The Quality Control System

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Summary
Quality Control System
- An understanding of analytical error
- Synthetic QC material
- A set of QC rules
- A process to follow if the rules signal

Quality Control (QC) Sera
- Reconstitution – staff trained
- Stability tested – post reconstitution and frozen

QC Rules
- Rules documented – basis of adoption
- Action to follow in case of failure documented
- Evidence of this procedure being used in place
- Are QC rules defined for both batch and continuous analysis – how is a 'run' defined for a continuous analytical process
- Means and standard deviations (SDs) of controls based on sufficient data points and reflects true state of system
- Evidence of staff training in the interpretation of QC rules
- Process documented
- Evidence of training of staff
- Evidence of regular review of Internal QC results

Patient-based QC Procedures in place
- If delta check/anion gap/rerun of samples used, then a documented procedure to describe the process and evidence of it being in use
- Critical values – documented and evidence of use and documentation

Action on QC Rule Failure
- Documented process to follow with patient samples if control failure occurs
- Evidence that procedure has been followed in instances of control failure

External Quality Assessment (EQA) Program
- Integration of Internal and External QC data

Introduction

The key features of any laboratory QC system are that the system is documented, understood, stable, reliable and supports continuous quality improvement. The laboratory must be able to demonstrate that there is a 'system' in place and not just a series of unco-ordinated activities. These activities must be subject to audit (external and internal) and review.

In 1997 Howanitz et al. described results from a Q-Probes survey of over 500 institutions in the United States provocatively entitling the paper "Clinical laboratory quality control: a costly process now out of control" and concluding that established QC processes were costly and that laboratory staff did not follow these procedures because they were too complex.[1] It is likely that many of the findings in those

laboratories are also current practice in Australian laboratories so those findings need to be used to improve current systems. Laboratories will often adopt systems without appropriate support in terms of training and customisation so these need to be the basis of any external audit.

QC System

We consider the QC 'System' used in most laboratories.[2] This system consists of (1) an understanding of analytical error; (2) synthetic QC material; (3) a set of QC rules (algorithms that specify actions based on the outcome of one or more control observations) which, with the results of the QC samples, are used to decide whether or not the analytical 'run' is in control; and, (4) a process to follow if the run is deemed to be 'out of control' by these QC rules, including well defined procedures to follow to ensure the process is returned to acceptable control.

Let us examine each of these components in turn and highlight the problems associated with them.

Understanding of Analytical Error

Effectively this is demonstrated by the emphasis the laboratory places on analytical QC. There should be an appropriately qualified QC co-ordinator who oversees EQA program results and summaries of internal QC results. Evidence should be obvious that these two sets of information are integrated to detect trends and that, based on this, changes are made to calibrations or processes. The head of department should be aware of the state of the QC in the laboratory and of any results which have had to be amended and recalled because of analytical error.

The operational staff should also be able to demonstrate a good understanding of the QC system and what the different types of error are, how they present, what causes them in the analytical system and how to fix them. There should be a documented training program which has evidence that training has been given and received by all staff releasing results.

There must be a system whereby there is demonstrated communication of problems with analytical systems between different shifts. Backup and support for non-expert staff in instrument troubleshooting and QC interpretation should also be evident.

QC Material

Both freeze-dried and liquid stabilised control materials are subject to inherent errors which may falsely flag if it is not well understood that there is a problem with the analytical process. There may be instability in certain analytes (for example creatine kinase, bicarbonate) after reconstitution (freeze-dried) or thawing (liquid stable). The act of reconstitution can introduce an error[3] far greater than the inherent error of the rest of the analytical process[4] and there may be introduced contamination from the diluent.

Each laboratory should perform stability testing for control material after reconstitution or thawing and for material in long term storage. This should be supported by manufacturer's documentation.

Internal QC

All QC systems based on synthetic QC sera require estimates of the mean and standard deviation (SD) that accurately reflect the stable, between run variability of the assay. This requires these estimates to be determined over a reasonable number of analytical runs. The more estimates that are performed then the greater the reliability of the measures, but also the greater the cost, which is a significant burden in the case of esoteric assays. Running new QC material over as many different runs as possible also will identify problems such as vial-to-vial variation or instability in certain analytes after thawing or upon reconstitution.

The calculation of the mean and SD should be an ongoing exercise but it is important not to exclude failed QC sample data from the ongoing calculation of mean and SD. This selective removal of 'failed' data leads to a false impression of the true variation in the assay.

QC Rules

Next we consider the QC rules used in the laboratory to interpret the results of the QC samples. These rules all have inherent shortcomings, no rule is perfect. That is, no rule used will detect all error that is present and sometimes the rule will suggest there is error present when there is not. QC material must be chosen to cover the range of clinical interest with particular care for critical cutoff points.

Different control rules can be combined by applying one sequentially after another in an effort to increase sensitivity to error for a given level of false rejection. The rules must cover the situations where one of multiple samples are out of control. The Westgard multirule procedure is a widely used example of this approach.[5]

The danger with complex rules is that staff may not understand how to effectively interpret them in practice.[1] There must be a procedure to record QC failure and a reviewed response to each failure illustrating that the core reason for the failure was identified, rectified and that the system was demonstrated to be 'back in control'.

