Best Practices for Lot Changes in Quality Control or Reagents

BIO-RAD

February 24th, 2021

1

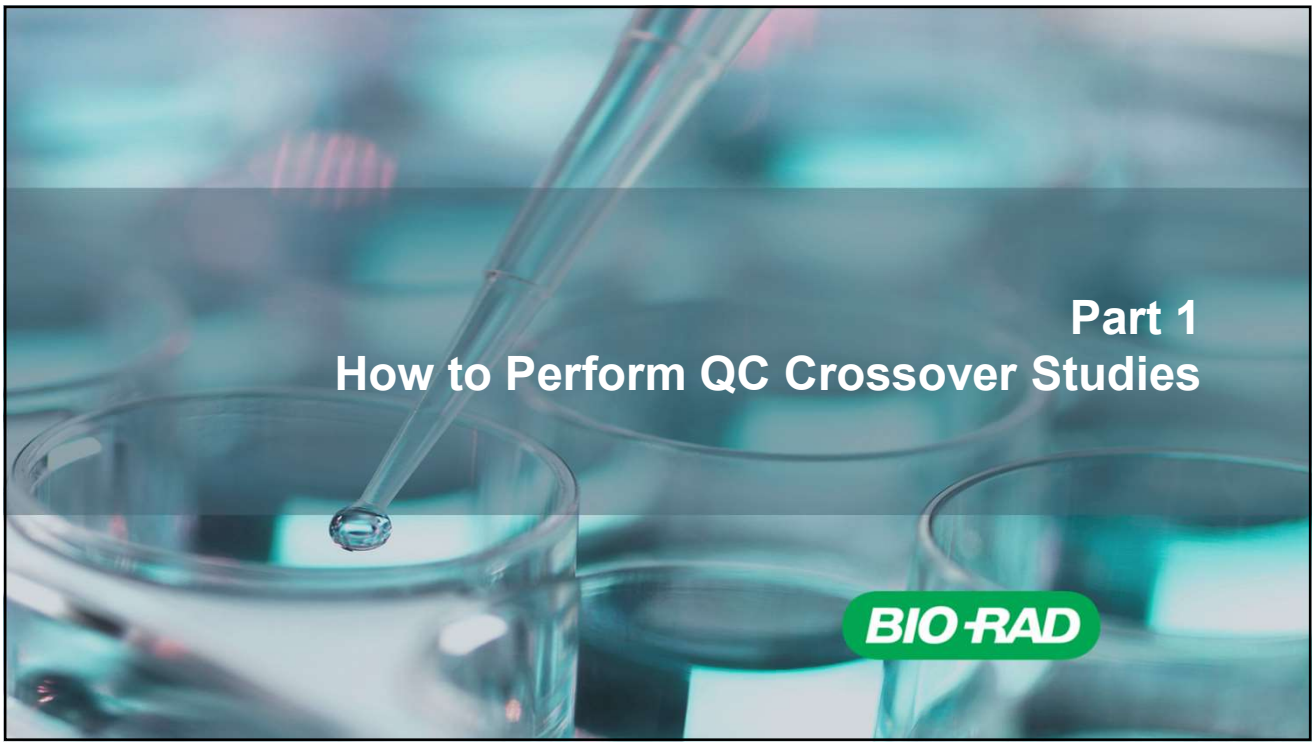
Learning Objectives

- Identify how to establish the new mean and standard deviation (SD)
- Describe the new simplified CLSI C24 (A4) guidance to perform cross-over studies
- Explain how to use QC and patient specimens to verify the integrity of a new reagent lot

2

BIO-RAD

2



3

QC Crossover Studies

- **What's our current process?**
- **Can we simplify our crossover studies?**

(Based upon CLSI C24 A4 Statistical Quality Control for Quantitative Measurement Procedures: Principles and Definitions; Approved Guideline – 4th Edition)

