QUALITY CONTROL

HOW TO ESTABLISH QC REFERENCE RANGES

RANDOX

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Introduction

Establishing QC reference ranges is an important aspect of laboratory quality. There are a number of reasons why a lab may wish to establish their own reference ranges:

- Assign target values and ranges for an unassayed control
- Improve accuracy of target values and ranges
- Improve stringency of acceptable limits
- To meet regulatory requirements

With assayed control material, it is common for labs to simply adopt the manufacturer's targets and ranges as their own. However, manufacturers often assign wide acceptable limits, which can mask issues in performance and greatly increase the risk of releasing erroneous patient results.

When correctly implemented, assigning new reference ranges can save money and improve error detection. This short guide will take you through the steps involved in assigning reference ranges for your lab.

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Establishing Reference Ranges

There are 4 main steps involved in assigning accurate targets and ranges:

1. Establishing Mean Target Values using Parallel Testing
2. Calculating Historical CV (CV_h)
3. Determining Appropriateness of Calculated CV_h
4. Establishing QC Ranges using CV_h

Step 1: Establishing Mean Target Values Using Parallel Testing

Parallel Testing is the name given to running the current QC lot and a new QC lot in tandem. To perform Parallel Testing:

a) The current QC lot should be tested to verify that all analytes recover within the previously established ranges. The new QC lot should then be analysed 2-3 times daily for approximately 10 days, ensuring that at least 20 data points are generated[1,2].

b) Review the data generated to ensure that assay precision (CV) is lower than the CV obtained in the manufacturer's specifications. This information can be found within the method or instrument documentation provided by the manufacturer. If the CV is found to be unacceptable (higher than manufacturer's specifications), investigate the root cause and implement corrective actions before repeating Step 1.

c) Calculate the Mean and Standard Deviation (SD) for each analyte. Outliers (any data points more than 3 times the SD from the mean) should be identified and removed from any statistical calculations[2].

Step 2: Establishing Historical CV (CV_h)

CV_h is the historical instrument precision for a specific method. It is best to establish CV_h over several QC lots (3 or more), and it can either be taken as the Mean CV for a specified time period, or alternatively (and preferably) the highest acceptable CV over that period.

The highest acceptable CV should be any %CV generated which is higher than the mean historical CV, but lower than the %CV stated in the reagent manufacturer's pack insert, Peer Group and EQA group for the same analyte/lot.

Any erroneous data generated during periods of instrument malfunction, or any error which would adversely affect the CV should be omitted from this calculation[3].

Why do we need CV_h? CV_h can be used to calculate the SD, QC ranges, and to monitor long-term instrument precision, in order to give more appropriate acceptable limits[3].

For example: A lab used data from their last 3 QC lots, obtained within the last 24 months, to calculate their CVh. A mean CV of 3% was calculated, but the highest acceptable CV within this time period was found to be 3.7%. The lab could use either 3% or 3.7% as their CVh, but 3.7% would be preferable, to avoid setting QC ranges which are too narrow.

Alternatively – If historic data isn't available, the CV calculated from the data generated in Step 1 can be used. However, as this data will have been generated over a limited period of time, it is advisable to increase the CV value by 1-2% to account for potential variability[3].

Step 3: Determining the Appropriateness of Your Calculated CV_h

The next step is to confirm the appropriateness of the calculated CV_h; which should meet the below requirements:

- The calculated CVh should not exceed the instrument-method CV provided by the manufacturer[3].

- The CVh should not exceed the average assay-specific CV provided by EQA schemes. EQA schemes (e.g. RIQAS) incorporate much more variability, ultimately giving a higher calculated CV for each analyte, therefore, your obtained CV should be lower[3].

- Some companies offer Peer Group Reporting programmes (e.g. Acusera 24•7). The calculated CVh for your lab should not exceed the peer group CV for the same analyte/lot[3].

Step 4: Establishing QC Ranges using CV_h

Using the data generated from Parallel Testing in Step 1, calculate the CV and SD.

Calculating the CV

Calculate the Mean and SD of the data generated in Step 1, then calculate the %CV using the below equation:

$$\%CV = (SD / Mean) \times 100$$

The calculated CV must be comparable to (lower than) the manufacturer's instrument method CV and should be close to the CV_h. If the calculated CV is higher than the Manufacturer's CV or the CV_h, this could be indicative of a precision issue. This should be investigated and resolved.

Calculating the SD

Using the SD obtained from Step 1 will likely result in ranges which are too narrow, as the SD has not incorporated a large enough data set. The CV_h should be used as this will better account for variation. The SD should be calculated using the below equation:

$$SD = (CV_h / 100) \times Mean$$

Assigning Reference Ranges

Many labs incorporate a ±2SD range. For example, if a lab had a calculated Mean of 70, and an SD of 2.1, a ±2SD range would be: 65.8 – 74.2.

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Practical Example

A lab ran Parallel Testing for Glucose, generating 40 data points over a 20-day period. The results obtained were:

Mean: 120 mg/dL
SD: 2.99
CV: 2.5%

The lab then calculated their CV_h using data from their last three QC lots. They took the highest acceptable CV generated in this time, which was found to be 3.6%.

The lab then compared the CV_h of 3.6% to their instrument/ reagent manufacturer's CV specifications, EQA CV and Peer Group CV, and their CV_h was found to be lower than all of these, and was therefore acceptable.

The final step was for the lab to calculate their reference ranges using the below calculation:

$$SD = (CV_h / 100) \times Mean$$
$$SD = (3.6 / 100) \times 120$$
$$SD = 4.32$$

As it is common practice for labs to assign a ±2SD range, the acceptable range was set as:

111.36 – 128.64

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References

1. Clinical And Laboratory Standards Institute. (2016). Planning a Statistical Quality Control Strategy. In: CLSI *C24 Statistical Quality Control for Quantitative Measurement Procedures: Principles and Definitions*. 4th ed. USA: CLSI. 27-32.

2. M. Laura Parnas, PhD. (2015). Best Practices in Establishing Quality Control Parameters. *Bench Matters*. Aug 2015 (1), 1.

3. Kurt Michael and Paul Richardson. (2010). *Chemistry Guideline for Establishing New Control Lot Means and Quality Control (QC) Ranges Through Parallel Testing and Historic Coefficient of Variation (%CV_h)*. Available: http://resources.psmile.org/ resources/process-control/section-specific-information/chemistry/Pro6.1-05%20Chemistry%20%20-%20Guideline%20for%20 Establishing%20QC%20Ranges%20and%20use%20of%20CV.doc/view. Last accessed 3rd Jan 2018.