BIOGENIX

POLICY PROCEDURE FOR ENSURING QUALITY AND EXAMINATION RESULTS

	NAME	DESIGNATION	SIGNATURE	DATE
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1. REVISION HISTORY

#	Version	Date	Changes Made by	Reason for Changes	Clause Changed
1	1.0				

2. REVIEW HISTORY

#	Version	Date	Changes Made by	Reason for Changes	Clause Changed
1	1.0				

3. POLICY STATEMENT

3.1. This policy covers the quality control program applied in the Biogenix Laboratory

3.2. Quality Control is the essential part of day to day laboratory work to identify and correct any errors that might occur during the processing of samples. Also, to identify if there is a contamination which could affect the quality of patient results

3.3. Continuous quality monitoring and quality improvement are essentials to ensure the quality sample testing and reliable reporting.

3.4. Certain quality measures which are applied to ensure contamination free laboratory environment that could affect the quality of patient results.

4. PURPOSE

The purpose of this procedure is to define and set up guidelines for the various internal quality controls and inter laboratory comparison activities to be carried out by the technical staff daily & periodically and the various records to be maintained pertaining to these activities. This procedure is as per clause no.5.6. of ISO 15189 standard for Medical Laboratories Requirement for Quality and competence.

5. SCOPE

5.1. Scope of this policy covers quality control processes covering pre-analytical, analytical and post-analytical aspects of patient sample testing.

5.2. **Target Audience**: BIOGENIX Laboratory technologists, coordinators, and admin staff.

6. DEFINITIONS:

6.1. **Quality Control:** It is a measure of precision, or how well the measurement system reproduces the same result over time and under varying operating conditions.

6.2. **Internal Quality Control:** Laboratory quality control is designed to detect, reduce, and correct deficiencies in a laboratory's internal analytical process prior to the release of patient results, in order to improve the quality of the results reported by the laboratory.

6.3. **Proficiency Testing (PT)**: The term "Proficiency Testing" refers to any activity undertaken by a laboratory in order to provide objective evidence that they are "proficient" or "competent" to perform measurements. It is the systematic measurement, comparison with a standard, monitoring of processes and an associated feedback loop that confers error prevention.

6.4. **Inter Laboratory Comparison:** is an external way of assuring quality control among laboratories. It allows the participants to detect unsuspected errors and deficiencies in their methodology.

6.5. **Random Error:** Random errors in experimental measurements are caused by unknown and unpredictable changes in the experiment. These changes may occur in the measuring instruments or in the environmental conditions.

6.6. **Systematic Error:** Systematic errors in experimental observations usually come from the measuring instruments.

7. ACRONYMS

7.1. **CAP:** College of American Pathologists
7.2. **SD**.: Standard Deviation;
7.3. **LJ**: Levey Jenning Chart

8. RESPONSIBILITIES

8.1. All BIOGENIX Laboratory **TECHNICAL STAFF**

9. PROCEDURE

9.1. **Quality Control:**

We in **BIOGENIX lab.** refer Quality control as internal quality control. We use only approved analytical kits, reagents, for testing.

9.1.1. **Quality Control Material:**

9.1.1.1. Quality control material are as close to patient's samples as possible;
9.1.1.2. Always check the expiry date of the reagents and kits before use. Do not use them beyond the expiry date.
9.1.1.3. Reagent grade water/deionized water is used in the laboratory for processing and reconstitution.
9.1.1.4. Whenever any lyophilized control material is reconstituted, the date of reconstitution, signature of the person and validity is mentioned on the vial and it is not used beyond the stability mentioned in the insert.
9.1.1.5. Reconstituted control material is stored in the conditions specified in the product insert or as specified by the manufacturer;
9.1.1.6. Internal QC samples are processed every 24hrs and for the analytes which has running days, process controls before processing patient samples.
9.1.1.7. Both Normal and Abnormal levels of QC are processed for all the analyte before processing patient samples.
9.1.1.8. The Internal QC specimens are tested in the same manner as patient specimens and analyzed by technical staff that routinely performs patient testing.
9.1.1.9. The controls are lyophilized material based on human serum and for CBC it's a stable material resembles human blood.

