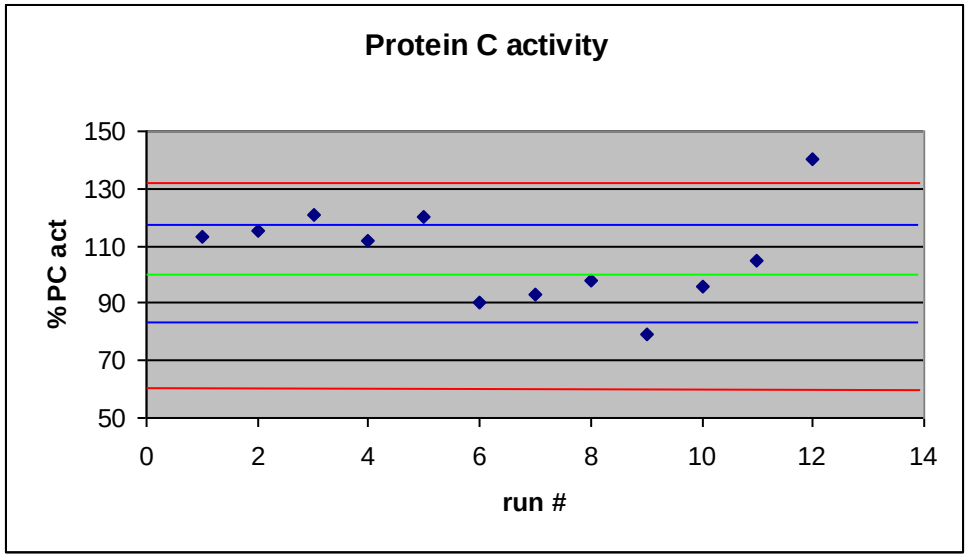
1980's Westgard Rules

- N = number of control observations
- Subscript = rule that is violated
  - e.g. 1_{2S} - one control level out by more than 2SD
- Multiple rules written with a slash between, e.g.
  - $1_{2S}/1_{3S}/2_{2s}/R_{4S}/4_{1S}/10_{x}$
- Rules may be designated as rejection rules or as warning rules

Westgard JO, Barry PL, Hunt MR, Groth T. A multi-rule Shewhart chart for quality control in clinical chemistry. *Clin Chem* 1981;27:493-501.

