DOI: 10.7860/JCDR/2023/58635.17447

Review Article

Biochemistry Section

Quality Control in Clinical Biochemistry Laboratory- A Glance

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ABSTRACT

Quality Control (QC) is a process, designed to ensure reliable test results. It is a part of overall quality management of the laboratory in terms of accuracy, reliability and timeliness of reported test results. Two types of quality control are exercised in clinical biochemistry: Internal quality control and external quality assurance. Internal Quality Control (IQC), are the methods, which are performed every day by the laboratory personnel with the laboratory's materials and equipment. It checks primarily the precision (repeatability or reproducibility) of the method. External Quality Assurance Service (EQAS) which are performed periodically (i.e. every month, every two months, twice a year) by the laboratory personnel, It checks primarily the accuracy of the laboratory's analytical methods. Consequences of inaccurate results could be unnecessary treatment, treatment complications, failure to provide the proper treatment, delay in correct diagnosis, additional and unnecessary diagnostic testing leading to result in increased cost, in time and personnel effort and often in poor patient outcomes. By running quality control, a laboratory self-monitors its testing process and substantiate that the results produced are accurate and precise. Quality management system, looking at every aspect of the laboratory from sample collection to result dispatch is very important for achieving good laboratory performance. A QC programme allows the laboratory to differentiate between normal variation and error. This review article outlines indispensable role of quality control in clinical biochemistry laboratory which ensures patient satisfaction, the credibility of laboratory, generate confidence in laboratory results and reduce unnecessary financial burden.

Keywords: Accuracy, Error, Precision, Quality management

INTRODUCTION

Laboratory investigations are indispensible tools in healthcare delivery system.The laboratory tests advised for patients are used for confirmation of diagnosis, to monitor the progress of the patient and response to the treatment [1]. In today's era of Evidence Based Medicine, a clinical laboratory acts like a platform on which all departments rely for timely delivery of patient care [1]. Approximately 70% of clinical decisions are unclogged with the help of diagnostic tests [2]. A sample goes through three phases before it is converted into a confirmed report, preanalytical, analytical and postanalytical [3].

- Preanalytical phase involves all the steps before a sample is acknowledged by the laboratory, ranging from order of a test, patient preparation, sample collection, transportation, accession, and specimen preparation.
- Analytical phase refers to the processing or analysis of the sample using an autoanalyser or standardised method.
- Postanalytical phase starts after a result/signal is received from an instrument starting from reporting it (either automatically via Laboratory Information System (LIS) or manually transcribing the report), interpreting it by the physician and further follow-up [3].

SOURCES OF LABORATORY ERRORS

There are number of possible errors that can affect the quality of the clinical laboratory output. These errors can occur in preanalytical, analytical and postanalytical phases. To improve the quality, all the three phases can be targeted individually, although it is well published that most errors occur in the pre- and postanalytical phases [4-6].

Preanalytical Errors

Common problems encountered and their possible resolutions in preanalytical phase are as follows [1].

Ordering investigations: Physicians should make an aware and conscious choice before ordering a test, keeping in mind the relevance for correct diagnosis and also the irrelevance of tests that may not add to the already available knowledge [1].

Incomplete laboratory request forms: Legibility and completeness of the form are important to ensure correct tests are analysed, e.g. Age or gender of the person not mentioned on the form [1].

Patient preparation: Certain tests require few precautions or steps of preparation to be followed by the patient. Like some tests require that the patient be fasting, e.g. blood glucose, lipid profile. There may also be special timing issues for tests such as, drug levels and hormone tests. This needs to be addressed to ensure that a reliable result is generated in the end since an error at this phase makes the following steps of analysis and interpretation irrelevant, even if performed to perfection [1].

Specimen collection (potential outcomes of collection errors): Incorrect phlebotomy practices and patient information can lead to an inadequate quantity of sample collection, lipemic or haemolysed samples making their further processing difficult or impossible and subsequent unreliable results. Blood tests might require serum, plasma or whole blood. Other tests might require urine or saliva [7].

Wrong patient-specimen identification/wrong labelling of the containers: Patient identification errors before sample collection account for up to 25% of all preanalytical errors [8]. It can lead to patients being diagnosed and treated based on a sample from another patient. If not identified or correlated, outcomes can be catastrophic.

Transportation: The conditions and time between sample collection and analysis, if not followed properly are enough to affect certain analyses' values.

Errors in specimen preparation: The time spent processing the sample, including centrifugation speed and temperature, light exposure, and aliquot preparation, are critical considerations that must be weighed before the sample processing is carried out.

Not properly processing a specimen before the test or substances which interfere with test performance may affect analysis results [9].

Limitations in reducing preanalytical errors: A more significant preanalytical error source is biological variance, not linked to and uncontrollable by human error [1].

