

Best Practices for Lot Changes in Quality Control or Reagents

Questions and Answers

Part 1 Best Practices for quality control lot changes

- 1. We run some tests such as 17OHP using RIA where it's not practical to run over 10-20 days to establish a mean. We only run this test once/week. How would you suggest that we establish a range for such testing?**

10 data points to establish a new mean are sufficient, but if here it would take 10 weeks to establish a new mean if you would only measure 1 result every run. In order to speed this up I would think that 3 to 4 runs would probably be ok to capture some of the variation between the runs. So maybe measure your new lot 3 times in a run for 4 runs (12 data points). Just think about monitoring the mean then when you get more data points.

- 2. If we are verifying our own in-house controls, is it recommended to use an external control to help establish the target?**

If your in-house control is like a pooled patient sample or another material not produced by the manufacturer then you can use the same process to establish a mean and SD. It is always a good practice to use an independent control instead or in addition to a manufacturer or in-kit control. But you would not need an external control to establish your in-house control target, that would just be done with the in-house material itself.

- 3. Do you evaluate assayed vs. unassayed controls differently?**

No, even for assayed controls you should establish your own targets.

- 4. Do you need more than 10 points for unassayed QC?**

No, establishing a new QC mean can be done with 10 data points for unassayed or assayed materials.

- 5. I was told I can't have my new lot interface and it would all have to be manually entered. Is this true? I was told it is because Unity will only take 1 active lot per QC material.**

Unity Real Time and UnityWeb can both have multiple different lot numbers in use at the same time. So this might have been a misunderstanding. Please feel free to contact your local Bio-Rad support group for advice.

- 6. What if due to supply issues or shipping issues we are unable to get 10 days worth of data prior to the old lot expiration? Should we just collect 10 data points to allow us to form the new mean?**

Yes, if due to any reason you can't measure during 10 days you can establish the mean faster, but you should then update the targets later when you have more data available. Even when you only have 1 day to set the target, try to measure multiple data points over different runs.

- 7. We do not have Unity Real Time right now (we use Unity 2.0). Is there a way to calculate the changes on the Unity 2.0 like you showed us with using Unity Real Time?**

If you use the online solution Unity Web 2.0 you have a fixed mean and SD setup screen in the Configure, Rules/Settings screen which provides the same functionality. Please contact your local support team for more information.

- 8. Please explain this floating and fixed statistics in unity for a crossover event. What is fixed CV versus floating CV ? Which should be used?**

When starting a new QC lot you can enter 10 results in the data entry screen. At that time you would not yet have a fixed mean established, so the fixed mean field is empty. You would have copied over your current QC lot CV when duplicating the lot. Once you have 10 data points in your new QC lot you can use the option called "Use floating statistics to set new fixed mean and SD". When you check that option you can select multiple date ranges to calculate the mean (make sure you uncheck the SD and CV boxes at the top of your table as you don't want to update these values). I used the cumulative selection in the presentation and that will use all your data to calculate and display your mean value. Apply or Ok will confirm and save these values as fixed. Please contact your local support team if you want more information.

- 9. Does it have to be 20 days, can it be 20 points?**

The CLSI C24 guidance only requires 10 data points to establish your new mean. It's best to measure during 10 days as that includes more variation like different reagent vials, calibrations, maintenance, ...

10. Do you have to choose to copy fixed SD or CV when using Unity Real Time to manage parallel testing?

Using the fixed CV will make sure you have a similar evaluation set. If you would copy the SD and the mean of the new lot changes significantly your imprecision target will be changed to. In Unity Real Time that means you must make sure you have the CV set as the fixed value in your evaluation mean/SD screen. When you then duplicate the lot and ask to copy the fixed SD (which is the only option) it will copy the CV.

11. Since we don't live in an "Ideal" world to be able to obtain 20 points over 20 days, how can we start our new QC lot data collection that we just received while our current QC will expire the next day?

The new CLSI C24 guidance only requires 10 days and 10 data points to establish your new mean. You copy the CV from the lot in use over to the new lot. If for any reason you don't have the 10 days available then all you can do is try to measure your 10 data points over as long a period as you can. If that's only 1 day then try to measure during different runs and try to include as much variation as possible. Also remember to update your mean later as you collect more data.