4

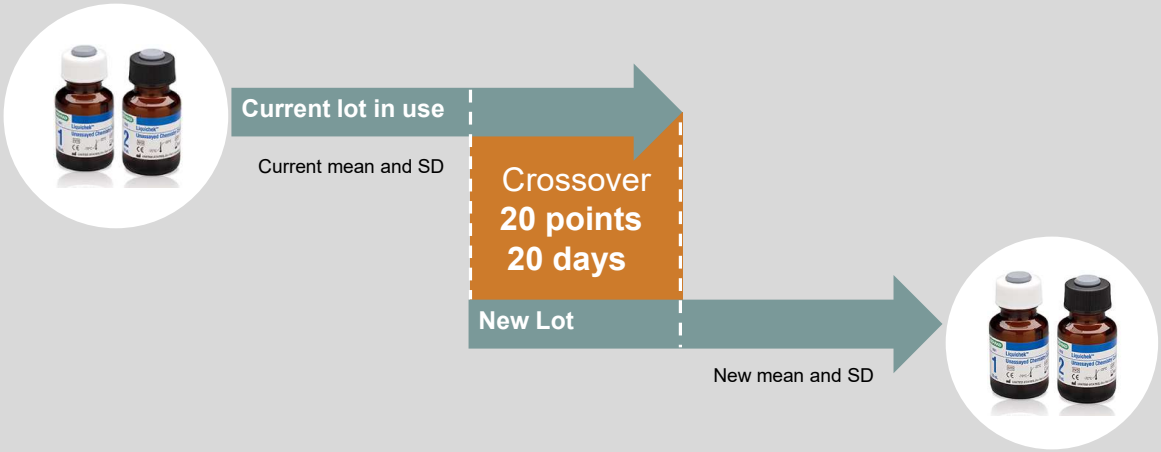
BIO-RAD

4

QC Crossover Studies

Values for the mean and standard deviation (SD) for a control material must be established by the lab.

New lots of control material should be analyzed in parallel with the lot of control material in current use.



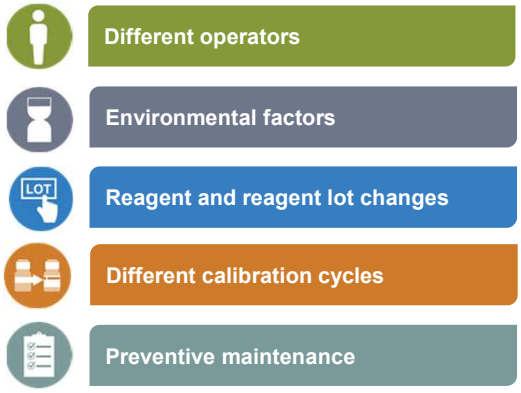
5

6

Determine the New Standard Deviation

Our **current SD calculated over an extended period of time** is the best possible estimation of our imprecision present in the measurement procedure.

It includes many events which influence our imprecision, for example:



7

Determine the New Standard Deviation

When the new target (mean) is close to the current target you can use the same SD.

It's better to use the coefficient of variation CV value to fix the new imprecision (or to calculate the new SD)

Current mean: 120	New mean: 142	New mean: 142
Current SD : 5	Copy SD: 5	Copy CV: 4.16%
Current CV: 4.16%	Current CV: 3.52%	Calculated SD: 5.9

8

BIO-RAD

8

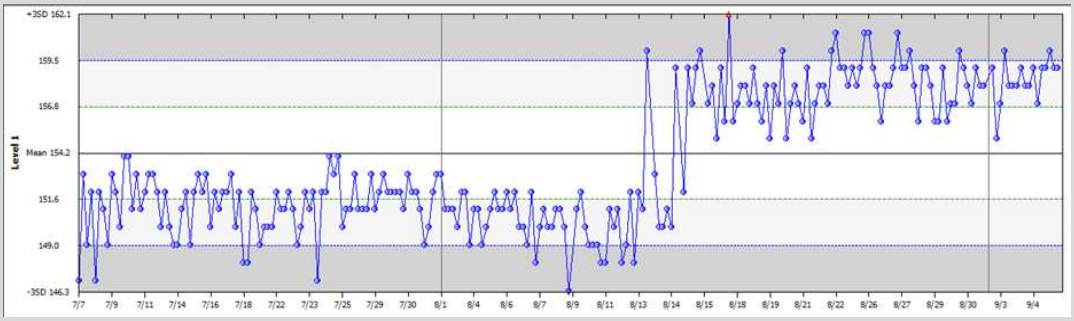
Determine the New Standard Deviation

$$SD_{pooled} = \sqrt{\frac{(n_1-1)SD_1^2+(n_2-1)SD_2^2+\cdots+(n_k-1)SD_k^2}{n_1+n_2+\cdots+n_k-k}}$$

For short shelf life QC materials you can use a pooled SD formula to combine data from different QC lots to estimate the long-term SD (CV).

BIO-RAD

Determine the New Standard Deviation



If the current lot had any shift in values (for example a significant reagent or calibrator lot change) it's better to use a shorter time range to calculate your SD, or use a pooled SD.

Determine the New Standard Deviation

Lot A

Mean:	**15**
SD :	**1.0**
CV:	**6.6%**
Points:	**100**

Lot B

Mean:	**17**
SD :	**1.1**
CV:	**6.5%**
Points:	**150**

Calculating the SD with both datasets across both lots would get you an SD of 1.44 (CV 8.9%)

Calculating a pooled SD will give you a SD of 1.06 (CV 6.5%)

BIO-RAD

Determine the New Standard Deviation

Don't use an insert value range or any other Analytical Performance Specification as your working SD or CV.

Insert ranges are based on a population of instrument variation and are too wide for an individual instrument.
(They are a range in which your target or mean should be located, but not a reflection of your instruments performance)

Analytical Performance Specifications are clinical performance targets only. They might give you a false feeling of control and good performance, but they could be missing statistical relevant out of control conditions.

BIO-RAD

Determine the New Standard Deviation

Don't use an interlaboratory comparison group (peer group) SD.

