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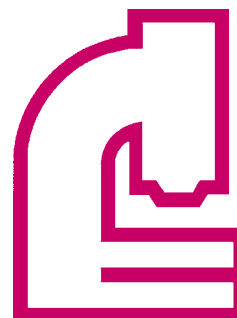
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## Quality Control Myths: Part II

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In the previous article in this series, we introduced two common “myths of QC” and discussed some basic principles underlying the use of statistical QC in the laboratory. We applied those principles to the first myth and outlined why we should not use the values printed on QC material package inserts for the acceptable ranges for our instruments in the lab. In this article we are going to tackle the second “QC Myth”.

**Myth #2: “Once the target values are set for QC samples, they should never be changed until a new lot of QC material is used.”**

This myth grows out of the idea that once you have established the “correct” values for your QC material, any change seen in QC results represents a “bad” change in instrument or assay performance and, if you change your QC targets, you cannot be sure your answers will continue to be accurate. At a very basic level this is true. You cannot just change your QC targets anytime you want to, unless there is a good reason. However, this idea is naïve in that it assumes that there is only “one true value” for your QC material and it never changes.

The reality is that there is only “one true value” for a given QC sample, but that value is not always the correct value for you to use as a target for statistical QC. Remember one of the key assumptions made by statistical QC is that, when everything is working correctly, QC results will be evenly distributed on both sides of the target mean (see Part 1 of the Myths of QC series). If your QC protocol is to be effective in detecting system problems over time, you may have to update your QC targets from time to time to compensate for changes in how the QC material interacts with your analytical system, even when everything is working correctly. These changes can be due to a variety of causes. The QC material may change over time as it ages

and give different results compared to when it was new. The first QC targets established may have been set up when the instrument was not operating at it’s best and now, after recalibration, preventative maintenance, or other repair, the system is back to optimal performance and the QC targets need to be updated for that change.

With any test performed on an instrument system, particularly immunoassays, a common reason for needing to update your QC targets is the dreaded reagent lot to lot QC shift. Everyone has been frustrated or confused from time to time because they started a new reagent lot and suddenly their QC results have shifted and they cannot find the source of the “problem”.

So they call the manufacturer and are told to update their QC targets. However, this always sounds suspiciously like the manufacturer is trying to “cover something up” ... probably some

change in assay performance they don’t want to disclose.

Let’s look at what is really going on. One of the best summaries of what is happening was a comment made by a colleague who said, “QC material is like a mummy .... It used to be human once.” What do mummies and QC material have to do with each other ... well, the basic requirement for selecting a QC material is to use something that is as close as possible to a fresh patient sample so that anything that might affect the quality of patient results will impact the QC sample result as well. QC material manufacturers know this and, in preparing QC material, most start with fresh human serum (“used to be human once”). However, with QC samples we want the concentrations in the samples to be at specific levels and not just what is naturally found in the large group of people whose blood was used. This is so that we can check the analytical system at different concentrations and make sure there have been no changes at medically important concentrations.

We also want QC material that is stable and can be stored for a long time so we can use the same QC material for a year or more to check



our analytical systems. So we start to modify the fresh human serum we collected (“used to be human once”). First, we pool serum from many people because we are making up hundreds of liters of QC material at one time and you cannot get that much serum from one person. The fact that we pool many samples of serum already starts to make the QC material different from a fresh sample from a single patient, but we’re not done yet. Next, we filter the serum through very, very fine filters to remove any particles and even micro-organisms. Then we remove many of the substances we want to measure. What?!

To get the final concentrations where we want them, we often have to remove the natural substance in the serum and put back in only the amount we want. Finally, we have to make the QC material stable so it is practical and economic to use. We add antimicrobials to prevent growth of bacteria, etc. Then we freeze dry the serum (the technical term is lyophilize, but it’s the same thing). So by the time we are finished manufacturing the QC material, what was once the same thing as a patient sample, is now heavily modified. This is generally described as having modified the “matrix” of the QC material. What is the “matrix”? The matrix is everything in the sample that is not the substance we are trying to measure. So, if we have a sample we are testing using a TSH assay, the matrix is everything in the sample except TSH.

Immunoassays, more than most types of assays used in the clinical lab, are especially sensitive to changes in sample matrix. The biologic materials used in immunoassay reagents (antibodies and conjugates primarily) interact with the proteins in the sample matrix. Changes in the quantity and nature of these matrix proteins can impact the performance of the immunoassay and the QC material manufacturing pro-

cess often affects the proteins in the QC material more than anything else.

