Best Practices in Quality Control

10 Simple Recommendations Webinar
Questions and Answers

1. **How should harm be categorized when the analyte has more than one clinical application? Select the most severe?**

   If the laboratory reports the same analyte results to different clinical departments for different applications, then choosing the most severe category is the safe choice. For example, if there are about equal situations where the severity is expected to negligible and minor, then if you design your quality control for minor severity the negligible cases will also be covered. However, if in 95% of situations it is expected the severity would be minor, but in 5% of cases it could be critical then designing your QC as if all cases of harm would be critical might put an unacceptable burden on your QC effort. In a situation like this, the lab might need to look for other ways, in addition to their QC, to reduce the risk for those potentially critical severity situations. This is an example of where input from medical professionals in the laboratory is valuable.

2. **Did you say people should not use the 10X rule? What does that mean?**

   Many laboratories don't really act on the 10x rule when it's flagged because often it turns out to be a false rejection, or at best, it indicates a small out-of-control shift of minor significance from a patient risk perspective. Often, the false rejection rate for the 10x rule is higher than expected because the established QC rule target is not exactly equal to the measurement procedure's in-control mean. The consensus of the document develop committee for the 4th edition of CLSI C24 was not to mention the 10x rule in the document, because the committee felt it had little to no value. The collective experience of the committee was that most labs either ignore the 10x rule or do not use it.

3. **Please explain how bias is calculated in the sigma analysis. Is the bias relative to CAP peer group?**

   The CLSI C24 4th edition discusses three different ways to assess bias for developing QC strategies.
   - The optimal approach is to compare results from fresh patient samples using the lab's measurement procedure and a reference measurement procedure. Of course, this approach is impractical in most situations.
   - A second approach is to assess relative bias by comparing your lab's results to a peer group mean. That can be done for example with the Bio-Rad Unity program where your internal QC is compared to your peers and can calculate your sigma in the data management software. But if you have another way of estimating your bias like a proficiency test program that can be also be used. Just try to estimate the bias you use in your calculation on more than just one measurement

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and it should reflect the same concentration used to calculate the CV part of the sigma formula. Alternatively, if your laboratory has more than one of the same measurement procedure performing patient testing, then each of your individual measurement procedures can be compared to the group mean of the multiple measurement procedures in your lab.

- Lastly, is to assume bias is equal to zero for the purpose of QC planning. The actual bias may not be zero, but in many cases, it may be small enough that it can be treated as zero. Just be aware that if you estimate bias it should be estimated at the same concentrations used to calculate the SD part of the sigma formula.

4. **How do these QC practices translate to molecular genetic assays, such as genotyping or sequencing, where TEa is typically not applicable?**

   Yes, it is not common yet to use an allowable total error in molecular genetic assays, especially if there is only a qualitative response reported. But more and more labs start using the underlying quantitative responses like the Ct (cycle threshold) to record the quality control results, and for some test like viral loads you can already estimate a clinical total error in units when a clinician might change therapy. This value can be used as a total error to calculate the test performance.

5. **Can a lab adopt a 1-2.5s rule especially in resource constrained areas with only one level of control?**

   Yes. The 1-2.5s rule will have a lower false rejection rate then a 1-2s but will also have a lower probability of error detection for smaller error conditions. When you design your QC then high performing tests (with high sigma) value wouldn't need a 1-2.5s rules, they are monitored with a 1-3s rule or even higher rule. But if you look at the difference between a repeat 1-2s rule and a 1-2.5s rule the repeat 1-2s rule will still be stronger at detecting these smaller error conditions with a smaller false rejection rate.

6. **Is there any reference for risk in general by test, since all laboratory measure the same analyte?**

   Not really, as the risk is based upon the clinical application of the test different laboratories will have different targets. Some laboratories might also allow a higher risk depending on the clinical setting of the lab.

7. **What about QC for pre-analytical variables, e.g. specimen transport? These are elements that affect results but are not related to the analytical standards and TEa.**

   You make an important observation. Quality control based on the periodic testing of quality control materials is designed to control the analytical phase of the testing process. However, we know that a large amount of laboratory error can be attributed to the pre-analytical phase. This realization led to the development of laboratory risk management guidelines such as CLSI EP23. It discusses quality management practices that primarily focus on the pre- and post-analytic phases of the testing process.

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Therefore, CLSI EP23 in combination with CLSI C24 cover quality control design and implementation for the entire testing process.