9.1.2. **Quality Control in COVID laboratory:**

Quality Control is the essential part of day to day laboratory work to identify and correct any errors that might occur during the processing of COVID-19 Real Time Fluorescent RT-PCR testing. Also, to identify if there is a contamination which could affect the quality of patient results

9.1.2.1. Internal Controls are done with each plate.
9.1.2.2. There are fixed position for Negative and Positive control.

9.1.2.3. Well number C3 is for negative control and well number H12 for positive control.

9.1.2.4. Open the quality control monitoring sheet file and fill in the results of the negative and positive controls for the corresponding plate. Fill the Ct values for the FAM and VIC/HEX channels, and comment whether the quality control has passed or failed

9.1.2.5. Comment on the shape of the VIC/HEX channels of the whole plate.

9.1.2.6. The criteria for passed and failed quality control of the qPCR run is as follows:

- Blank control: Ct value values at FAM and VIC/HEX channels are 0 or no data available. If the Ct value is ≥38 at FAM channel, it means there is a contamination, so all positive patient samples should be re-extracted. If the Ct is >35 at VIC/HEX channel, accept it and continue reading the plate
- Positive control: Standard curves at channel FAM and VIC/HEX channels are in S-curve with Ct value values not higher than 32. If Ct value is zero or ≥32, repeat qPCR for the whole plate.

9.1.3. Quality Control Data:

9.1.3.1. Accepting / Rejecting a Quality Control run

a. If the QC values within the target range and the standard deviations obey the westgard QC rules then the values are accepted.

b. Following rules to be followed:
Warning if:

1: 2S	If control value exceeding either the +2SD limit or the -2SD limit.

Reject QC if:

1:3S	A Single control measurement exceeds± 3SD
R:4S	The difference between two consecutive control values exceeds 4SD's(One control measurement exceeds a + 2SD limit and another exceeds a -2SD limit)
2:2S	Two consecutive control values on the same side of the mean exceeding either the +2SD limit or the -2SD limit.

9.1.4. **Steps to be taken for Out of control situation:**

9.1.4.1. If the QC is not within the acceptable range specified do corrective action mentioned in corrective action form.

9.1.4.2. If the QC is outside the range even after QC rerun, take appropriate corrective and preventive action which may involve:

a. Check whether maintenance done or not, if not perform needed maintenance

b. Checking the Expiry date of the reagent and QC material;

c. Checking the calibration status for the analyte;
d. Checking the QC lot. and values;
e. Changing to a new reagent from the same lot;
f. Changing to a new lot of reagent;
g. Changing QC material;
h. Recalibration for the reagent
i. After calibration verify the result by processing patient sample which were processed in the last batch before QC was out of range. Check the difference and it has to be in acceptable limits.

9.1.5. Record the details of out of range QC values and the action taken in the corrective action form for Internal QC, which is reviewed by laboratory director and Quality Manager.

9.1.6. Exclude the QC which is out of range after doing corrective action.

NOTE: NO SAMPLE SHOULD BE PROCESSED TILL THE CONTROLS ARE WITH IN ACCEPTABLE RANGE

9.1.7. In case of patient's samples are processed before corrective action, check the corrective action if it is related to systematic error then in that case sample is reprocessed after corrective action.

9.1.8. In case the results are released and then QC fails: After root cause analysis and finishing the corrective action for failed controls, Process one sample from the last batch of samples and calculate the bias to check if it is within acceptable limit (±10%). If not then repeat all the samples from that batch and send the revised report. Trace the samples from previous batches too and check the acceptability on the condition that samples should be in stable condition.

9.1.9. LJ charts are checked and printed from the machine (Where we are following our lab. mean).

9.1.10. Assuring the results throughout the day: Process one sample from the morning batch in the evening and calculate the bias to check if it is within acceptable limit (±10%) or not. If not then process the controls.

