Building an Effective Laboratory QC System

Using path of workflow to design an internal quality control system to meet basic accreditation requirements for quantitative tests

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The first step in the pathway toward assuring quality of the analytical process and building an effective internal Quality Control (QC) system for your laboratory is to establish overall quality goals for analytical performance. This strategy of establishing goals sets the stage for creating a meaningful QC plan designed to meet basic accreditation requirements for quantitative tests. It is worth noting that many of the same principles will also apply to qualitative testing.

The laboratory should establish the level of risk they are willing to accept for reporting an erroneous patient test result. This goal should be the cornerstone of the quality plan for QC, and all aspects of the plan should be based on this.

The laboratory should also define, in general terms, what it strives to achieve for analytical quality. These quality goals could be based on analyte-specific performance goals, such as total error, imprecision and/or bias. In terms of monitoring these performance goals, the laboratory should establish policies on quality control testing, including the control materials and the process control system to be used.

In developing analyte-specific performance goals, the laboratory may consider the following:

1. Which tests in the laboratory pose a higher risk of harm to the patient if an erroneous result is reported?
2. Should the laboratory plan make special provision for higher risk tests?
3. Is the laboratory aware of any tests that might be considered inconsistent performers requiring tighter control?
4. What is the expected frequency/probability of failure or malfunction (i.e., reliability) of the instrument, kit or method?
5. How important is it to be alerted when medically relevant analytical error occurs?
Once quality goals are established, a tactical plan designed to meet these goals should be prepared. The plan should be fairly specific and, when possible, should identify QC measures for each test based on risk of reporting an erroneous patient test result and the severity of the outcome if an erroneous result is reported. The plan should also consider assay limitations, probability of device failure and level of technical expertise required to perform the test. In accordance with good laboratory practice, the plan should ensure that control materials are treated like patient samples during testing.

Elements of the plan may include the following:

1. Analyte-specific performance goals. Performance goals may be:
   a. Unique and defined by the individual laboratory.
   b. Represented by long-term between-run imprecision, as reported by the manufacturer or as measured by the laboratory.
   c. Total allowable error (TEa), as defined by CLIA or other government agencies or professional organizations.
   d. Based on biological variation, or some government/regulatory requirement.
   e. Total error (TE) for the test, as published by the manufacturer, or as determined by the laboratory.

2. Acceptable limits for bias, imprecision and total error using biological variation or some other published targets to better regulate performance.

3. Frequency of including quality control materials for each analyte tested, based on risk assessment. If electronic controls are used, both the use of electronic controls and the frequency of testing should be based on risk assessment.

4. Concentrations (or levels) of quality control materials based on risk assessment. Some countries support testing a minimum of two different concentrations (usually a normal and abnormal concentration) depending on assay limits and the range of patient test results commonly reported. Other countries require controls covering the analytical range of the test.

5. An effective process control system for each analyte using Westgard Rules and/or biological variation. The laboratory should avoid:
   a. Indiscriminate use of the 2s rule for run rejection.
   b. Setting the same process control rule, or multirule, for all tests regardless of test capability or clinical utility.

6. Placement of QC materials within the run of patient samples. There are many patterns for testing control materials or electronic controls, some of which may include the following scenarios, where C = control testing event, normal or abnormal level; CN = control testing event, normal level; CA = control testing event, abnormal level; and P = patient sample.

<table>
<thead>
<tr>
<th>Control Scenario</th>
<th>Control Placement Within Run</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start of run</td>
<td>(start) CPPP.....................PPP (end)</td>
</tr>
<tr>
<td>Bracketed run</td>
<td>(start) CPPP.....................PPPC (end)</td>
</tr>
<tr>
<td>Bracketed run with split control levels</td>
<td>(start) C_NPPP.....................PPPC_A (end)</td>
</tr>
<tr>
<td>Throughout run with split control levels</td>
<td>(start) C_NPPP........................PPPC_APPPC_NPPP........PPP (end)</td>
</tr>
</tbody>
</table>

Note: The number of patient samples (P) between controls will vary depending on laboratory policy.
Develop a Plan by defining laboratory policies

7. Statistical parameters; e.g., mean, median, standard deviation, CV% and Total Error, for control materials, as established by the laboratory through repetitive testing. The plan should discourage long-term use of product insert values for establishing acceptable performance. Procedures should describe how to calculate a valid and reliable mean and standard deviation; i.e., setting target values and ranges of acceptable performance.

8. Requirements for parallel testing of all new lots of controls alongside current validated lots to establish new target values and ranges of acceptable performance.

9. Specific intervals at which the laboratory will reassess the relevance and appropriateness of all statistical parameters used by the laboratory, with particular attention given to the mean and standard deviation for each test.