12. We have always used 20 data points of QC to establish new mean. Am I understanding that you need 20 data points for SD but only 10 to establish a new mean?

You don't need to establish a new SD, you can use the current lot SD (or better CV) to set your new lot target. And for your mean you only need 10 points during 10 days to estimate your mean target. If you would have a brand new control and no previous data you would still use 20 points over 20 days to establish both mean and SD.

13. Due to shipping affected by the weather, I only have 5 days to establish ranges for my new lot numbers. Can I do 4 runs per day for 5 days?

You only need 10 points to establish a new mean, so if you only have 5 days than 2 runs a day for 5 days would be sufficient. But this value should be seen as temporary and updated if needed as soon as you have more data available.

14. Would it be appropriate to establish your own QC ranges, if recovery is not that of the package insert?

Yes, you should always establish your own ranges. You can use the insert range as information and your QC mean should be within the range of the insert (if not it's better to contact the manufacturer).

15. Out of all the reports available in the Unity Interlaboratory program, which reports are most insightful in test performance?

All Unity reports can be used to monitor your labs performance, but the Laboratory Comparison report has your most current data available and the Histogram reports shows you a 12 month overview of your labs performance

16. If new reagent and QC lots are available, which crossover study should be done first? should we verify both new reagent and new QC lot at the same time?

As it is faster to crossover to a new reagent lot, I would do that first.

17. How effective is Pre and Post calibration specimens to validate lots/QC?

While using calibration specimens is interesting, it would be better to use specimens that are independent of the test method.

18. What is your %bias limit before you need to change your target mean?

Good question. There is no real value which would indicate at what time a difference between the fixed mean and the actual mean would need a reset of the mean. We always want to see if the drift or shift can't be corrected first? If not we might need to adjust the mean, most of the time you will see more rejections appear during the normal runs which would need rework, when this starts to increase it's probably time to adjust.

19. For Nico, Is there a different approach for qc determination for coagulation studies (eg. clotting assay)

No, I would use the same approach for a new QC lot for coagulation.

20. Will you please explain the value of comparing peer group targets to my instrument on a monthly basis.

When participating in an interlaboratory program like Unity where your daily QC is compared to a peer group a monthly comparison is a quick check. As long as your QC results haven't shifted during the last 30 days, you will not be moving away from the peer group. But sometimes events happen where smaller shifts might not be picked up by the internal QC due to wider ranges for example and these could be picked up by a peer group comparison. Unity reports offer a Monthly Evaluation report which only list analytes outside a 2 SDI limit of your peer group.

21. Can we use manufacturer's CV to initially establish SD?

It's always better to establish your own SD or CV. If you have a new control (so no previous data) you can start with 20 datapoints to estimate the initial CV. If you don't have time to establish your own SD or CV you could use the manufacturer SD or CV to start with, but update this value as soon as you have more datapoints available.

22. My facility is using a CLSI Acceptable limits approach to getting an SD. There was a presentation from another company that expressed this "new way" to set the SD which takes the Acceptable Performance Limit of say, 15% for example, and dividing that by 3 to get a CV of 5%. I am for a more conventional QC approach and appreciate this CE. What is my best course of action to encourage change, or moving towards a more conventional QC program?

Based on our experience and many other sources, using an Analytical Performance Goal as a QC limit is not the best practice. For some analytes this limit might be close to the actual performance, but when the target is too wide you might miss significant statistical errors. Even if these would not lead to clinical errors it's still best practice to detect and correct these errors. Using a Levey-Jennings chart can help to visualize if these limits would be too wide.

23. What is the best way to document this testing both reagent and QC? Is there a program? Right now our lab documents on paper which isn't easy to document all of these statistics.

There are many Laboratory Information Systems that can provide a solution to document your QC and reagent crossover studies. Bio-Rad's Unity Real Time software can help with the QC crossover study documentation.

24. Which SD formula should be used for Excel?

For a regular QC SD you can use the STDEV command in excel

25. If I get 1 mean at 120 and my new mean is 110. CVs are the same.

What does this mean for my sample measurement? are samples then also measured lower? Do I have to work with a factor then?