Peer group SDs reflect the variation of all participating instruments combined and include a bias component. This SD doesn't reflect the individual instrument performance.

Lab 1: 105 mg/dL, SD 5 (CV 4.7%) 20 points
Lab 2: 115 mg/dL, SD 5 (CV 4.3 %) 20 points
Lab 3: 120 mg/dL, SD 5 (CV 4.2 %) 20 points

What is the peer SD?
Mean = 113.33 mg/dL
SD= 7.98 or CV= 7.04%
Points = 60 , labs = 3

13

BIO-RAD

13

14

Determine the Target Value (Mean)

Estimating the target or mean can be done with **10 measurements on separate days.**

- Try to include calibration events during the 10 day interval
- Try to use same QC vial frequency as in daily routine. If you would use a new vial every 2 days, do the same for your crossover
- When your current lot QC shows out of control conditions, always reject the crossover data and extend the crossover period with an additional run.

15

BIO-RAD

15

Determine the Target Value (Mean)

Don't use the insert target value!

These values are provided as a guideline only, each lab needs to verify and establish their own target value

If a target value needs to be established more quickly, more then one measurement a day can be used, but this value should be seen as temporary and updated as soon as sufficient data are obtained.

16

BIO-RAD

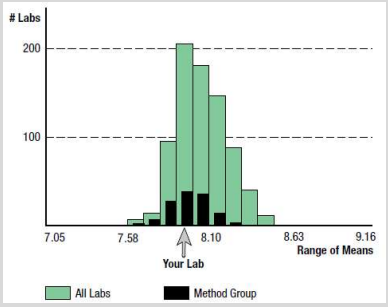
16

Determine the Target Value (Mean)

Don't use an interlaboratory comparison peer group mean!

These values can't be used as an individual instrument value.

Interlaboratory means are calculated across different reagent lots, calibrator lots, types of instruments,… and so do not reflect the actual target in your lab.

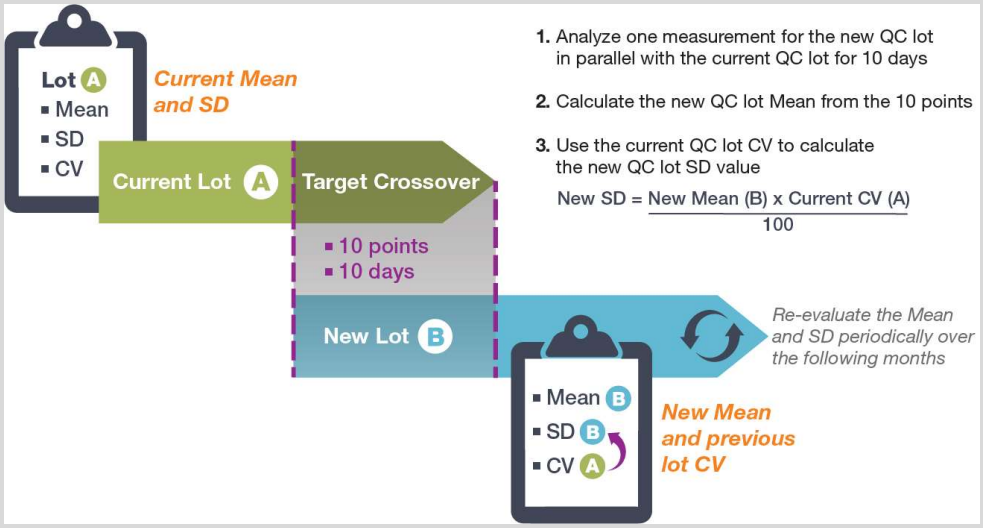


17

BIO-RAD

17

New Crossover Procedure



18

Multiple Instruments

If you use a group mean as target for several instruments combined, then a minimum of 10 points across the instruments would still be sufficient to estimate the target.

Example: 1 QC a day on 4 instruments for 3 days would give you 12 data points.

