THE IMPORTANCE OF LAB QC AND MDL’S

And how to do them

Denise L Seman
City of Youngstown
Quality Control (QC) is defined as the process of detecting analytical errors to ensure both reliability and accuracy of the data generated.

QC can be used to ensure the equipment is functioning properly, the reagents are good, and the technician is skilled at the analysis.
QC involves a statistical evaluation of data and the use of quality control materials

- Ideally, the use of third party, certified materials

- Statistical evaluation acceptance criteria may be defined within the approved methodology
- QC must be performed on a regular basis

- QC must be included in regular runs, not a special QC only run

- QC materials should be treated the same as samples, from beginning to end of run
Good QC means:
- regular calibration of the equipment
- Frequent checks of known standards against the calibration to verify the cal is working
- (do NOT use the same standard to verify cal)
GLOSSARY OF QC TERMS

- **Mean**
  - Commonly called the average

- **Standard deviation**
  - A statistic quantifying how close the numbers in a data set are to each other

- **Accuracy**
  - How close to the true value you are

- **Precision**
  - How close your duplicates are to each other
- **Coefficient of variation (CV)**
  - Ratio of the standard deviation to the mean
  - Expressed as a percentage

- **Coefficient of variation ratio**
  - Comparison of your labs CV to the values of a peer groups CV

- **Standard Deviation Index**
  - Also peer based
  - Mean of your lab minus the mean of the group
  - Divided by the standard deviation of the group
These 2 will have the most impact on your analytical data

You can be accurate - and always fall within the acceptable range of a known standard

You may be imprecise - and your results are “all over the spectrum within that acceptable range”
ACCURACY AND PRECISION
BULLSEYE CHART

Low precision – low accuracy
High precision – low accuracy
High precision – high accuracy
Low precision – high accuracy
ACCURACY AND PRECISION BELL CURVE DEPICTION

- Low accuracy, Low precision
- Low accuracy, High precision
- High accuracy, Low precision
- High accuracy, High precision
Control charts are an important part of lab QC.

Levey-Jennings charts are used to track the day to day statistics of any analytical parameter.

Charts are created for each test, and for each QC value within the test.
A control chart gives you a visual display of method stability or instability over a period of time.
Every method has some normal variation

Use of control charts will allow you to track the normal variation, and quickly observe any abnormal variations
Some variation is simply the result of numerous, ever-present differences in the method.

This is common cause variation
EXAMPLES OF COMMON CAUSE

- Chance occurrences
- Random issues that can’t be controlled
Some variation may be the result of causes which are not normally present in the method.

This could be special cause variation.
examples of special cause variation

- Incorrect reagents
- Expired reagents
- Inaccurate measurements
- Dirty glassware
Control Charts differentiate between these two types of variation
A corrective action investigation will isolate the possible special causes of a set of data
Control charts are tools used to determine whether or not an analytical process is in a state of statistical control, or stability.
Stability is defined as the state in which a method has displayed a degree of consistency in the past and is expected to continue to do so in the future.
This consistency is demonstrated by a stream of data falling within control limits based on plus or minus 3 standard deviations of the calculated mean.
Control charts can help you determine if any analysis is in control (statistically acceptable for all parameters) over a period of time.
If the analysis is in control, the data generated can be reported with a relative degree of certainty.
If the control chart indicates the analysis is NOT in control, a corrective action investigation should be conducted to correct the errors, and samples re-run before reporting.
Control chart parameters should never be adjusted to be able to report data.

This will result in skewed, inaccurate data AND you will be reporting false data to the regulating agency 😞.
CHART CONSTRUCTION
Calculate the mean and standard deviation to begin.

These 2 values will be used to determine the zones of the chart.
The mean will be used as the “center line” on your chart.