No, if you start a new QC lot the change in target for a QC lot does not affect any patient results. As long as your current QC is stable and no other changes were made to the measuring system you can change the target for the new QC and continue. The change in value is due to the change in QC material, it will not affect the patient results.

26. Nico, what is the formula for finding the SD for pooled QC?

If you are pooling patient samples to make your own QC then you can use the same formula's to calculate the SD. If you are referring to the pooled SD formula then this is the formula

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

27. How do we measure a new control across multiple analytes? For example, we do a solid-phase antibody test with an array of microspheres. Each test well has a matrix of 100 analytes.

If a composite result is derived from the multiple analytes, I would focus my cross-over study on that. If each of the 100 analytes is reported individually, then you need to evaluate them individually. Hopefully with a small number of patient specimens that can be used for multiple analytes.

28. Patient base daily QC ? recommended

Patient based QC is a great additional tool to monitor the instrument performance in real time. It should be used in combination with the current traditional QC as it also has some limitations.

Part 2 Best Practices for reagent lot changes

29. Can Proficiency Testing samples be used in reagent crossover study if we don't have patient samples with the analyte concentration we want?

Yes, if no patient samples are available at the needed concentrations or the analyte isn't stable enough you can use other materials with an assigned value.

30. Is there a handout with Mr. Yundt-Pacheco's formula referred to in the presentation?

Yes, you can find the presentation handout and the summary handout in the event resources on the top right of your webinar page.

31. Doesn't the manufacturer address matrix effect before sending new lots? Can you use that data to confirm conformability?

There is no way for a manufacturer to check for matrix effects on all the available QC materials - and in some cases, the matrix effects are acknowledged by the manufacturer.

32. John, how is the rejection limit determined in the last slide?

The rejection limit is the fraction of the CD that is used to determine acceptability. You can either base the fraction on the criticality of the test - 0.55 for critical tests, 0.9 for non-critical tests, or you can search for the first column in the EP-26 appendix that has a probability of error detection of > 0.9 and use the corresponding fraction. The rejection limit is computed as the fraction*CD.

33. Reagent crossover studies are not usually carried out by manufacturers? Or in case they are done, do we need to perform the analysis locally?

This needs to be done either locally or in conjunction with another lab. The reagent crossover study is an independent check on the quality of the manufacturer's product.

34. When a mean shifts with a reagent lot change, how do you recommend using peer data to justify a mean adjustment?

At this time most peer group values are calculated across reagent lot numbers, so there is no real way to use the peer group as a justification for a reagent lot shift. In extreme cases where reagent lot changes create significant changes in the peer data Bio-Rad will advise to select a specific reagent code to identify your reagent lot number. You should use the EP26 patient sample protocol to define if the change is acceptable or not.

35. What are your thoughts on the Percentiler and Flagger programs developed by Belgian scientists to use patient results for QC over time ?

While I am not familiar with these specific programs, I am a huge fan of using patient results for QC, I think that monitoring patient statistics has high value.

36. Please explain how to determine SDwrl, SDwl, and SDr again. What samples to use and how many ? Give concrete examples of how each would be determined

The SDwrl and SDwl are the same thing - they refer to the SD of the reagent lot. The SDr is repeatability. The CLSI document EP5 - Evaluation of Precision for Quantitative Measurement Procedures details the necessary experiments to compute them. You can use the within lot SD of your quality control material for SDwrl.

37. Do assay manufacturers run patient samples to check potential impact of their reagent lot changes on patient results ?

While most manufacturers test reagent lots with patient specimens, this is not universally true. The reagent crossover study is the final check that the reagent lot, as it has arrived at your lab performs in an expected way.

38. If you do not have endogenous patient samples for a crossover study that report where is needed, is it acceptable to spike matrix with recombinant material to test?

The critical thing to do is evaluate the suitability of a new reagent lot for your use. Normally, this requires the evaluation of patient specimens. If these are not available, then use the closest thing you can get to them - which may be a spiked specimen.

39. Is adjusting the mean within 5% acceptable?

The rejection limit depends on the quality specification of the test (the CD) and how much power of detection is needed (the fraction of the CD). Whether 5% is acceptable depends on the test method.

40. Does a lot to lot need to be performed for all reagents or only reagents that do not have a set of calibrators?

All reagents, there can always be a change in performance due to changes in reagent component materials, instability of a component of the reagent or issues during transport.