10. A comprehensive training program that covers the following:
   a. Basic QC statistics and interpretation.
   b. How to handle control materials and prepare them for use: storage, reconstitution or thawing.
   c. How to interpret QC patterns: trends, shifts, random error, systematic error, error that requires action, and error that does not require immediate action.
   d. How to react to out-of-control situations.
   e. How to log and maintain QC results and document that QC was performed.
   f. Where to go to for additional troubleshooting assistance, if necessary.

11. Participation in an external interlaboratory comparison program for all parameters tested in the laboratory. Such programs include those provided by commercial companies, government run schemes, and private individuals or organizations. If no comparison program is available for certain tests, the laboratory should have some other means of demonstrating the competency of laboratory staff and the reliability of test results.

12. The nature of the control materials to be used. A number of options are available, including electronic controls, commercial products and patient pools. It may be appropriate to use a combination of different types of QC materials throughout the laboratory.
Develop a Plan by defining laboratory policies

When selecting the nature of control materials to be used, the laboratory may consider the following:

1. **Electronic Controls**
   The plan should identify which tests may be monitored using electronic controls, and any additional measures that might be needed to assure quality of patient test results.

   If electronic controls are used, the laboratory should understand what portion of the analytical process is being monitored, and if there is a need for additional controls to sufficiently mitigate the risk of reporting patient test results with medically important error.

2. **Commercial Control Products**
   (Includes in-kit controls, instrument manufacturer controls, and independent third party controls)

   The plan should describe when commercial control products are suitable materials for controlling the analytical process.

   The laboratory should compare the effectiveness of in-kit, instrument manufacturer and third party controls at detecting trends, shifts and medically important error. Consideration should be given to control matrix (human vs. non-human). Some accreditors/regulators may require the laboratory to know whether matrix effects are present that could potentially mask analytical errors.

   In-kit or instrument manufacturer controls that are designed for specific test methods may not be suitable for use on other test methods or instruments. When in-kit or manufacturer controls are used to calculate assay cutoff ranges, some regulatory bodies may recommend the use of independent control materials to monitor the analytical process.

   The plan should discourage use of control materials as calibrators and vice versa. This is not considered good laboratory practice. Sensitivity of the control product for detecting changes in the test system can be an issue for in-kit or instrument manufacturer controls when they are manufactured at the same time and from the same raw materials as the calibrator(s).

   **Note:** Almost all commercially available control products are neither intended nor labeled for “trueness of measurement” and therefore the laboratory does not have to document traceability\(^2\). However, if the control material chosen by the laboratory is labeled by the manufacturer as intended for “trueness of measurement”, the laboratory should document the metrological traceability of the product.

3. **Patient Pools**
   The plan should describe when patient pools are suitable materials for controlling the analytical process. Some questions that might need to be answered include:

   a. Should all patient samples be tested for infectious diseases before mixing with the pool?
   b. Does the plan address national ethics regulations regarding patient consent before using the patient’s sample as part of a patient pool?
   c. Is it important to have pools with analyte concentrations at the medical decision points? Is it possible to achieve these concentrations?
   d. How will the laboratory achieve and maintain homogeneity of the material?
   e. How will the pool be stabilized and stored?

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If the plan developed by the laboratory includes testing of commercial control materials, it should address the following:

1. **Selecting a QC Vendor**
   The plan should identify attributes of the QC vendor that are important to the laboratory. Consideration may be given to the following:
   
a. Presence of an established manufacturing quality system to ensure confidence in products.

b. Products that can be used on any instrument or method, to avoid using multiple different products to cover all laboratory platforms.

c. Broad range of products to allow purchasing consolidation.

d. Flexible shipping options that are practical and convenient for the laboratory. For example, long-term reserve of a lot number by the manufacturer for delivery over a period of time.

e. Availability of an interlaboratory comparison program to allow review of valuable peer group information.

f. Availability of QC data management software that could improve laboratory efficiency and performance by utilizing tools such as automated data import, flexible process control rules, and QC review options.

g. Experienced technical support and after-sales service.

h. Availability of educational programs and materials.

i. Established reputation for quality and reliability.

2. **Evaluating and Selecting QC Materials**
   The plan should identify attributes of the QC material that are important to the laboratory. Consideration may be given to the following:

a. **Analytes**—Does the product include the specific analyte(s) of interest? Is it more convenient to use multi-analyte controls or single-analyte controls?

b. **Target Levels**—How many different control levels does the laboratory prefer? Are the analyte concentrations at desirable levels? Are the materials supplied as assayed or unassayed controls?

c. **Form**—Does the laboratory have a preference for liquid or lyophilized material? *Liquid controls reduce vial-to-vial variability by eliminating reconstitution, while lyophilized controls can be easier to store.*

d. **Matrix**—Is it important to the laboratory to use human based materials? *Human matrix materials are more similar to patient samples.*

e. **Shelf Life**—Is it important to have a long shelf life in order to maintain consistent QC?

f. **Open Vial/Reconstituted Stability**—Will the product be used within the stability limitations, or will there be waste?