9.1.11. For serology or qualitative test daily records are maintained;

9.1.12. Most of our machines calculate mean, CV% and SD automatically.

9.1.13. Establishment of Mean:

- Collect 20 data points of the new control lot. over a period of 20 days
- **Calculate mean**
- mean is changed once per lot of control.

9.1.14. Establishment of SD: SD calculated over an extended period of time, is the best possible estimation of our imprecision present in the measurement procedure.

- SD is changed after collecting 100-120 data points over a period of 4-6months
- SD can run through the control lots till very major change is there.
- Check SD. it has to be less than manufacturer SD otherwise check for the cause.
- When the new mean is close to the current mean you can use the previously calculated SD (From 100-120 data points).

9.1.15. If there is any trend seen in the chart, preventive action is taken (When seven control measurements trend in the same direction, i.e., get progressively higher or progressively lower) to prevent the harm.

9.1.16. Monitor monthly %CV and comparing with allowable imprecision value/ CVh/ Company provided with in precision guidelines.

- For the calculation of CVh (historic CV)
  - Take 6 months data
  - Calculate %CV of the analyte
  - calculate average %CV and use it as target %CV.
- If monthly %CV is out then check if controls which are out are excluded or no after corrective action.

9.1.17. All QC results are reviewed by the technical staff responsible for running the controls. Laboratory director is checking all the controls on monthly basis and in between if needed.

9.2. Inter laboratory Comparison:

9.2.1. Participation:

9.2.1.1. The Laboratory Director is the one who decide by which means inter laboratory Comparison can be done i.e. Proficiency testing or comparison with another laboratory, depending upon quality, price, convenience of lab staff and other considerations.

9.2.1.2. AMC laboratory participates in inter laboratory comparison program by CAP proficiency testing.

9.2.1.3. Proficiency sample testing is performed in the same manner as patient's sample testing.

9.2.2. General Procedure for processing PT sample:

9.2.2.1. At the time of receiving PT samples the technical staff who receives the samples check the acceptability of samples by checking the packing is intact or not, temperature is acceptable or not, and note the date of receiving.

9.2.2.2. The technical staff is responsible for performing the analysis in the specified time and of sending the results.

9.2.2.3. The results are returned within a specified time.

9.2.2.4. Check all the results and if any discrepancy do corrective action as mentioned in the Investigation Form for External Control out of range.

9.2.2.5. All samples are processed as per the instructions of the sample provider.

9.2.2.6. The remaining quality control sample is stored as per instructions until receiving the results.

9.2.2.7. Submission of results and checking of results

FOR CAP SAMPLES

i. After checking result the result sheet is filled.

ii. Method code, instrument code and test code are filled in result sheet properly.

iii. Send the result online by logging at www.cap.org.

User name: and password:

log in → e.lab solutions →proficiency testing → Result form→ view → carefully enter data.

iv. The same way as we logged in for result submission login again to check our proficiency testing result
log in → e.lab solutions → proficiency testing →Result review →view →print report → approve by laboratory director → put in external qc file.

v. The provider of Proficiency testing material issues comprehensive reports which include histograms for each analyte, SDI, mean and comparison of the results with other participating laboratories.

vi. The results are verified and comments regarding the general performance is documented by the laboratory director and circulated to all section staff.

vii. For results falling outside the range, corrective actions are documented by the concerned technologist.

viii. The received report and the corrective actions if any are communicated to all section staff.

9.2.3. **Root cause Analysis in case of unacceptable results:**

In case any result is out of range:

9.2.3.1. Check the control of the reagents on the same date you had run the sample before you sent (document it in PT file).

9.2.3.2. Check the latest control values on the same date you received the report and rerun the sample.

9.2.3.3. If the values are within range so it could be some random error but if still out of range, monitor the next cycle results and inform the instrument application specialist (manufacturer) if the two cycles are out of range.

9.2.3.4. Errors:

9.2.3.4.1. <u>Random error</u>:

i. Causes

- Un calibrated pipettes;
- Defect in reaction temperature;
- Un appropriate Timings;
- Improper Mixing.

ii. Suggested actions If there is Evidence of Random Error:

- Rule out errors from non-analytical sources (transcription error, misplaced specimens, calculation error).
- Investigate components of the analytical system (sample probes, reaction cells, reagents).