41. John, how do I troubleshoot patient crossover studies when analyte stability is questionable?

For analytes that are not stable for the time that it takes to either change reagent lots or repeat, I would look at the change seen between running the specimen twice on the current reagent lot (with the time between evaluations equal to the time to change lots) and then do it on the new lot. You expect to see something similar between the specimen ran twice on the current lot and the specimen ran on the current and new lot. I would use at least 3 specimens to get a good assessment of the performance. If the performance is questionable, I would do this in both directions - from the new lot to the old lot and from the old lot to the new lot.

42. John, if a reagent crossover study fails, can a repeat study be done to approve the lot or would a larger sample size be needed to combine all of the data and get a total picture?

Yes - this is good practice. Running a larger study requires more work and is more expensive but will give you more accurate results. For a reagent crossover study that did not very clearly fail, I would evaluate more specimens and more replicates to increase the power of detection.

43. I'm sure this is best practice, but golly...we are dealing with hundreds of chemistry lot changes per year and have never done these calculations. We are lucky to get techs to run 3 samples hoping to cover the reportable ranges as best a possible and then use our established TEa's to determine acceptability for controls and patient results as well as confirming that QC is within assay or peer range. Would you consider this an acceptable cross over study?

I think you should consider using a fraction of your TEa for the limit, but the rest sounds very reasonable.

44. What should be done if QC does not shift with new reagent lot, but patients do? Does this rule out matrix effect? Should this reagent lot be rejected if you can rule out sample handling problems?

Having the patients shift, but not the QC can happen. When it does, you need to make sure that there are no clinical implications to the patient shift and to alert those using your results if there are. A significant shift in patient results will likely require different reference ranges and a notification to the clinicians that the new results need to be considered independently from prior results.

45. What should you use if you do not have patient samples near the cut off values for reagent cross over studies?

Use what you can find. Closer is better, but any viable patient specimen is better than none.

46. We are a veterinary lab. We make our QCs from pooled patient samples. Is running these sufficient to track reagent lot variation?

I think the key thing is to use actual patient specimens to check for matrix effects - using pooled patient specimens works.

47. What are the acceptance criteria to validate the lot comparisons when we carry out the experiments-?

Use rejection limits derived from your quality specification (TEa) - the CD and the fraction suitable for the criticality of the test.

48. In regard to using reagent lot evaluations, most vendors will do this. Does that mean utilizing their evaluation and our assessment of QC would be adequate in your opinion?

As long as the assessment is done in a lab testing patient specimens, with patient specimens - yes. As a reagent crossover study is the final, independent check on the quality of the manufacturer's product, it should not be done by the manufacturer.

49. We perform Immunoassay tests, that we may not run weekly (or before the specimens are not stable. How do we do reagent crossover testing on these tests?

If possible, save specimens for this purpose. For analytes that are not stable for the time that it takes to either change reagent lots or repeat, I would look at the change seen between running the specimen twice on the current reagent lot (with the time between evaluations equal to the time to change lots) and then do it on the new lot. You expect to see something similar between the specimen ran twice on the current lot and the specimen ran on the current and new lot. I would use at least 3 specimens to get a good assessment of the performance. If the performance is questionable, I would do this in both directions - from the new lot to the old lot and from the old lot to the new lot.

50. For John, how do you determine the acceptable range of a patient sample "around 40 IU/L"?

You can use +/- 40 or the nearest that you can get. The 2 main concerns are to evaluate something near the decision limits and near the concentration of your precision studies.

51. Hello Sir, what shall we do when our calibrator lot is changed?

Unfortunately, there is not general guidance for calibrator lot changes as this may be very dependent on your test method. You need to follow manufacturer recommendations.

The following questions were asked during the presentation. Please see the webinar recording for the responses.

1. Do I really need to use patient specimens for a reagent crossover study?
2. How often do I need to check my mean and SD values if they are still appropriate?
3. Should we also establish new means for each different QC or reagent shipment?
4. Can I establish my mean value in multiple measurements on the same day?
5. Do I have to remove outliers from my crossover period?
6. How can I tell if there has been a change in performance with my new lot of reagents?