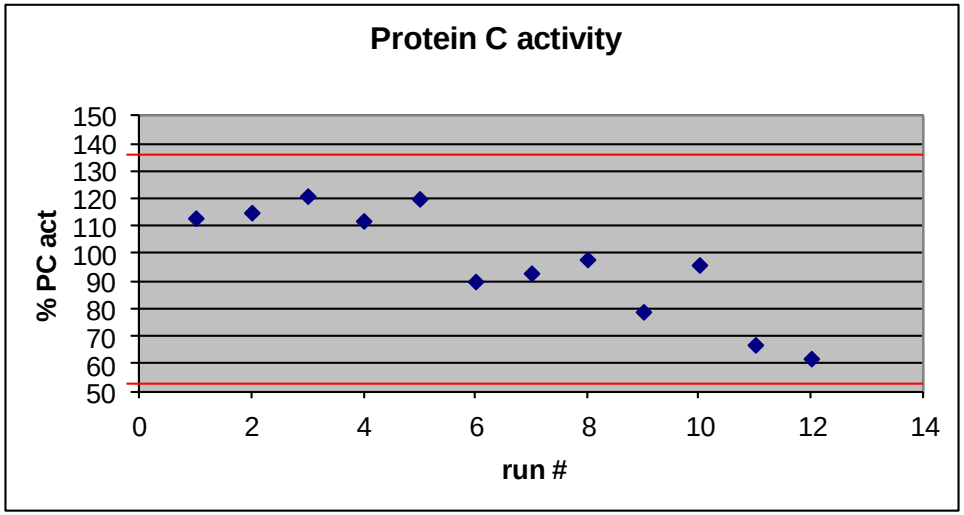
Commonly Used Westgard Rules

1_{3S} - Reject Run Random error



Commonly Used Westgard Rules

22S -Reject Run Systematic error

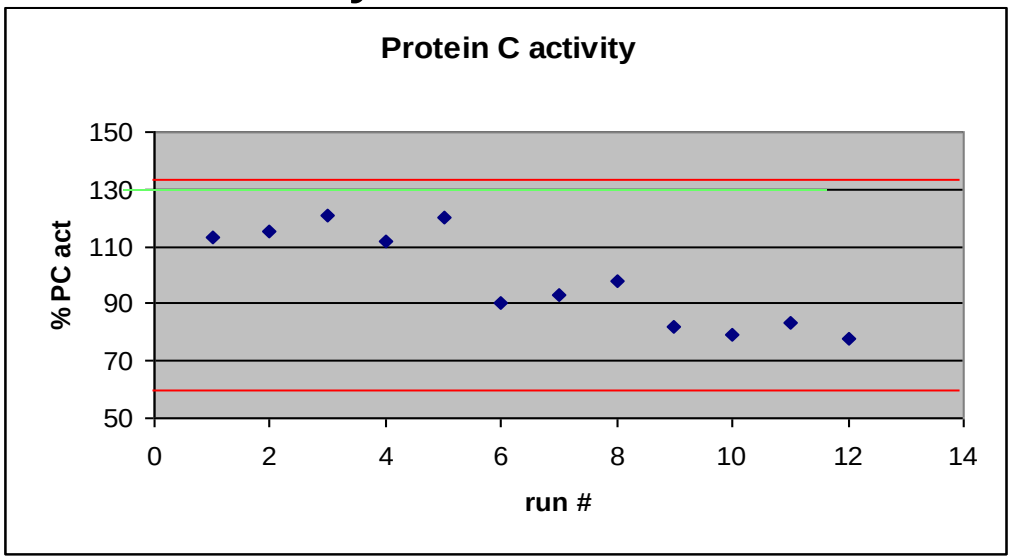


2 consecutive values outside the same 2SD (across runs) OR 2 consecutive values outside the same 2SD (within run)

Commonly Used Westgard Rules

4_{1S} –Warning (reject at lab's discretion)

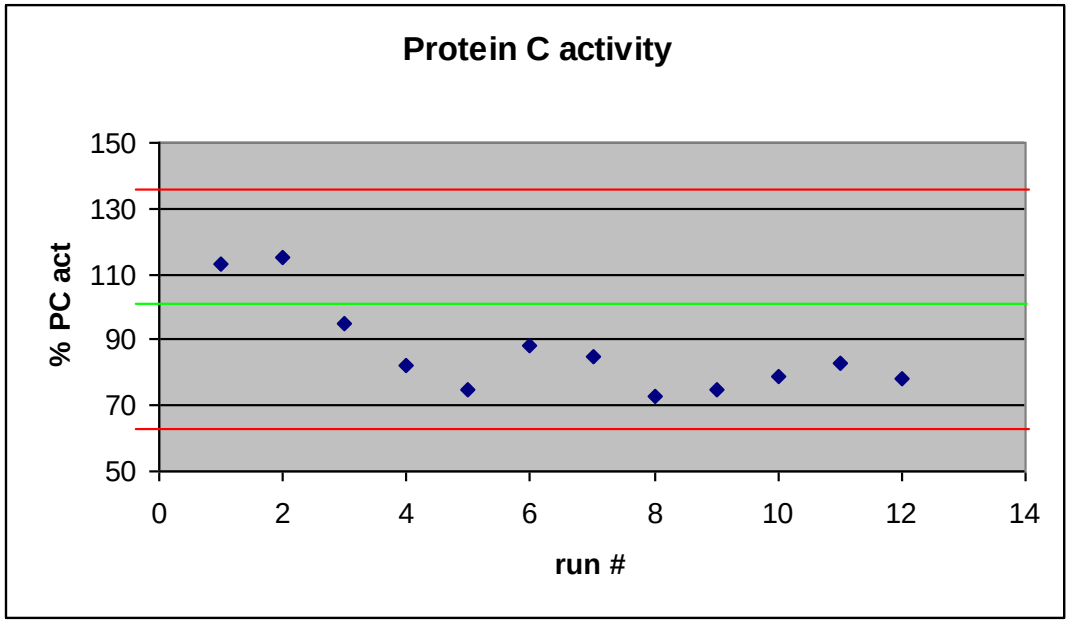
Systematic error



4 consecutive values on one side of the mean and more than 1SD from the mean; one control over 4 runs, or 2 controls across 2 runs