An Analytical 'Run'

Control materials are analysed periodically in general and define an analytic "run", thus the concept of a run is related to the QC process and is the period when the control rule can next be tested.

- A run represents "for purposes of QC, an interval, that is, a period of time or series of measurements, within which the accuracy and precision of the measuring system is expected to be stable."[5]
- A run for a batch analysis is well defined, it is the QC and patient samples for that batch.
- For a high volume, continuous feed analyser, the concept of a run is more difficult, and it is often the number of specimens between two QC samples. If the last QC sample is in control, then the previous patient samples are released.

Patient-based QC Procedures

Another approach to monitoring the analytical quality of analytical runs is to use patient data.[4,6,7] One of the potentially attractive aspects of using patient results is that it should be possible to detect an out of control situation before it would be detected by a synthetic control sample method. This is because each patient sample that is analysed, adds to the information about the state of the analytical process. Patient data can be used in several different ways, for example patient duplicates, discordance checks, delta checks, multi-parametric checks of individual patient data (e.g. anion gaps) and average of patient results. Limit checks to ensure that results are compatible with life and screening for critical results are the most basic use of these checks and would be routinely performed in laboratories using the Laboratory Information System or instrument software. If this option is not available then there should be some documented procedure for dealing with critical or unexpected results.

Delta checks or differences between consecutive results can potentially alert the laboratory to specimen mix-up,[8] however they have been shown to have a poor predictive value for the detection of this error, with a sensitivity of 50% and a false positive rate of approximately 5%. Sheiner et al. showed that with a 1% mislabelling rate, 5.5% of all specimens failed the delta check, with only approximately half of the truly mislabelled specimens detected and 90% of the possibly mislabelled specimens investigated unnecessarily.[9]

A negative anion gap should alert the analyst to a problem with the electrolyte measurement system but as a control procedure it lacks sensitivity.[10]

Some networks use patient samples as QC material internally within the network. A patient sample, or pool sample, is sent to all laboratories in the network and the results compared. This is to introduce abnormal results not obtainable in synthetic material and to ensure matrix effects are not hiding true bias. These control samples should be compared using similar rules to conventional QC, i.e. with mean ±2SD charts.

Action on QC Rule Failure

Once the QC rule system has flagged a failure what does the analyst do? Merely repeating the QC serum sample will not identify if random error is present as there is a high likelihood that the QC sample result will be within control limits when run the second time. Another common first action is to reconstitute another QC serum vial. Similarly re-analysing the entire run is not an acceptable corrective action if there is a real problem with the analytical system as this increases turn-around time and cost. The action to be taken will depend on the degree of confidence the analyst has in the QC system and the analytical procedure.

Once an out of control situation has been detected by a QC process it is necessary to determine firstly if there is a real problem and not just a false positive, and then to effectively troubleshoot the system to find a solution to the underlying problem. This requires a good understanding of the analytical system and of the control system. It is inevitable that not all staff will have this same level of understanding so the importance of training, documentation and access to some form of knowledge management is critical. The use of effective communication devices such as flowcharts and computerised decision support systems are invaluable in bridging the gulf between the expert and the average user.

The best solution is to introduce control rules that have a low probability of false rejection and carefully analysing the rules that have failed. This will suggest the type of error present, and the most effective troubleshooting to be followed.[11] There needs to be a documented, systematic procedure used to investigate the failure and take appropriate action otherwise the whole quality control process has been a waste of time and effort.

EQA Program - Integration of Internal and External QC data

A key component of the QA system is the External Quality Assurance Program (QAP) data. These data provide the laboratory with assurance that the results it is producing are fit for clinical use. External QAP results should be traceable to some form of primary, secondary or defacto standard, so that the laboratory can see that the results they are reporting are consistent with the results reported by other laboratories. Thus the laboratory is able to assess its accuracy. There are many limitations with the samples and assays that clinical

laboratories use as there may not be a well defined standard material or a suitable reference method. But external QAP gives the best indication of comparability with other laboratories.

The end of cycle QAP data also allow a laboratory to assess if they are performing a particular assay on a particular platform to an acceptable level of precision. Thus a laboratory can detect, by comparison with its peers, if it is not performing an assay, or set of assays, well.

The other very useful information that can be determined from External QAP data is 'the state of the art' in terms of assay performance across all methods by all participants. The end of cycle report will detail, for each assay, all methods and their relative rankings in terms of imprecision and closeness to the targets or means. This provides critical information to a laboratory when it is time to consider a change in method or analyser.

Summary

Laboratories need to continually improve all their systems including QC. The purpose of a QC system is to identify a situation where erroneous results are reported, and then to identify the cause of the error and rectify it. If laboratories are not getting value from their current system then they should review it. Often organisational systems such as the QC system are poorly designed and implemented, giving the impression of something which might not be.

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