Measure at least 2 QC points per instrument

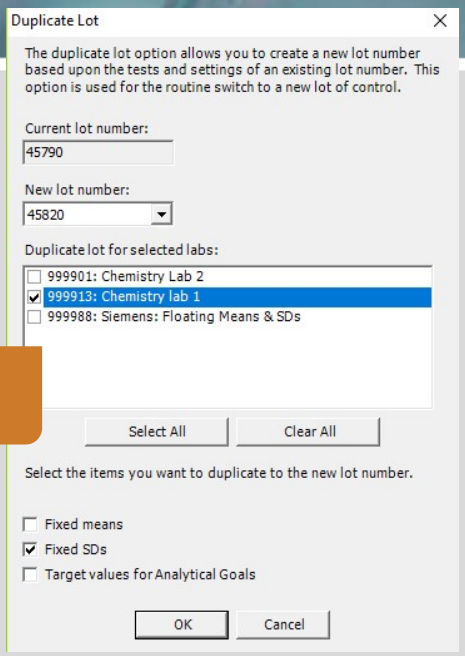
19

BIO-RAD

19

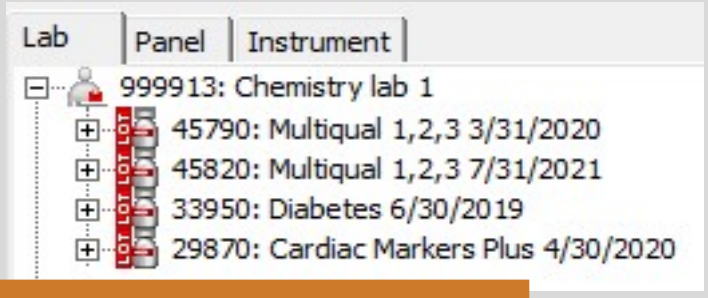
Using Unity Real Time

When duplicating the current lot, we can select to copy over the fixed SD



20

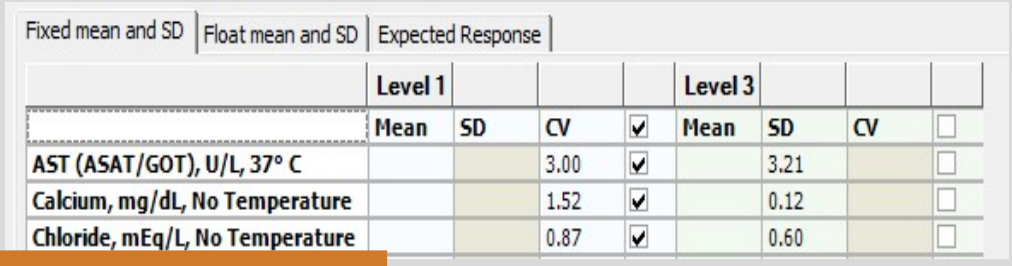
Using Unity Real Time



Now both current lot and new lot are available for data entry

21

Using Unity Real Time

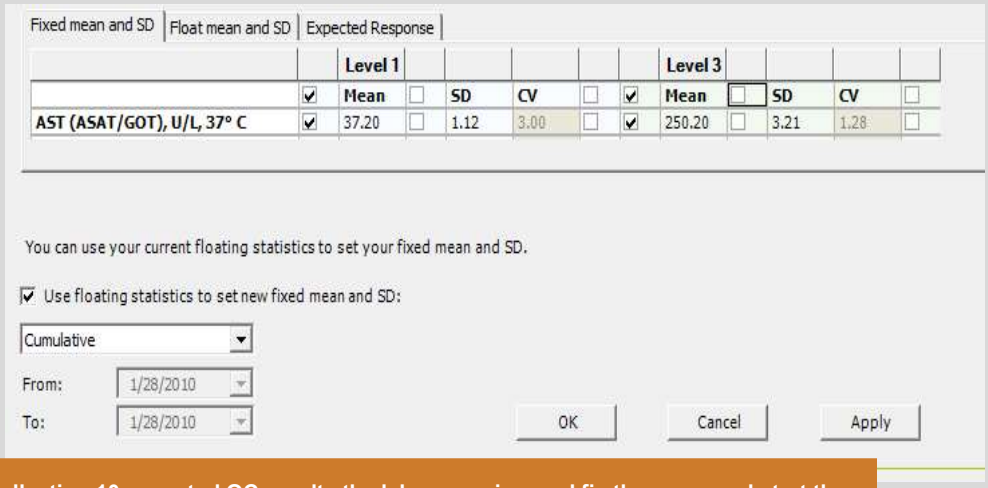


	Level 1				Level 3			
	Mean	SD	CV	☑	Mean	SD	CV	☐
AST (ASAT/GOT), U/L, 37° C			3.00	☑		3.21		☐
Calcium, mg/dL, No Temperature			1.52	☑		0.12		☐
Chloride, mEq/L, No Temperature			0.87	☑		0.60		☐