- Review internal QC performance. Look for trends or shifts that may not yet trigger your rejection rules. Assess the process of setting and changing QC target values.
- Use assayed control material to evaluate performance.

9.2.3.4.2. <u>Systematic error:</u>

i. Causes

- Altered composition of control materials;
- Altered composition of calibrators;
- Deterioration or expired reagents or controls

ii. Suggested Actions If There Is Evidence of Systematic Error:

- Review internal quality control (QC)performance. Look for trends or shifts that may not yet trigger your rejection rules. Assess the process of setting and changing QC target values.
- If recalibration has not already occurred, recalibrate the instrument.
- If participating in an external QC performance program, review comparative reports for QC performance. If the laboratory performance on a lot of QC material is at consistent variance with the group performance mean, further investigation is warranted.
- Use assayed control material to evaluate performance.

9.2.4. Alternative Approaches:

9.2.4.1. In case of not sharing in PT we do comparison by choosing any of following method:

- Exchange of samples with other laboratories: exchange of 12 samples in duration of one year in a way 1 sample per month.
- control materials that are tested daily in inter laboratory comparison programs

9.2.4.2. Reports are checked for any discrepancies and if any corrective action needed that is done in timely manner and is documented.

9.2.5. Analysis of Inter laboratory comparison Samples:

9.2.5.1. Tests are performed as per the manufacturer instructions.

9.2.5.2. Samples are tested along with the laboratory's regular workload **by personnel who routinely perform the laboratory test** using routine methods.

9.2.5.3. Personnel are testing the PT samples the same number of times that they routinely test patient samples.

9.2.5.4. Results are submitted back to the provider within the required time period.

9.2.5.5. Records of test handling, examination, and reporting of results are retained for two years.

9.2.5.6. Communication between laboratories about the results of proficiency testing occurs only after the last date of submission of the laboratory results for the testing event to the provider.

9.2.5.7. No PT sample is sent to other laboratory for confirmation before the deadline of submission of results.

9.2.6. Evaluation of Laboratory performance:

CAP Reports:

9.2.6.1. The CAP issues comprehensive reports which include histograms for each analyte, SDI, mean and comparison of the results with other participating laboratories.

9.2.6.2. For CAP results we are monitoring **SDI** and allowed/acceptable deviation from the mean: If SDI is >3 and Percent deviation from mean is >80% then we do root cause analysis.

- **SDI:** The SDI is obtained by subtracting the group mean from our result and then dividing by the group SD

$$\textbf{SDI} = \frac{\text{Our Result} - \text{Group mean}}{\text{Group SD}}$$

- **Allowed/ Acceptable deviation**:

If our result is greater than the target mean:

$$\textbf{Percentage of Acceptable Deviation} = \frac{\text{Our Result} - \text{Target mean}}{\text{Upper limit} - \text{Target Mean}} \times 100$$

If our result is Less than the target mean:

$$\textbf{Percentage of Acceptable Deviation} = \frac{\text{Our Result} - \text{Target mean}}{} \times 100$$