Preanalytical errors can be minimised by checking the test requisition form, name of patient on vacutainer and the requested tests. Invention of bar coding technology used in the specimen identification has been the major advance in the automation of the laboratory. Bar code label generated by LIS is read by one or more bar code reader that is placed in key positions in the analytical system. Bar code technology gives advantages of no work lists for system and prevention of mix up of tubes in the analysers during sampling [10]. Pre analytical errors can also be kept in check by asking the patient regarding food intake, alcohol intake, any drug usage, smoking, etc as these factors may influence the result, instructing patients properly for the collection of the sample, confirming the use of correct anticoagulant and the adequate amount of the sample, Inspecting the serum for haemolysis or lipemic index, maintaining the record of the time at which sample is received and when the report is ready and dispatched and observing standard operating procedures for sample processing as even time of separation, centrifuge speed and temperature at which sample get separated and the person doing that are important [7].

Analytical Errors

Reliable test results can be achieved by a careful selection, evaluation and implementation of analytical methods for investigations. Equipment, reagents and consumables forms integral parts of analytical process. Good equipment management system helps to maintain a high level of laboratory performance; reduces variation in test results, improves the technologist's confidence in the accuracy of testing results; lowers repair costs, reduces interruption of services due to breakdowns and failures. Improved quality and reproducibility of test results is also one of the biggest advantage of use of automation in the analytical phase by minimisng errors due to carry over of samples and inadequate sample mix up [11]. One of the goal of the QC is to identify between normal variation and errors.

Common Problems encountered in analytical phase are

Reference ranges: While reporting results, laboratories should have well-established reference ranges based on physiological parameters such as age, the period of gestation in case of pregnancy, gender rather than ambiguous and general ones, as the interpreting physician will be treated based on these ranges provided [7].

Participation without action: Although the lab participates in quality programs, until and unless they use that information received because of participation to ensure quality, mere participation will not help improve analytical errors.

Verify test performance: For any laboratory test parameter, its performance should be evaluated and verified with respect to its sensitivity, specificity, linearity, and precision.

Total Allowable Error (TEa): Errors that occur during the analytical phase could be either random or systematic. TEa sets a limit for combined imprecision (random error) and bias (inaccuracy, or systematic error) that are tolerable in a single measurement or single test result to ensure clinical usefulness of that particular result. Defining the allowable error is important for high accuracy and precision of the analytical process [12,13].

Analytical errors can be kept down by use of auto analysers for analysis of test parameters, ensuring the validity and acceptability of a new program, instrument, and technique for a particular test. They can also be minimised by verifying the reportable range, precision, analytical sensitivity, interferences, and accuracy, as provided by the test-specific kit insert. Analytical errors can also be held in check by using reference range specific to the physiological conditions of the patients, such as age, gender, gestation in case of pregnancy. These reference ranges should be verified by running samples of healthy individuals, scheduling daily and monthly preventive maintenance for each instrument, keeping a check on water quality, power supply, calibration of electrical balance, and calibration of glassware and pipettes, maintaining records of date for reagents and kits when received and when opened, running new lots of the reagents with the old lot in parallel before being used for analysis, monitoring quality controls using Internal quality program and external quality assurance programme [7].

Postanalytical Errors

This stage refers to transmission of data from analysers to the LIS (Laboratory Information System), validation of results that have been produced and posting of the results to physicians or patients on time and to be of diagnostic and therapeutic utility. A wrong result is equally bad as a late one, especially for critical values that, if not reported at the right time to the right physician, would delay lifesaving intervention. Common postanalytical errors include incorrect calculation or unit of measurement, transcription error, delay in delivering the results to the physicians, clinics or patients results sent to wrong patient, loss of the results [7,13].

Automation has helped reduce these errors by directly transferring results in the Laboratory Information Systems. Linking the availability of critical values directly to the mobile of the healthcare provides has further reduced time to a notification [14].

Consequences of errors at any level can lead to delayed results, repeated visits, avoidable multiple pricks, incorrect results and thereby incorrect or delayed diagnosis and treatment. The quality of patient care is compromised adding to the overall cost, patient dissatisfaction, even having lethal repercussions [15].

Irrespective of the phase during which an error occurs defending the authenticity of the result lies with the laboratory [16].

Reducing laboratory errors not only increases the confidence of reporting physicians but also of the patients in the system and helps curb any unnecessary expenditure of the hospital and lab. Thus it is of interest to check laboratory errors occurring in each laboratory and formulate corrective measures to avoid them [1].

QUALITY CONTROL

The terminologies used are as follows:

Accuracy: It refers to the closeness of a result to the actual value (True value). It is generally measured by direct comparison to a reference by using quality control serum, with an accurate value assigned to it by the manufacturer [13].