New lot has fixed CV or SD available

22

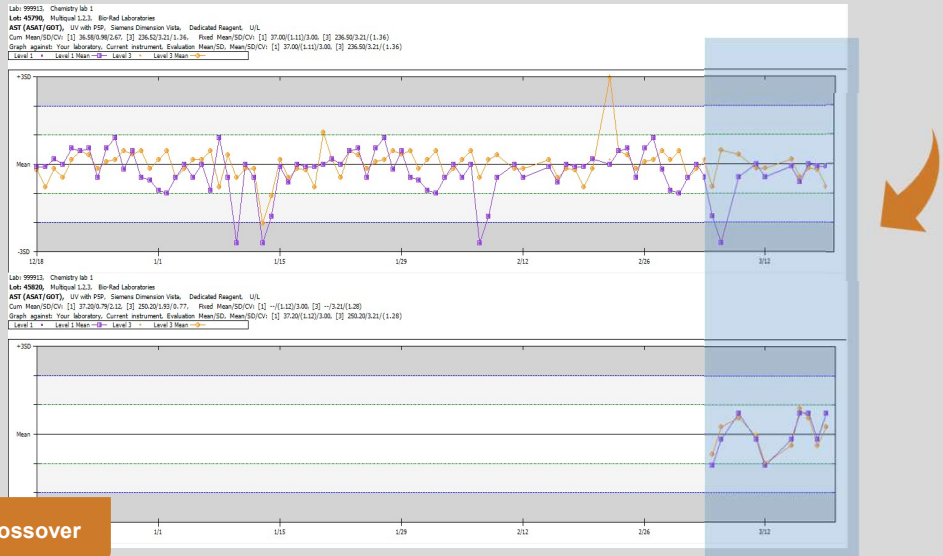
Using Unity Real Time



After collecting 10 accepted QC results the lab can review and fix the mean and start the evaluation of the new lot

23

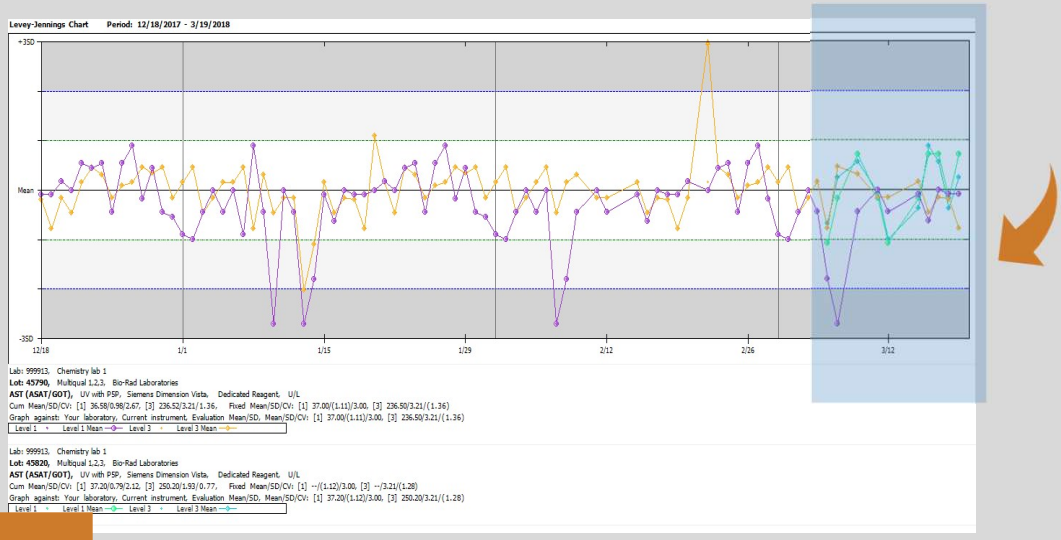
Using Unity Real Time



Crossover

24

Using Unity Real Time



Crossover

25

26

Why Reagent Crossover Studies?

ABC NEWS

Health executive sacked after prostate cancer blunder gives patients wrong diagnosis

By Wendy Glamocak, staff

Updated Sun 3 Apr 2016, 2:47am

About 100 patients in South Australia were given false positive results for prostate cancer in a bungle that has now led to the sacking of a key health executive.

Health Minister Jack Snelling demanded an independent inquiry when he found out from the media about the blunder.

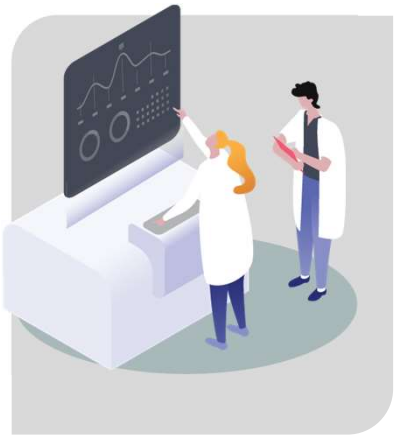
27

BIO-RAD

27

Why Reagent Crossovers are Important

- Test method reagent systems are a critical component to many clinical diagnostics.
- A lot of reagent stored per manufacturer instructions is usually stable until the expiration of the lot, but new lot numbers of reagent must be evaluated to determine if there are any issues or changes with respect to evaluating patients or QC materials.
- A Reagent Crossover is a study to evaluate a possible change in either patient or QC testing from the introduction of a new reagent lot number.



28

BIO-RAD

28

The Matrix Effect

- Sometimes, a reagent lot specific change takes place in QC results while the patient results are not affected.
- Sometimes a reagent lot specific change takes place in patient results while QC results are not affected.
- The differences in the behavior between patient specimens and QC specimens with respect to a reagent lot are called “matrix effects”.
- Both patient and QC specimens must be evaluated on reagent lot changes to ensure the continued production of QC patient results.