Target Mean - Lower limit

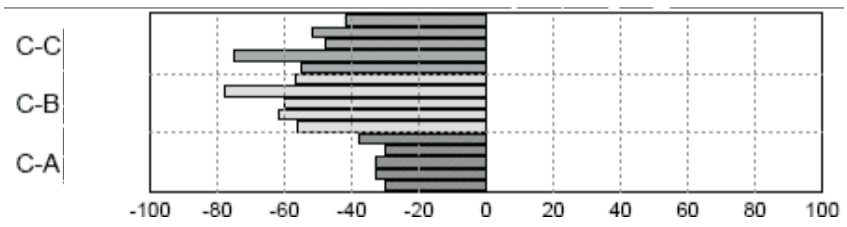
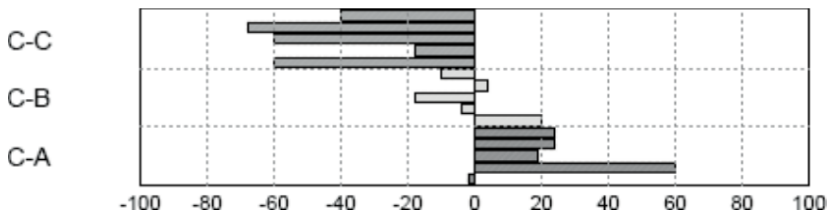
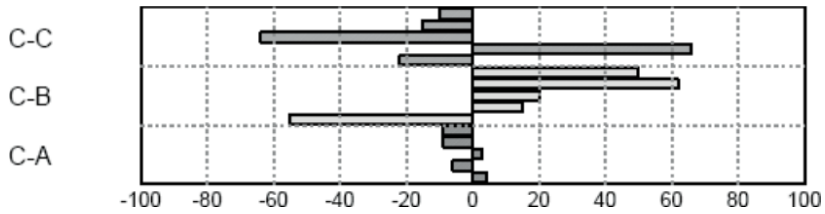
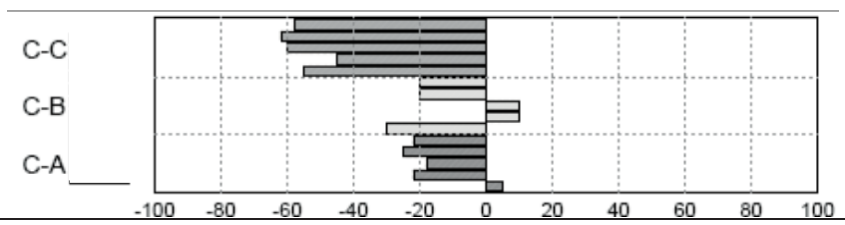
9.2.6.3. Guidelines for monitoring PT performance using the evaluation graphs

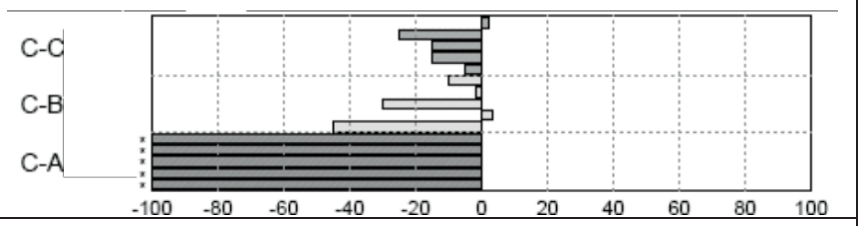
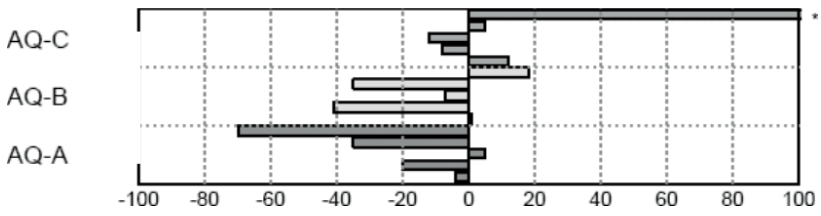
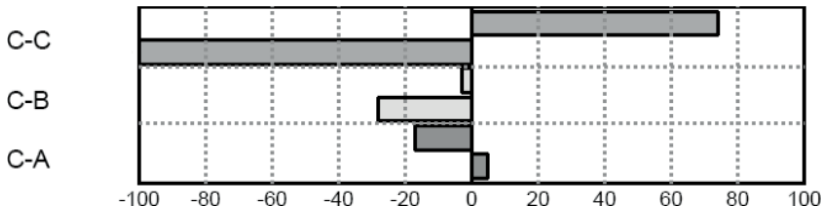
Patterns in PT Evaluation Graphs for a Single Mailing		
Rule	**Comments**	**Suggested Actions**
One result in a mailing exceeds ±75% of the allowed deviation	Review results to rule out possible problems; identify possible errors from non-analytical sources such as clerical errors for results that exceed ±100% of the allowed deviation	If the data fail either of the rules below, follow the suggested actions for systematic or random error, as appropriate
All results are on one side of the target values with at least 1 difference exceeding ±50% of the allowed deviation	Shows bias indicating a possible calibration drift; there would be less concern if the relative differences were all close to 0	See listing of suggested actions for evidence of systematic error
Large positive and negative differences; combined lengths of longest positive and negative bars is > 140 out of total range of 200	Shows possible random error	See listing of suggested actions for evidence of random error