g. **Packaging**—Is the fill volume suitable for the laboratory's usage rate?

h. **Storage Requirements**—Does the laboratory have sufficient refrigerator/freezer space?

i. **Cost**—Is the cost within the laboratory budget? *The laboratory should consider the total value provided, not just compare cost/mL.*

3. **Establishing Infrastructure**
   The plan should determine the proper receipt and handling of QC materials. The infrastructure should exist to support this. Consideration may be given to the following:

a. Acceptance and distribution protocols for the Receiving Department.

b. Rejection and return protocols for the Receiving Department.

c. Acceptance protocols for the laboratory.

d. Storage requirements for the materials.
   - Appropriate storage conditions, as labeled by the manufacturer; e.g., 2-8°C, -20°C, etc.
   - Sufficient storage space for materials to be kept on site.
   - Convenient location for laboratory personnel.
The laboratory should have detailed procedures in place that reflect laboratory policy and meet the plan requirements. A standardized format should be adopted. A successful system will maintain distribution and revision control of laboratory procedures.

Laboratory procedures should address the following:

1. **Training**
   Preceded by risk assessment, training is the next most important element of the plan for assuring the quality of patient test results. It should be an ongoing element in implementing changes in procedures and/or personnel. Training should be conducted by qualified personnel and documented.
   
   The training program should cover all aspects of the plan, including:
   
   a. How to use the controls.
   b. How to recognize and verify an out-of-control situation.
   The procedure should specify who is responsible for verifying an error and evaluating its importance.
   c. How to determine the nature of the process control warning or failure.
   d. How to troubleshoot the process control warning or failure (find root cause).
   e. How to take corrective action and document such action.

2. **Interpreting and Acting on Results**
   Procedures should be in place to describe how to interpret QC warnings or failures detected by the process control system. Process indicators may point to random error or systematic error. Error may be persistent or proportional, medically important or merely an artifact.

   The laboratory should have a procedure(s) that describe(s):
   
   a. How to evaluate results of the QC testing event.
   b. How to characterize analytical error when such error is present.
   c. What corrective actions are appropriate for specific out-of-control error conditions.
   d. Who is responsible for the evaluation.
   e. What the requirements are for retesting patient samples when an out-of-control condition has been verified.

3. **Reporting Patient Test Results**
   Laboratory procedures should describe how and when patient results should be reported. An important element to be considered is the uncertainty of measurement for each test performed. Uncertainty of measurement may be used to assess the effectiveness of treatment.
   
   Before a patient result is reported, the laboratory should have procedures to address the following:
   
   a. Describe how to calculate the uncertainty of measurement for each test performed, where possible.
   b. Describe the specific conditions when patient test results may be reported.
   In addition to QC data, conditions may include the status of calibration, the integrity of the patient sample, condition of reagents, and the status of prescribed instrument maintenance.
   c. Identify who is responsible for making the final determination to release patient test results.
   d. Document receipt of the patient test results by the appropriate or designated care giver.
   e. Provide instructions on how to document and report corrected patient test results, if necessary.

   As of August 2006, there is no internationally accepted protocol for calculating uncertainty of measurement for tests performed in clinical/medical laboratories. The Clinical and Laboratory Standards Institute (CLSI) and ISO have formed working groups to address uncertainty of measurement and its calculation.
Process control systems should reflect current laboratory conditions and requirements. Conditions may change, which might require a reassessment of the QC plan for ongoing relevance, appropriateness and effectiveness. Laboratory staff must understand their individual role and responsibility in implementing, maintaining and modifying the plan as external factors in the laboratory change.

Particular attention should be paid to the sensitivity of the system. If the system is too sensitive, it will likely generate an unacceptable number of false positive alerts leading to costly and unnecessary troubleshooting and repeats. Conversely, an insensitive system may miss important analytical errors. Consequently, the laboratory should have a feedback mechanism that provides data relative to the relevance and effectiveness of the process control system in use.

The laboratory should have a policy that requires at least annual review of its process control system. Such a review could include:

a. An assessment of the continued relevance of the mean and standard deviation used to establish Levey Jennings charts. *It is important to understand that instrument age and volume throughput can affect performance over time.*

b. An assessment of calibration frequency. *If the calibration frequency is in excess of the frequency recommended by the manufacturer, it could indicate a problem with the process control system, the test system or possibly the control product.*

c. The total error of each test versus the allowable error established by the laboratory.

d. The six-sigma score for each level of control for each test.

e. The frequency of warnings and failures for each test (rejection rate).

By following this path of workflow technique, the laboratory can build an effective internal Quality Control System to meet basic accreditation requirements for quantitative tests. The process of establishing goals, developing a clearly defined plan, implementing carefully thought out procedures, and regular review of the system will demonstrate a serious commitment to maintaining high quality analytical performance, and ultimately providing good patient test results.