29

BIO-RAD

29

CLSI EP26A – Reagent Crossover Studies

The CLSI EP26A User Evaluation of Between-Reagent Lot Variation Guideline describes in detail how to do a Reagent Crossover Study.

EP26-A

User Evaluation of Between-Reagent Lot Variation; Approved Guideline

30

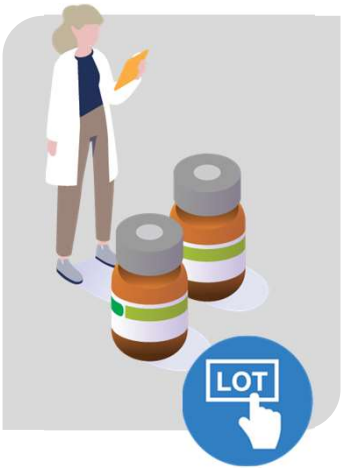
BIO-RAD

30

Overview of Reagent Crossover Study

A Reagent Crossover study must be designed.

- The specified number of patient and QC samples at the required concentrations are evaluated on the current reagent lot.
- The new reagent lot is loaded.
- The patient and QC samples are evaluated on the new reagent lot.
- If the difference between samples on the current and new lots are below the study thresholds, the new lot passes.
- If not, the new lot requires further investigation.



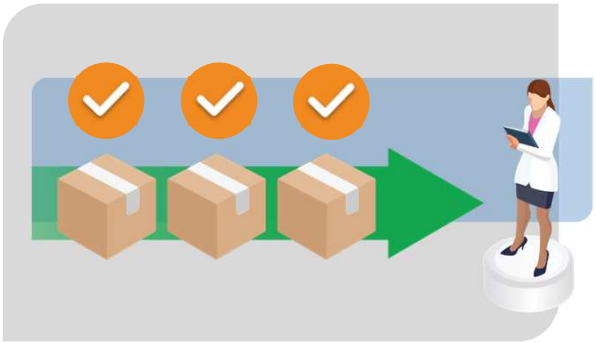
31

BIO-RAD

31

Skipping a Reagent Crossover Study?

- New shipments of a reagent lot that has already passed a Reagent Crossover Study do not need to be re-examined beyond normal QC evaluation.
- Reagent lots that have passed a Reagent Crossover Study with an affiliated laboratory using the same test methods do not need to be re-examined beyond normal QC evaluation.



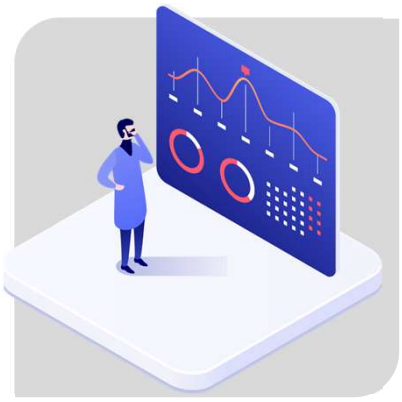
32

BIO-RAD

32

Determining Critical Difference (CD) (1/3)

- The Critical Difference (CD) value for a test method is how much change can be tolerated in a result before it would influence a clinical decision.
- This is very similar to the quality specification for a test method or the TE_a.
- CD values may come from
  - Clinician's Expert Opinion,
  - Biological Variation Studies,
  - State of the Art, etc.



33

BIO-RAD

33

Determining Critical Difference (CD) (2/3)

- Designing a Reagent Crossover Study requires the within-laboratory imprecision (SD_{WL} from EP5) which is referred to as SD_{WRL} and repeatability (SD_R from EP5).
  - SD_{WRL} stands for Within Reagent Lot SD
- SD_{WRL} and SD_R may come from a laboratories' precision studies or from the manufacturer's instructions for use.
- SD_{WRL} and SD_R should be concentration specific.

34

BIO-RAD

34

Determining Critical Difference (CD) (3/3)

Using the Biological Variation approach, we would compute a CD based on the test method RCV computed with the SD_{WRL} expressed as a CV in place of the CV_A in the RCV equation.

$$RCV = 2^{1/2} * Z * [(CV_A)^2 + (CV_w)^2]^{1/2}$$

$$CD = 2^{1/2} * Z * [(CV_{WRL})^2 + (CV_w)^2]^{1/2}$$

For CV_W of 6, CV_{WRL} of 1.6:

$$CD = 1.41*1.96*(1.6^2 + 6.0^2)^{1/2} = 17.2$$

BIO-RAD

Determining Rejection Limits

The Rejection Limit should be based on the clinical utility of the test (like Severity of Harm) where the most critical tests use a low factor (0.6 or 5.5) and least critical tests use a high factor (0.9 or 0.8).