Commonly Used Westgard Rules

10_x – Warning rule Systematic error

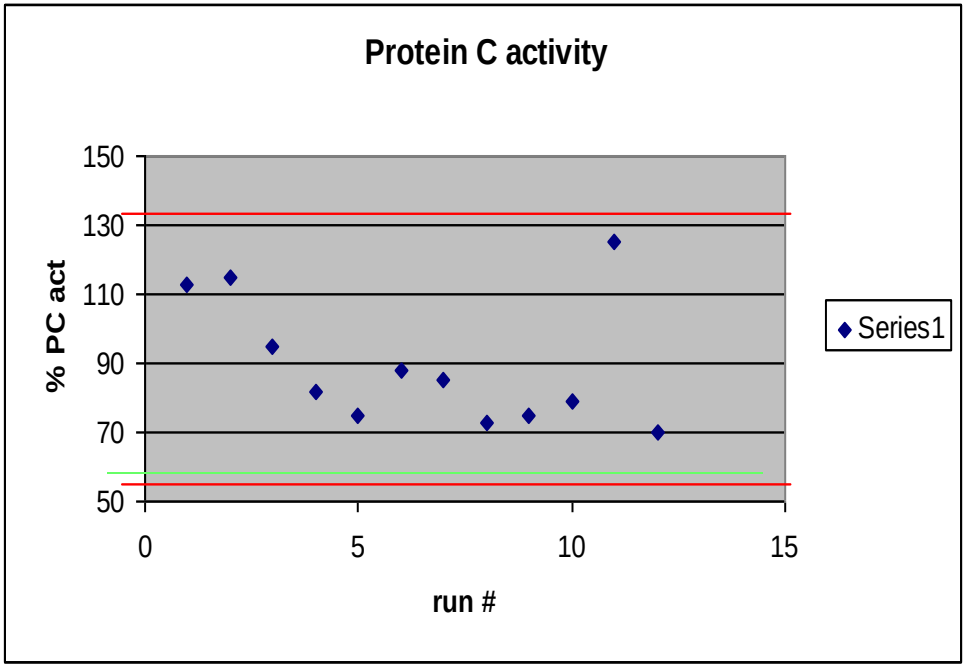


10 consecutive values on ONE side of the mean; can be one control across 10 runs, or 2 controls over 5 runs

Commonly Used Westgard Rules

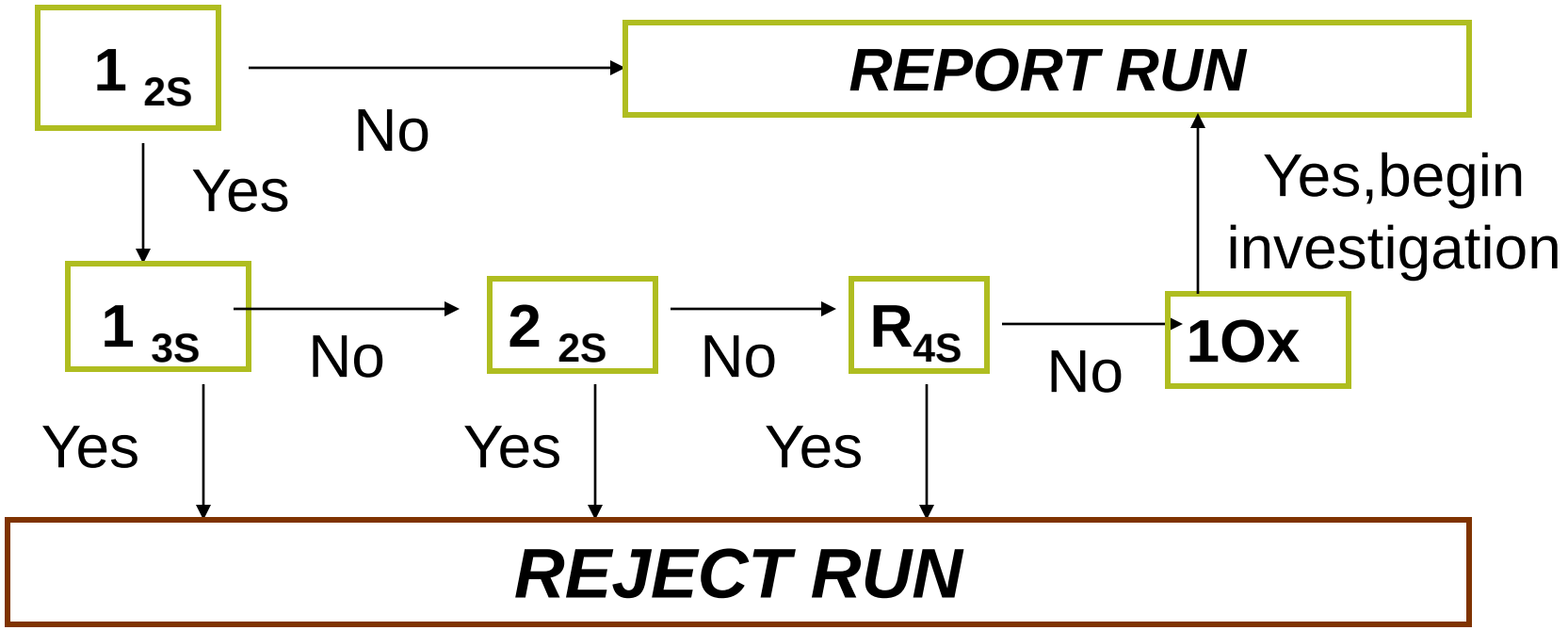
R_{4S} - Reject Run (Warning rule at lab's discretion)