The standard deviation will be used to develop the various zones of acceptance on the chart.
When an analytical method is in control, 68% of the data will fall within +/- 1 std dev

96.5% of the data should fall within +/- 2 std dev
About 99.7% of the data will fall between +/- 3 std dev

Data within the +/- 2 std dev is considered to be reportable, and method is well within control
Data that falls outside of the +/- 2 std dev, but within the +/- 3 std dev is considered reportable - but you should start checking the method for any possible sources of problems.
Things to look at:
- Age of reagents
- Does probe need to be cleaned
- Is equipment due to for maintenance
If you monitor your data as it falls outside of the +/- 2 std dev, but before it falls outside the +/- 3 std dev - you can almost eliminate having any data fall outside the +/- 3 std dev (which indicates the method is out of control)
You should have at least 20 data points before developing a representative chart for quality control.
Data should be updated frequently to incorporate new data into the values.

You don’t need to do this daily 😊
Ideally, you should work on developing an infinite set of data for the control charts. This will give you more reliable QC than tossing half of your data set to add in a new group of data.
After calculating the mean and standard deviation, it’s time to set up a chart.
The chart is used as a visual aid for analysis.
Plot the data on a graph

- Draw the Center Line (mean)
- Draw in the Warning limits
- Draw in the Control limits
Establish your zones on the chart

- Zone A is between 2 and 3 std dev
- Zone B is between 1 and 2 std dev
- Zone C is 1 std dev
Due to normal variation (Common Cause)

Upper Control Limit (UCL)

Process Average

Lower Control Limit (UCL)

Out-of-control Point (Special Cause)
New charts should be started for new methods or for any method that undergoes a significant change/ modification
WHAT'S “IN”
All data points should be included in the evaluation of the control charts
Data that is affected by "normal" variability should be left in use
Data should ideally only be excluded if and when it can be linked to a specific cause variability.
Specific cause variability would be something linked directly to an error in the method:

- Incorrect reagents
- Dirty glassware
- Poor technique
OUTLIERS

I'm the outlier that messes with your data
There are other factors, or trends, that must be taken into consideration as well as whether the data is inside or outside the control limits to determine if a method/data is in control.
look for systematic patterns of points (e.g., means) across samples, because such patterns may indicate that the process average has shifted
A run of 9 consecutive points on the same side of the mean indicates the method is “out of control”
probability of this happening statistically is .00195 - same probability that a point will fall outside the 3 std deviation line
if this pattern is detected, then chances are the average has probably changed
Successive samples with less-than-average variability may be worth investigating, since they may provide hints on how to decrease the variation in the method.
Note that it is assumed that the distribution of the data points will be symmetrical around the mean.
BAD TRENDS

- 6 points in a row steadily increasing or decreasing.

- This also signals a drift in the average
Often, such drift can be the result of equipment wear, deteriorating maintenance, improvement in skill, etc.
More Bad Trends

- 14 points in a row alternating up and down.

- If this trend is present, it indicates that two systematically alternating causes are producing different results.
Still More

- 2 out of 3 points in a row in Zone A or beyond.

- This provides an "early warning" of a process shift.
15 points in a row in Zone C ( +/- 1 std dev) (above and below the center line).

This test indicates a smaller variability than is expected (based on the current control limits).
TIME TO REDO THE CHARTS??

- 8 points in a row in Zone B, A, or beyond, on either side of the center line (without points in Zone C).

- This indicates that different samples are affected by different factors, resulting in a bimodal distribution of means.
This may happen, for example, if different samples were processed by two different techs, where one follows good measurement protocol and the other doesn’t.
**TRENDS**

- A trend indicates a gradual loss of reliability in the test system.

- Trends are often subtle.

- The data slowly shifts from the norm to a new pattern.
Trends may be caused by:
- Deterioration of instrument light source/membrane, etc
- Gradual accumulation of dirt/contaminants within the test system
- Age of reagents
- Gradual deterioration of control materials
- Gradual deterioration of calibration
SHIFTS
An abrupt change in the control mean is a shift.