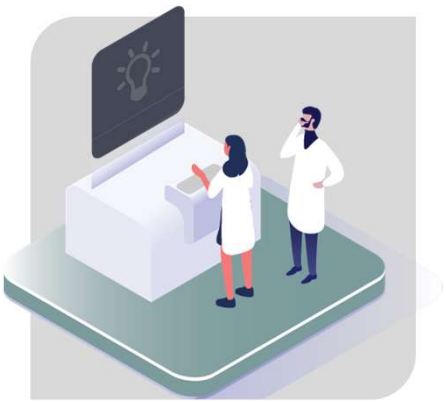
- Reagent Cross Over Study rejection limits are computed as a fraction of the CD.
- CLSI Reagent Cross Over Study Design tables are based on 0.9*CD, 0.8*CD, 0.7*CD, 0.6*CD and 0.55*CD.

BIO-RAD

Determining Sample Concentrations

Ideally, Reagent Cross Over Study samples should be at concentrations that match clinical decision points.

- The number of sample concentrations should match the number of clinical decision points.
- Reagent Cross Over Study design guidance from CLSI is provided for 1, 2, or 3 sample concentrations.
- Matching patient samples with concentrations near QC levels is also desirable.



BIO-RAD

Determining Number of Samples (1/3)

- The Appendix Tables A1, A2, and A3 of EP26 should be used to determine the number of samples at each concentration.
- Table A1 is for a single concentration, A2 for 2 concentrations, and A3 for 3 concentrations.
- These tables determine how many samples are required for a given Rejection Limit, and what the false positive rate and power of detection are.

BIO-RAD

Table A2 for Two Concentrations

Table A2. Sample Size to Detect a CD Between Reagent Lots for Two Decision Limits (With False Rejection Rate ≤2.5% for Each Comparison)

		Number of Samples to Compute Mean Difference (False Rejection Rate, Power if True Difference=CD)				
		Rejection Limit for Mean Difference				
CD/S_{WRL}	S_r/S_{WRL}	0.90•CD	0.80•CD	0.70•CD	0.60•CD	0.55•CD
1.0	1.00	13 (0.022, 0.601)	16 (0.024, 0.714)	21 (0.023, 0.835)	28 (0.025, 0.933)	34 (0.023, 0.968)
1.0	0.95	—	—	—	—	—
1.5	1.00	6 (0.019, 0.602)	7 (0.025, 0.713)	10 (0.019, 0.843)	13 (0.022, 0.937)	15 (0.024, 0.968)
1.5	0.95	11 (0.024, 0.599)	20 (0.025, 0.713)	74 (0.025, 0.832)	—	—
1.5	0.90	—	—	—	—	—
2.0	1.00	4 (0.011, 0.611)	4 (0.024, 0.714)	6 (0.015, 0.851)	7 (0.025, 0.933)	9 (0.020, 0.972)
2.0	0.95	5 (0.016, 0.606)	6 (0.023, 0.715)	10 (0.022, 0.836)	20 (0.025, 0.933)	40 (0.025, 0.967)
2.0	0.90	7 (0.021, 0.601)	13 (0.024, 0.713)	160 (0.025, 0.832)	—	—
2.0	0.85	17 (0.024, 0.599)	—	—	—	—
2.0	0.80	—	—	—	—	—
2.5	1.00	2 (0.024, 0.599)	3 (0.014, 0.730)	4 (0.013, 0.856)	5 (0.018, 0.943)	6 (0.017, 0.974)
2.5	0.95	3 (0.012, 0.610)	4 (0.013, 0.733)	5 (0.019, 0.843)	8 (0.021, 0.938)	10 (0.025, 0.967)
2.5	0.90	3 (0.019, 0.603)	4 (0.024, 0.714)	8 (0.022, 0.837)	24 (0.025, 0.933)	—
2.5	0.85	4 (0.019, 0.603)	6 (0.025, 0.712)	27 (0.025, 0.832)		

CLSI. *User Evaluation of Between-Reagent Lot Variation; Approved Guideline.* CLSI document EP26-A. Wayne, PA: Clinical and Laboratory Standards Institute; 2013.

BIO-RAD

Determining Number of Samples (2/3)

To use the CLSI table, you need to compute 2 ratios:

- **CD/S_{WRL}**
- **S_R/S_{WRL}**

- CD/S_{WRL} is the ratio of the critical change to the analytical precision – the higher this is, the lower the number of samples is required.
- S_R/S_{WRL} is the ratio of repeatability to analytical precision. The smaller S_R is compared to S_{WRL}, the higher the number of samples is required.

BIO-RAD

Determining Number of Samples (3/3)

- First locate the section of the table that matches your CD/S_{WRL} ratio. For values in between, choose the next lowest value.
- Next choose the row that matches your S_R/S_{WRL} and your CD/S_{WRL} ratio.
- Use the column that corresponds to your Rejection Limit.
- The number outside the parenthesis is the number of samples required. The first number inside the parenthesis is the probability of a false positive result, the second number is the probability of error detection.