Random Error



The range between 2 controls **within run** exceeds 4 SD

Multi-rule Flow Chart
2 Controls per Run



This scheme will lead to <1% false rejects

QC Example 1

Technologist is performing an AT activity assay using 2 levels of controls

- Control 1 = 97% (2SD limit is 95 to 115%)
- Control 2 = 29% (2SD limit is 30 - 40%)

Should the run be accepted?

- Must look at the previous run's result for that control.
- Control 2 read 31% on the previous run. Passes 2_{2S}.
- Looking back, the previous 9 runs have read below the mean. Fails 10x; Accept run, but troubleshoot shift.

QC Example 2

Technologist is performing an APTT assay using 2 levels of controls.

- Control 1 = 35 sec (2SD range = 27 - 33 secs)
- Control 2 = 56 sec (2SD range = 51 - 57 secs)

Should the run be accepted?

- Must look at the previous run's result for that control.
- Previous result for Control 1 was 36 secs.
- Fails 2_{2S} rule. Reject Run.

Important points when using Westgard Rules

- The mean and SD must be current and accurate for the lot numbers in use.
- The mean and SD must have been based on an acceptable number of data points; minimum of 20 values obtained under normal testing conditions
- Westgard rules should not be used when using a manufacturer’s package insert range on an assayed control