Time Trends in PT Evaluation Graphs over Multiple Mailings		
Rule	**Comments**	**Suggested Actions**
Persistent results on one side of the target values	Shows persistent bias, even if small; recalibration should have occurred within this time frame	See listing of suggested actions for evidence of systematic error
Results flip from one side of the target to the other	Shows impact of system and/or process changes; longer bars are of more concern	See listing of suggested actions for evidence of systematic error

Over time, length of bars increase	A sudden shift may show impact of system and/or process changes; may reveal new source of either systematic or random error	Follow the suggested actions for systematic or random error, as appropriate
Over time, length of bars decrease	Shows impact of system and/or process changes, particularly as a result of corrective action	Retain as documentation that corrective action has been successful

9.2.6.4. Various patterns in cumulative PT results

Evidence of persistent bias spanning recalibration. Review process of setting QC target values; evaluate performance with assayed control material.	
Results flip from positive to negative bias. Review records to confirm system and/or process change. Follow suggested actions for systematic error.	
Over time, lengths of the bars increase on both sides of 0. For this pattern, follow suggested actions for random error.	
Over time, lengths of the bars increase primarily on one side. For this pattern, follow suggested actions for large systematic error.	

Lengths of the bars decrease. Corrective action following a previous failure can be easily demonstrated.	
Plot shows a result exceeding ±75% of the allowed deviation. This problem was due to a transcription error where results for Hgb and hematocrit were switched.	
Many PT challenges are for non-regulated analytes that can be identified as having only two samples. The same general patterns appear for non-regulated analytes, though with fewer data points on each plot. Here the C mailing samples were switched.	

9.2.6.5. Additional Comments on Incorporating Daily QC into the Interpretation of PT Performance

9.2.7. When reviewing proficiency testing performance, it is important to identify current and potential failures by inspecting the SDIs and graphs of relative distances. Evaluation of QC data preceding the challenge, at the time of the challenge, and following the challenge helps to identify possible problems and solutions. The QC records indicate when recalibration and reagent lot changes occurred. All other laboratory records used in evaluating the proficiency samples and reporting the proficiency results are collected and examined when reviewing possible sources of problematic PT results.

9.2.8. The laboratory director review the report received and review is documented.

9.2.9. The results are verified and comments regarding the general performance is documented by the laboratory director and circulated.

9.2.10. The results are circulated among all staff of the lab. so that they are aware of the lab. Performance and they are signing after going through the results.

9.2.11. Remedial actions are documented for any single or multiple challenge(s) of each analyte that does not fall within acceptable limits.

9.2.12. The effectiveness of root cause is monitored by checking the results of PT results for next cycle and also through Internal controls results.

9.2.13. The results of PT samples are checked by Laboratory manager for any trend.

9.2.14. For results falling outside the range, corrective actions are documented by the concerned technologist.

9.3. Comparability Testing:

9.3.1. The analyte which can be processed in two instruments we are doing comparability testing by comparing 20 samples in both the instruments.

9.3.2. All the results and raw data are retained.

10. CROSS REFERENCE

10.1. www.westgard.com/lesson18.htm

10.2. www.cap.org.(Trouble shooting guide for proficiency testing data)

10.3. ISO 15189 standard for Medical laboratories Requirement for Quality and competence.

11. RELEVANT DOCUMENTS & RECORDS

11.1. BG/REC/QC/001 CV monitoring sheet

11.2. BG/REC/QC/002 Internal control Corrective action form