Shifts in the QC data represent a sudden and dramatic positive or negative change in the performance.
Shifts may be caused by:

- Sudden failure of light source/ fouling of membrane
- Change in reagent formulation
- Change of reagent lot
- Major instrument maintenance
- Change of room temp/ humidity
- Failure of sampling system
- Failure of the automatic equipment
- Bad calibration
USE CARE WHEN REMOVING DATA FROM THE CHARTS
Once the data has been evaluated - and a known variable for a source of error has been determined - outliers can be removed from the statistical pattern.
Using the outlier rules: If you continue to eliminate points without confirming there was special cause for them to occur, you will eventually end up with a control chart so tight you will almost always be “out”
Every time you eliminate outliers, you need to recalculate the mean, and the standard deviation
USING THE CONTROL CHART FOR DATA REPORTING
When evaluating the run, look at the QC from that run as it relates to the parameters generated from the control chart.
If the data is in control, report the results

If a data point is out of control, look for special causes and re-analyze the sample(s) affected
Good data is data that is accurate and precise - and can be documented to demonstrate those characteristics.
Quality assurance is the program developed for the laboratory QC.

This involves rules on when to perform the QC, how to perform the QC, and storage of the QC data.
This also includes documenting the instrument maintenance.

Written SOP’s for all methods, based on the exact equipment you use to perform the analysis is part of a good QA program.
Quality assurance is a necessary component of a good laboratory practice.
Method detection limit
The level where you know the analysis can actually generate/ detect values within a given sample with a relative degree of certainty.
This limit is based on the entire analytical process, including any distillation and/or digestion steps, as it incorporates all avenues of potential error.
Detection limits are a statistical evaluation of a series of known analytical results from the same sample/standard.
The concentration in the sample being used for the determination should be within 2 to 10 times the anticipated detection limit.
If you are prepping a standard (a spiked blank) - the conc should be 1 to 5 times the expected limit.
A series of 7 analysis of the same sample are done, and the results calculated to determine the MDL
The average of the data is calculated, as well as the standard deviation.

The standard deviation is multiplied by the t-value for a 99% confidence interval (for 7 samples it is 3.14).
The resulting value is your MDL

For a more realistic value - use the S-pooled to calculate the result
From your 7 samples, calculate the variance of the data

Using the previous set of data for the MDL of this analysis - calculate the variance of that set
\[ S^2 = \frac{1}{n-1} \left[ \sum_{i=1}^{n} X_i^2 - \left( \frac{\sum_{i=1}^{n} X_i}{n} \right)^2 \right] \]

\[ S = \left( S^2 \right)^\frac{1}{2} \]
$X_i; \; i=1 \text{ to } n$, are the analytical results in the final method reporting units obtained from the $n$ sample aliquots and $\Sigma$ refers to the sum of the $X$ values from $i=1$ to $n$.

6. (a) Compute the MDL as follows:

$$\text{MDL} = t_{(n-1,1-a=0.99)} \times (S)$$

where:

- **MDL** = the method detection limit
- $t_{(n-1,1-a=0.99)}$ = the students' t value appropriate for a 99% confidence level and a standard deviation estimate with $n-1$ degrees of freedom. See Table.
- $S$ = standard deviation of the replicate analyses.
Divide the larger variance by the smaller variance to determine the ratio

- If this value is > 3.05 - redo the analysis
If the ratio is less than 3.05 - use this equation to determine the S pooled value:

\[ \sqrt{\frac{(\text{variance } 1 \times 6) + (\text{variance } 2 \times 6))}{12}} \]

Multiply by 2.681 to determine the MDL \( t_{(12, 1-a=.99)} \)
MDL’s should be revisited at least once a year.

MDL’s should be done for any new methods and method modifications.

MDL’s are NOT the limit for most accurate reporting levels, but the point at which you are sure you CAN detect results.
Questions?

Contact info:

DSeman@CityofYoungstownOH.com

oweastatelac@gmail.com