QC File Management

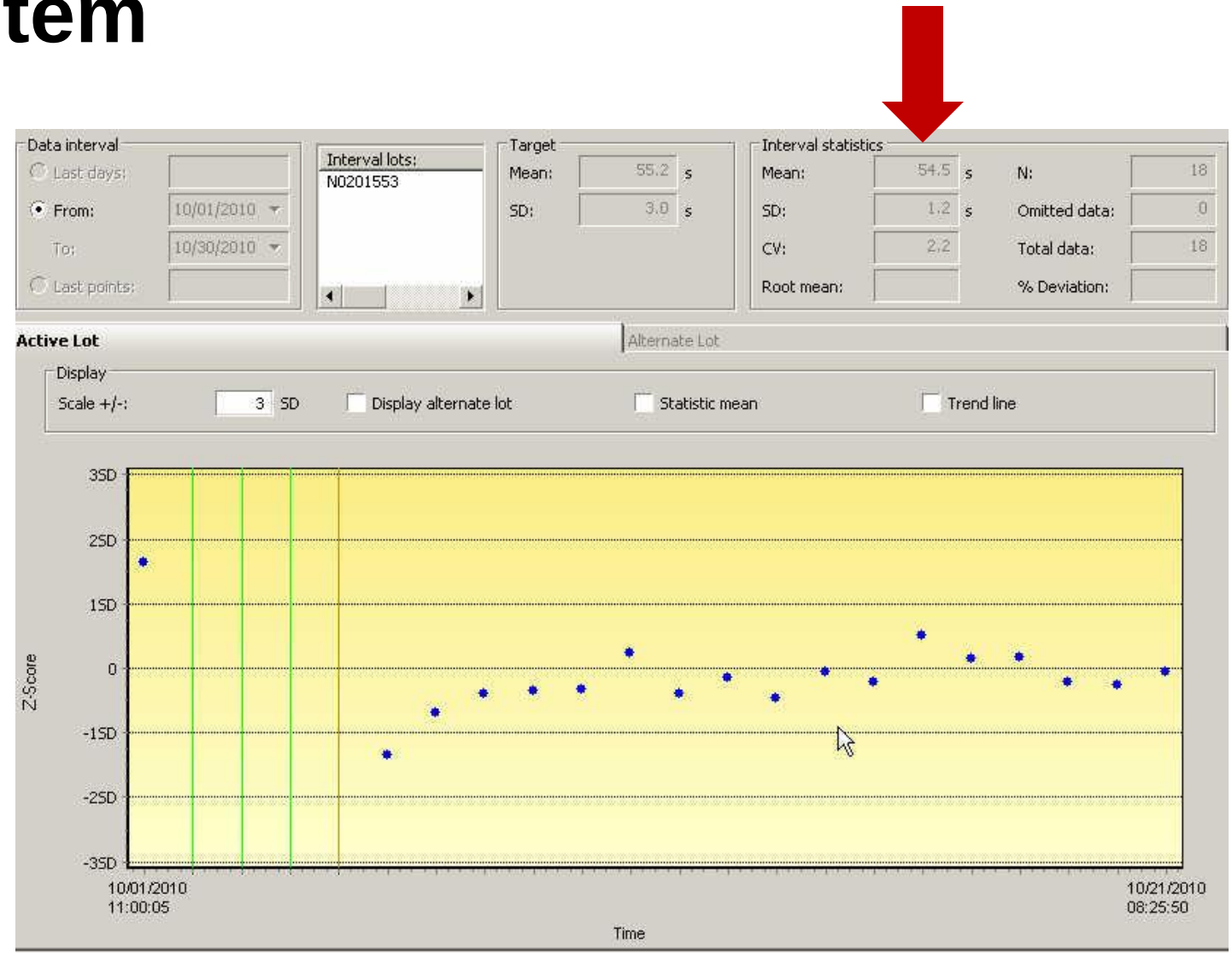
- The frequency of outlier occurrences should be carefully monitored. A high outlier frequency may indicate excessive or systematic error.
- All control results less than 3 SD should be used in statistical calculations.
- In some labs it is still common practice to omit the outliers; however this practice may artificially narrow the control range if recalculated.