8. **For around a 1,000 samples, how many QCs (runs and levels) is necessary which is cost effective as well and that ensures best results?**

   I can't answer this without more information. This all depends on the analyte, the measurement procedure, and the patient-care implications. As shown in the presentation, it will be easier to control a reliable, high sigma test with low severity of patient harm consequences than an unreliable, low sigma test with high severity of harm consequences. There are tools on the market like Bio-Rad Mission:Control software which can help you to design your quality control plan based upon your labs data and settings.

9. **For analytes whose reagents are limited by number of tests per cartridge and, for example, must be mixed together before use, should QC frequency be adjusted to account for this risk?**

   This would depend on the risk that the preparation of these reagents would fail and influence the results of the samples. Some reagents are very stable and robust and small dilution errors would not really affect the results. On the other side some reagent errors might have such a big effect that you would immediately notice this. Laboratories which have such a high throughput that the largest reagent volumes would already be finished between quality control events might need to evaluate that risk. Some newer instruments can already be programmed to perform a quality control at the start of each new reagent vial.

10. **Around the world, does Bio-Rad implement and ensure stringent QC rules?**

    I would not say Bio-Rad implements the QC rules, the laboratory is responsible to implement the QC rules and plans. Bio-Rad can provide the lab with the tools, education and latest guidelines to evaluate and plan your quality control. Bio-Rad wants to ensure each lab can provide the highest level of patient safety by providing the quality control materials and software tools to design your quality control plans.

11. **Is it OK to run QC at end of the day?**

    Yes, it's actually a very good practice. See my first recommendation. When you finish running patient samples at any specific event that could alter the performance of a test it's always good to confirm the test was performing within its specifications before that event.

12. **Should QC be done at the beginning of each shift of work during the day?**

    That depends. In some situations, a new shift could be the moment most patient sampling has ended and instruments are being reloaded or maintenance is performed; that is, the new shift is considered a critical control point. However, if a shift change

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happens in the middle of a busy run for the analyzer then you may not consider this a critical control point and would probably not need to run a QC at that specific time.

13. **Suppose in a run, a QC result is beyond 3 SD (standard deviations), but within tolerance limits. Can patient results be released?**

    If your QC design dictates the necessity of a 1-3s rule, then the 3 SD rule violation would always need to be investigated. You can better estimate the real size of the out-of-control condition by running additional QC and perhaps evaluating some patient results. If the estimated out-of-control shift is within the tolerance limits by more than 2 analytic SDs then releasing patient results should still assure that less than 5% of the results would be unacceptable. If, on the other hand, the estimated out-of-control shift is just within the tolerance limit, then close to 50% of patient results could be unacceptable. There are circumstances where QC design allows you to use a more generous rule like 1-3.5s or a larger rule. In that case you would not stop with a 1-3s rule violation.

14. **Recommendation #1:**
    Suppose that the control is 1-2s. Suppose then, that the next control (the next day) is also 1-2s: That makes it a 2-2s failure. Good practice says to go back to the last good control. So shouldn't the last control NOT END WITH A 1-2s WARNING?

    The goal of quality control is to detect clinically significant errors within a single analytical run and your QC design should reflect that. Using a repeat 1-2s rule will take care of this and won't end a run with a pending 1-2s.

15. **Recommendation #5:**
    A chemistry instrument with say 30 tests is almost guaranteed to have a 1:2s flag on one of the tests...do you really suggest that it be repeated?

    QC design determines which rules are most appropriate for your test. The repeat 1-2s rule should only be used for low performing test where this is needed. If you have any well performing test there is no need to use a 1-2s rule, you can use the 1-3s which will have a lot lower false rejection rate. If labs decide to use a 1-2s for all tests then yes, you will see more of these rules, but by repeating the run you will be able to identify if it's a real or if control error condition or a false rejection.

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

16. As you know, most labs test have hundreds of different tests. It would take a major effort to do risk assessments on all our tests. Is that feasible or are labs just doing this for some tests?

17. Our next question: you showed us 10 recommendations to implement, from your experience, which would be your two first practices to start with?

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18. By dividing my analytes into high and low sigma tests, how would the lab deal with different QC frequencies by analytes and number of patients?

19. Your second recommendation said to set QC to no longer than it takes to correct results before they are acted on.... what is your recommendation when the results are auto-verified and released and the next QC may not be until the next shift or day?

20. The third recommendation is to know number of patients between QC evaluations... what are your thoughts for labs whose patient volumes vary from day to day?

21. Dr Parvin, on your last slide you indicate the laboratory's tolerance for reporting erroneous patient results should depend on the likelihood that erroneous patient results lead to harm and severity of patient harm". This tolerance also depends on the context and specific situation for the testing; for example an emergency room, diagnosis, or disease monitoring. How have you seen labs do this?

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