BIO-RAD

AST Example with 2 Sample Concentrations

Target Concentration	CD	S_{WRL}	S_R	Rejection Criteria	CD/S_{WRL}	S_R/S_{WRL}
40 IU/L	10	1.3	0.8	0.7*CD	7.7	0.62
200 IU/L	20	4.1	1.3	0.7*CD	4.9	0.32

BIO-RAD

AST Example with 2 Sample Concentrations

For 40 IU/L, CD/S_{WRL} = 7.7, S_R/S_{WRL} = 0.62

		Number of Samples to Compute Mean Difference (False Rejection Rate, Power if True Difference=CD)				
		Rejection Limit for Mean Difference				
CD/S_{WRL}	S_r/S_{WRL}	0.90•CD	0.80•CD	0.70•CD	0.60•CD	0.55•CD
6	1.00	1 (0.000, 0.664)	1 (0.001, 0.802)	1 (0.003, 0.898)	1 (0.011, 0.955)	1 (0.020, 0.972)
6	0.95	1 (0.000, 0.664)	1 (0.001, 0.802)	1 (0.003, 0.898)	1 (0.011, 0.955)	1 (0.020, 0.972)
6	0.90	1 (0.000, 0.664)	1 (0.001, 0.802)	1 (0.003, 0.898)	1 (0.011, 0.955)	1 (0.020, 0.972)
6	0.85	1 (0.000, 0.664)	1 (0.001, 0.802)	1 (0.003, 0.898)	1 (0.011, 0.955)	1 (0.020, 0.972)
6	0.80	1 (0.000, 0.664)	1 (0.001, 0.802)	1 (0.003, 0.898)	1 (0.011, 0.955)	1 (0.020, 0.972)
6	0.75	1 (0.000, 0.664)	1 (0.001, 0.802)	1 (0.003, 0.898)	1 (0.011, 0.955)	1 (0.020, 0.972)
6	0.70	1 (0.000, 0.664)	1 (0.001, 0.802)	1 (0.003, 0.898)	1 (0.011, 0.955)	1 (0.020, 0.972)
6	0.60	1 (0.000, 0.664)	1 (0.001, 0.802)	1 (0.003, 0.898)	1 (0.011, 0.955)	1 (0.020, 0.972)
6	0.50	1 (0.000, 0.664)	1 (0.001, 0.802)	1 (0.003, 0.898)	1 (0.011, 0.955)	1 (0.020, 0.972)

Use 1 sample near 40 IU/L

CLSI. *User Evaluation of Between-Reagent Lot Variation; Approved Guideline.* CLSI document EP26-A. Wayne, PA: Clinical and Laboratory Standards Institute; 2013.

43

BIO-RAD

43

AST Example with 2 Sample Concentrations

For 200 IU/L, CD/S_{WRL} = 4.9, S_R/S_{WRL} = 0.32

		Number of Samples to Compute Mean Difference (False Rejection Rate, Power if True Difference=CD)				
		Rejection Limit for Mean Difference				
CD/S_{WRL}	S_r/S_{WRL}	0.90•CD	0.80•CD	0.70•CD	0.60•CD	0.55•CD
4.5	0.60	1 (0.004, 0.625)	1 (0.011, 0.738)	2 (0.014, 0.854)	5 (0.024, 0.934)	—
4.5	0.50	1 (0.004, 0.625)	1 (0.011, 0.738)	2 (0.017, 0.846)	—	—
4.5	0.40	1 (0.004, 0.625)	1 (0.011, 0.738)	2 (0.020, 0.840)	—	—
4.5	0.30	1 (0.004, 0.625)	1 (0.011, 0.738)	2 (0.023, 0.836)	—	—
5	1.00	1 (0.001, 0.638)	1 (0.005, 0.760)	1 (0.013, 0.856)	2 (0.003, 0.977)	2 (0.006, 0.988)
5	0.95	1 (0.001, 0.638)	1 (0.005, 0.760)	1 (0.013, 0.856)	2 (0.004, 0.972)	2 (0.009, 0.984)
5	0.90	1 (0.001, 0.638)	1 (0.005, 0.760)	1 (0.013, 0.856)	2 (0.006, 0.967)	2 (0.012, 0.980)

Use 2 samples near 200 IU

CLSI. *User Evaluation of Between-Reagent Lot Variation; Approved Guideline.* CLSI document EP26-A. Wayne, PA: Clinical and Laboratory Standards Institute; 2013.

44

BIO-RAD

44

AST Example with 2 Sample Concentrations

Analyte	Target Concentration	Current Lot Result	Candidate Lot Result	Difference	Average Difference
AST	30–50 IU/L	62	62.6	0.6	0.6
	200–400 IU/L	285.7	284.3	−1.4	
		361.8	350.7	−11.0	−6.25

Analyte	Decision Concentration	Absolute Value of the Average Difference	Rejection Limit	Acceptable?
AST	40 IU/L	0.6	7	Yes
	200 IU/L	6.25	14	Yes

CLSI. *User Evaluation of Between-Reagent Lot Variation; Approved Guideline.* CLSI document EP26-A. Wayne, PA: Clinical and Laboratory Standards Institute; 2013.

45

BIO-RAD

45

46