Accutrak Reporting

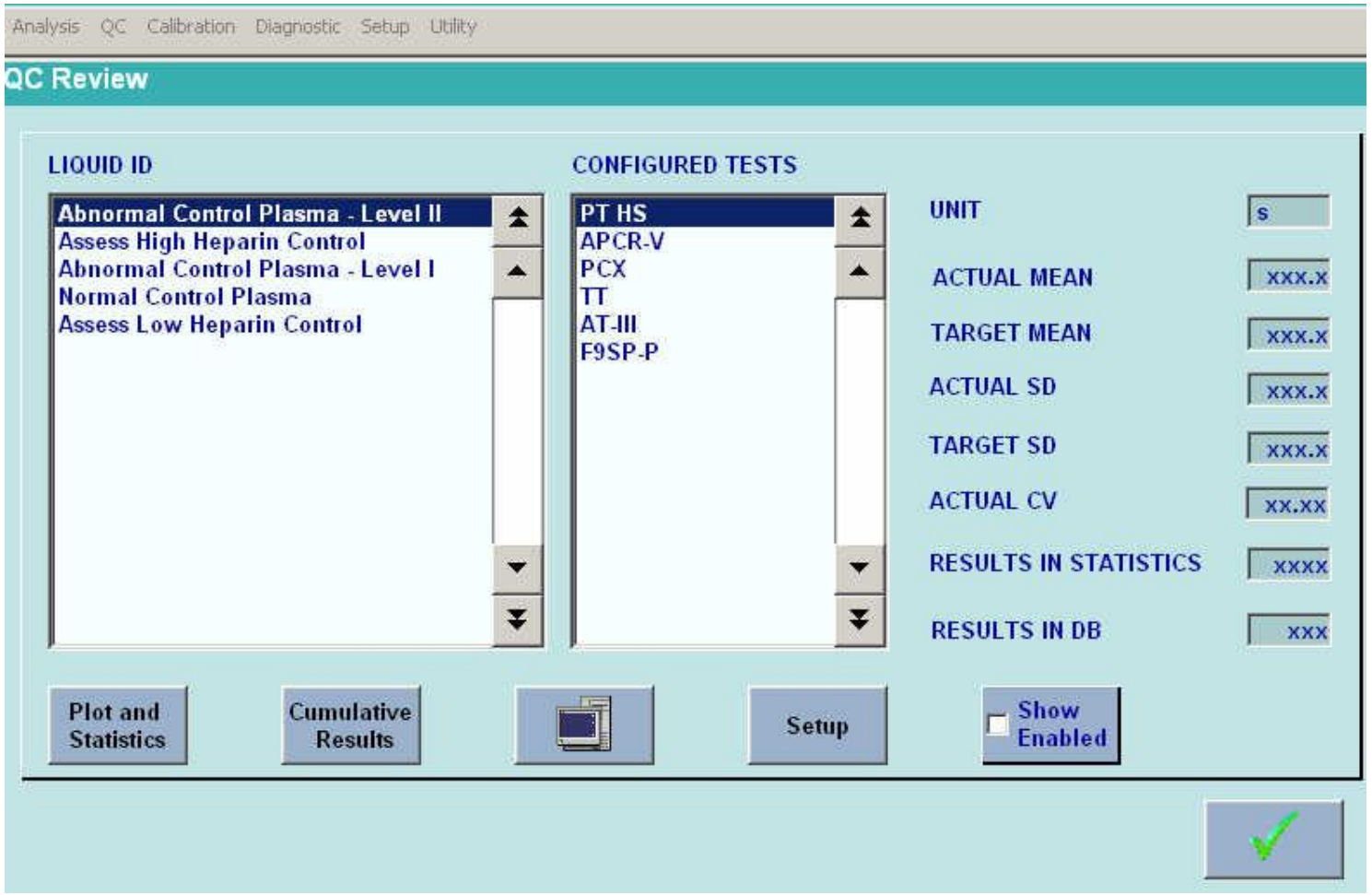
Submitting Data to Accutrak Monthly

- Filter QC data to show only the last month
- Review points for outliers (+/- >3SD) and omit from statistics
- Enter the ACTUAL mean and SD for the month, not the TARGET.

Actual Mean and SD on an ACL TOP® System



Actual Mean and SD on an ACL ELITE® System



Accutrak Data

Using Accutrak to assess accuracy

- Data is now reagent lot number specific in the full report
- A minimum of 20 labs is statistically significant
- Confidence limits of the peer group is a range of means

Accutrak Data

Using Accutrak to assess precision

- Average peer group CV may not reflect all reagent lot numbers in use

Reasons Control Data May Flag in Accutrak

- An instrument problem
- A reagent problem
- A control storage and/or handling problem
- A change in laboratory environment, including pipettes/water
- Has this problem been fixed already?

Accutrak Report Message:

"Your Lab's 2 SD range is wider than the Group's 3 SD range."

- Verify lot numbers
- Instrument maintenance
- Instrument problem
- Isolate cause of Imprecision

Conclusions

- QC ranges must be correctly established and maintained to catch errors before they occur
- One can guide troubleshooting based on the Levey-Jennings graph and type of error – random vs. systematic
- Comparison of mean and CV with peer group labs via Accutrak is a valuable tool

References

- CLSI C24-A3. Statistical quality control for quantitative measurements: Principles and definitions; Approved guideline - second edition. NCCLS, Wayne, PA, 2006.
- CLSI EP23A.Laboratory Quality Control Based on Risk Management. CLSI, Wayne, PA, 2011.
- Westgard JO, Barry PL, Hunt MR, Groth T. A multi-rule Shewhart chart for quality control in clinical chemistry. *Clin Chem* 1981;27:493-501**.**
- Levey S, Jennings E. The Use of Control Charts in the Clinical Laboratory. *Am J Clin Pathol 1950;20:1059-66..*
- www.westgard.com/mltirule.htm

Additional Reading

- Quality in Laboratory Hemostasis and Thrombosis edited by Kitchen, Steve, et al. Blackwell Publishing Ltd. 2009