Precision: It refers to the reproducibility or closeness of values to each other [13].

Ideally a laboratory should be trying for both good accuracy and precision.

Statistical Tools Used in Laboratory for Quality Control

It is very well-known that treatment of patients depends to a great extent on the reports generated by the clinical laboratory. So, the results generated by the laboratory should be accurate. The laboratory data which is generated need to be summarised in order to monitor test performance known as quality control [17].

Normal Distribution or Gaussian Distribution

It is the basis of statistical quality control theory. Gaussian curve indicates that about 68% of all values would fall within 1SD from the mean, 95% would be expected to fall within 2SD and 99.7% would be expected to fall within 3SD value. If the value falls between 1SD range, it indicates a good control [13].

Mean: It is the most commonly used term. It is the sum of data divided by the number of observations.

Mode: It is the value that occurs most frequently in a list of observations. It is not affected by extreme values.

Median: It is the number that occupies the central position when the data is arranged in ascending or descending manner.

Standard Deviation (SD): It is a measure of how much the data varies around the mean. It is a primary indicator of precision. It is very useful to the laboratory in analysing quality control results.

Coefficient of Variation (CV): It is the ratio of standard deviation to the mean and is expressed as percentage.

Standard Deviation Index (SDI): It is the difference between individual value subtracted from the group mean divided by the SD of the group also known as Z-statistic. It is used for peer-group comparison [13,18].

QUALITY CONTROL IN LABORATORY

Quality Control (QC) monitors and evaluates the analytical process that produces patient results. The aim of QC is to evaluate the errors in prenalytical, analytical and postanalytical phase before test results are reported.The question of reliability for most testing can be resolved by regular use of quality control materials. Reliability of test results is ensured by regular testing of quality control products and statistical process control [18] before running patient samples. Quality control results will be acceptable when these are in the acceptable range of the error limit and are unacceptable when these results show excessive errors and are out of the range [18].

QC Material

These materials resemble human serum, plasma, blood, urine and cerebrospinal fluid and contain analytes of known concentration which are determined by the laboratory ideally in concentration close to the decision limits where medical decision is required. It can be liquid (ready to use) or freeze dried (lyophilised) material. It needs to be stable for prolonged periods without any interfering preservatives, should be easy to store and dispense, free from communicable diseases like bacteria, viruses, and fungi and affordable. Control samples with same analytes but different concentrations are called levels. Normal level control contains normal levels for the analyte being tested. Abnormal level control contains the analyte at a concentration above or below the normal range for the analyte. Different levels check the performance of laboratory methods across all their measuring range. In most cases, control samples are manufactured by analysers' or reagents' manufacturers, but they can also be made by the laboratory personnel [7,13,18].

Irrespective of the size of the laboratory, minimum two levels of QC should be run once on the day of performing the test. If the laboratory is operational round the clock, two level controls should be run in the peak hour subsequently one level every 8 hours [19]. In addition to above, after an instrument's servicing, change in reagent lots, after calibration, and whenever patient results seem inappropriate, QC material should be run to assure the results.

This can be done with the help of internal quality control and external quality control which are complementary to each other [20]. Internal Quality Control includes all QC methods which are performed everyday by the laboratory personnel to check primarily the precision (repeatability or reproducibility) of the method with the laboratory's materials and equipment. While EQAS comprises of all QC methods which are performed periodically (i.e. every month, every two months, twice a year) by the laboratory personnel with the contribution of an external centre (referral laboratory, scientific associations, diagnostic industry etc.) reflecting primarily the accuracy of the laboratory's analytical methods. IQC and EQAS are compared in [Table/Fig-1].

Quality Control Charts (QC Charts)

Quality control is a statistical process. QC charts are used to represent the values of control material within the defined upper and lower limit.

Internal Quality Control (IQC)	External quality control (proficiency testing)
The QC samples are internally evaluated in the laboratory in order to decide whether the results are reliable enough to be released	Compares one's lab results to other labs,
Any malfunction as the levels of the instrument, reagent, or lab personnel can be identified.	Evaluate IQC program
Performed daily by the laboratory personnel with laboratory's materials and test methods and equipment.	Performed periodically (i.e. every month, every two months, twice a year) by the laboratory personnel with the contribution of an external agency.
It primarily checks precision of test results by using control materials	It checks primarily the accuracy of the laboratory's analytical methods
Used for immediate decisions	Maintains long term accuracy (periodic and retrospective)

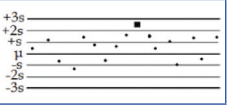
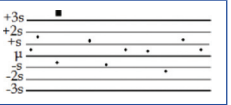
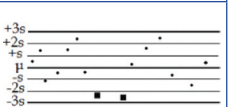
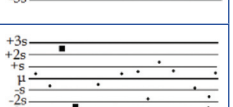
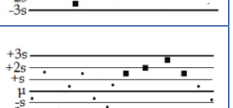
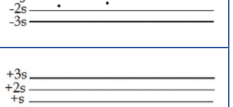
[Table/Fig-1]: Comparison between IQC and EQC.