What does this have to do with QC? We have seen that the process of turning human serum into QC material can substantially alter the matrix proteins. This can affect the performance of all assays, and immunoassays particularly. When the values are being established for QC material package inserts, the testing is done with one or two lots of reagent available at the time. In the future, when new lots of reagent are manufactured, the new lot may not react with the altered matrix proteins in the same way that the older lots did ... and we see a shift in the QC results as a result. This generally has no impact on patient results because the matrix proteins in patient samples have not been altered by any manufacturing process. So now the results obtained testing QC samples have changed, but

the results obtained testing patient samples did not change. We see a shift in QC results that does not indicate any problem with the instrument or with patient results, only a change in how the reagent reacts with the QC material.

It even gets more interesting. Since the manufacturing processes are not identical

for all QC materials, reagent lot to lot changes in QC may be seen with Brand A controls, but not with Brand B controls, or vice versa. One manufacturer’s HCG assay may see a shift, but another vendor’s HCG assay does not. There is just no way to know in advance what will happen and none of it means anything about the quality of the assays or the control material.

So now we understand why we can see reagent lot related QC shifts, but that raises the questions, “Why don’t manufacturers tell us this will happen? Why do we have to struggle troubleshooting until we cannot find a cause and then call the manufacturer only to be told it was expected?”



QC



Those are both good questions, but there are no easy answers. If the manufacturer is able to reliably confirm a significant shift in QC during release of a new reagent lot, they often do inform customers. However, the larger challenge is that the manufacturer cannot always effectively characterize the QC shift with the limited amount of time and data available during release of a new lot of reagent. Since most all of these shifts are modest in size, it can be very difficult to effectively characterize the shift so that the manufacturer can inform their customers exactly what kind of shift to expect unless the manufacturer has a lot data from a sizeable number of instruments. This quantity of data is not generally available during the release of a new reagent lot, so the manufacturer may see what looks like a possible shift, but not have enough data from enough instruments to be able to predict effectively for ALL customers what to expect. The first time the necessary quantity of data becomes available is when customers start using the reagent lot on a daily basis. Then they start calling, the manufacturer puts together the reports and is finally able to say something. This is frustrating for all involved.

So how do we manage this in our laboratory? How can we be sure patient results are not affected as well.? If we see an apparent shift in QC with a new reagent lot we should run a few more replicates of the QC material to verify that it is repeatable. Then we should test a few (6–10) patient samples that were run with the “old” lot to verify that patient results are not impacted. The comparison of patient results is a simple side by side judgment. It does not require any statistical analysis. If we do not have any patient samples run on the old lot, or the samples are no longer any good, one thing we can do is contact the reagent manufacturer to see if they have any data comparing patient results from lot to lot. Another way we can check for these lot related changes is to use peer group reports to see if others are seeing the same reagent lot related shift.

It should be apparent at this point that there are specific occasions when QC targets may need to be updated to reflect changes in the way the QC material interacts with the method. These updates are necessary to make sure the results obtained with our QC samples will accurately

indicate future changes in instrument performance that may affect patient results. Failure to appropriately update QC targets will compromise our ability to detect real errors.

## Summary

The most effective way to reduce the challenges and frustrations of reviewing QC results is to understand the basic principles underlying the use of statistical QC and use those principles to establish a logical and effective QC program that detects real problems without generating “out of range” results when no problem exists. In these articles, we have reviewed some of the underlying principles behind how we do QC in the lab. We have used these principles to develop practical methods of setting effective QC targets and we have discussed how and why these targets may need periodic updates. If we use this information consistently and effectively, many of the common frustrations of reviewing QC results will be significantly reduced.

The principles discussed in these articles are a good start. There are more principles and guidelines to effective use of statistical QC in the lab; more myths to challenge. If we continue to learn more about them, we can reduce the time and effort involved in reviewing QC results, reduce the number of times we have to test additional QC samples to see if there really is a problem, and make monitoring our instruments easier and more economical.

## Resources:

1. Brooks, Z.C. *Performance Driven Quality Control*. AACC Press, Washington, DC. 2001
2. CLSI. *C24-A3. Internal Quality Control Testing for Quantitative Measurements: Principles & Definitions: Approved Guideline*. 3rd Ed. 2006.
3. Westgard, J.O. *Basic QC Practices: Training in Statistical Quality Control for Healthcare Laboratories*. AACC Press, Washington, DC. 2001
4. [www.Westgard.com](http://www.Westgard.com)