Levey-Jennings Chart

It is the most important control chart in laboratory quality control. It can be used in internal and external quality control as well. It detects all kinds of analytical errors (random and systematic) and is used for the estimation of their magnitude [21]. It is a graphical method for displaying controls values and evaluating whether a procedure is in control or out of control. Daily control values are plotted versus time. Lines are drawn from point to point do understand any systematic or random errors [21].

Westgard Rules [22]

Error detection in the analytical phase of sample processing can be done with the help of Westgard rules. Westgard devised a shorthand notation for expressing quality control rules like NL where N represents the number of control observations to be evaluated and L represents the statistical limit for evaluating the control observations. These rules can be applied as single rules and as multi-rules. It also helps to decide whether the analytical run is in control or out of control. [Table/Fig-2] shows Westgard rules and their interpretion.

Westgard rule	Violation	Indication	Diagram
12s	One control value lies between μ+2sd/ μ+3sd or between-μ 2sd/- μ 3sd.	It is only a warning rule	
13s	One control value lies over μ+3sd or under μ -3sd.	Sensitive to random errors. It's a rejection rule.	
22s	Two successive control values lie between μ+2sd and μ+3sd or between μ -2sd and μ -3sd	Sensitive to systematic errors. It's a rejection rule.	
R4s	The distance of two successive control values, values, is over 4sd.	Sensitive to random errors. It's a rejection rule.	
41s	Four successive control values lie between μ+1sd and μ+3sdd or between μ -1sd and μ -3s.	Sensitive to systematic error. It's a rejection rule.	
10x	Ten successive control values lie between μ and μ+3s or between μ and μ3s.	Sensitive to systematic error. It's a rejection rule.	

[Table/Fig-2]: Westgard rules and its interpretation.

Important steps to follow in case of quality control failure are stop testing samples/release of reports, search for recent events that could have caused the changes, examine environmental conditions like change in room temperature or humidity, follow manufacturer's

troubleshooting guide, Root Cause Analysis (RCA), Corrective and Preventive Actions (CAPA) should be taken. Corrective action stops the occurrence of non conformities. Corrective action has to be taken when there is a problem. Preventive action gives the opportunity to prevent potential non conformities, determine the type of error [17].

Quality control errors (errors in analytical process) are classified into systematic errors and random errors. Some errors encounter as both systemic and random errors. Random error affect individual sample in random and unpredictable manner lack of reproducibility It may be due to air bubbles in the reagents, inadequately mixed reagents, unstable temperature and incubation, unstable power supply, Fibrin clot in the sample probe, poor operator technique, sudden failure or change in the light source. Systematic error displace the mean value in one direction, which may go up and down affect every test in a constant predictable manner [17].

Shifts and Trends [17]

A shift is when the QC values move suddenly upwards or downwards from the mean and continue the same way mathematically changing the mean which in turn may be due to change in reagent lot or/ and calibrator lot, change in temperature of incubators and reaction blocks, inaccurate calibration etc. A trend is when the QC value slowly moves up or down from the mean and continue moving the same direction overtime which in turn may be due to deterioration of reagents/calibrators/control material, deterioration of instrument light source, gradual accumulation of debris in sample and/or reagent tubing and failing calibration.

Random and Systematic errors must be detected at an early stage and every effort should be taken in order to minimise them. These can be avoided by well-trained staff, well-designed standard operating procedures, regular maintenance of instrument, temperature, electrical supply and thorough checking of the results.

CONCLUSION(S)

Laboratory investigations are one of the major contributors to most clinical decisions and one of the indispensible tool in the modern healthcare. Quality control is one of the components of quality assurance which is a statistical way to monitor and evaluate the analytical process. Quality Control not only ensures credibility of the laboratory but also generate confidence of customers in laboratory results. Reliable and confident laboratory testing avoids misdiagnosis, delayed treatment and unnecessary costing of repeat testing. It is the need of hour that individual laboratory should assess and analyse their own quality control process to find out the possible route cause of digressive test result which is not correlating with patients clinical presentation or expected response to treatment. Vigorous quality control processes observing latest technical advancements will contribute to reduction in wastage of resources and also minimise errors in patient management.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Jun 25, 2022
- Manual Googling: Nov 07, 2022
- iThenticate Software: Nov 11, 2022 (24%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Jun 23, 2022**
Date of Peer Review: **Aug 22, 2022**
Date of Acceptance: **Nov 14, 2022**
Date of Publishing: **Feb 01, 2023**