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# Six-Sigma Methodology for Quality Monitoring in a Teaching Hospital Biochemistry Laboratory in Nepal

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## ABSTRACT

### Introduction

Six-sigma is emerging method of choice for performance testing of clinical laboratory. This study was designed to evaluate the performance of 12 routine biochemical analytes on sigma-scale and calculate the quality goal index (QGI).

### Methods

A cross-sectional study was conducted at Tribhuvan University Teaching Hospital (TUTH), Biochemistry Laboratory for 3 months. BT1500 and BT3500 automated biochemistry analyzers were used. Internal quality control (IQC) performed routinely for 12 clinical analytes for both control levels were recorded from both analyzers and used for calculation of coefficient of variation (CV%). Bias was estimated based on the average difference obtained for each analyte from the target values provided. Values for total allowable errors (TEa) were taken from Clinical Laboratories Improvement Act guidelines. Variables used for calculation of sigma values and QGI were CV%, percentage bias and TEa.

### Results

Both levels of control for alanine-aminotransferase (ALT) in BT1500 and only control level L2 for aspartate-aminotransferase (AST) in both analyzers showed the sigma value greater than six. Sigma-values between three and six were found for uric acid for both levels of control in both analyzers. Less than three sigma values were obtained for parameters urea, creatinine, albumin, triglyceride, total-cholesterol, alkaline phosphatase (ALP) and magnesium for both levels of control in both analyzers indicating the need towards improvement in these methods.

### Conclusion

The quality of test for urea, creatinine, albumin, triglyceride, total-cholesterol, ALP and magnesium were unacceptable. Hence, appropriate actions should be taken towards measurement method in these parameters to improve accuray and report quality.

**Keywords**
*Bias, IQC, quality goal index, six-sigma, total allowable error*

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## INTRODUCTION

Clinical laboratories are crucial part of the healthcare system.[1] Most of the clinical decisions are based on the reports dispatched by the laboratory. On the other hand, maintaining the quality performance for each individual clinical analyte is very challenging. Internal and external quality control run cannot estimate the exact number of errors for any analyte processed in a laboratory.[2] A recent method of quality control named Six-Sigma is emerging rapidly. Although first used by Motorola Inc. in 1986, it has become very useful tool in laboratories for proficiency testing.[1,3] It helps to achieve desired quality of the laboratory by quantifying the errors. Define, measure, analyze, improve and control steps incorporated in six-sigma methodology are the basis for improvement in the quality process.[4] Following these steps errors can be reduced, quality reports can be generated with minimum process variability.

Six-sigma as a quality control tool helps to quantify the errors with 99.99966% accuracy accompanying just 3.4 defects per million (DPM).[1,5] Higher the sigma value indicates the lower errors produced. Six-sigma has been set-up as a limit for cost effective production of results.[6] Performance at minimum 3 sigma scale is considered to be acceptable for a given process below which the results produced are judged unreliable and should not be continued for routine tests.[1,6]

The present study was conducted to observe the performance of two automated biochemistry analyzers BT1500 and BT3500 by calculating the sigma value of 12 clinical analytes and to determine the errors associated with each individual parameters.

## METHODS

This cross-sectional study was conducted in biochemistry laboratory, Tribhuvan University Teaching Hospital (TUTH). Internal quality control (IQC) material from Giesse Diagnostics, Italy was used. The lyophilized material for both control levels were mixed with 5 ml of distilled water and aliquoted into different Eppendorf vials which can be used for a month storing at 2-8$^0$C. Every month lyophilized control material was made and stored. Three months, June to August 2019, internal quality control data using fully automated biochemistry analyzers BT1500 and BT3500 was recorded for both levels of control, normal (L1) and pathological (L2). Twelve biochemistry parameters included under study were- glucose, urea, creatinine, uric-acid, total protein, albumin, alanine-aminotransferase (ALT), aspartate-aminotransferase (AST), total cholesterol, triglyceride, alkaline phosphatase and magnesium. Both the biochemistry analyzers were calibrated as per manufacturers' guidelines and both levels of controls were run for each parameter. The obtained internal QC data for all 12 analytes were also plotted on Leavy-jennings chart and westgard rules were followed to monitor quality of each individual clinical analytes under study.

Sigma metrics involves a simple calculation, all that is needed is to decide the quality goals (TEa)- taken from Clinical Laboratories Improvement Act (CLIA) guidelines for various clinical analytes and the method's imprecision i.e. coefficient of variation (CV%) and bias level as is done in the method validation studies.[1,7]

The CV (method imprecision) was calculated using the formula:

$$CV(\%) = [\text{Standard Deviation (SD)}/\text{Mean}] \times 100$$

The bias which is systematic difference between expected results obtained in laboratory by its method and the result that would have obtained by accepted reference method. Percentage bias was calculated by the difference of the average obtained from the target values provided for each parameter. Therefore, the bias is 'relative' rather than 'absolute' in this study.[8]

$$\text{Bias}\% = [(\text{Mean of measured value} - \text{target value})/\text{target value}] \times 100$$

Then, using the formula below sigma matrices can be calculated as

$$\text{Sigma} = (\text{TEa} - \text{bias})/\text{CV}$$

Where, TEa is total error allowable (quality goal), bias and CV (coefficient of variation) are the indicator of systematic and random errors respectively.

The number of defects that occurs at a certain sigma value and percentage accuracy is represented by the Table 1.

For the automated analytical tests to achieve quality

*Table 1. Sigma level and defects per million*

| Sigma value | Accuracy (%) | Defects per million |
|---|---|---|
| 6 | 99.9997 | 3.4 |
| 5 | 99.98 | 233 |
| 4 | 99.4 | 6210 |
| 3 | 93.3 | 66,807 |
| 2 | 69.1 | 308,537 |
| 1 | 31 | 698,000 |

*Table 2. Quality goal index (QGI) ratio interpretation criteria*

| QGI | Problem |
|---|---|
| <0.8 | Imprecision |
| 0.8-1.2 | Imprecision and Inaccuracy |
| >1.2 | Inaccuracy |

improvement it is very important to understand the shortcomings of the tests, either it is excessive imprecision, bias or both. Quality goal index ratio represents the relative extent to which both bias and precision meet their respective quality goals.[9] It was used to clear the reason behind low sigma score by various analytes. QGI ratio was calculated as, QGI= Bias/1.5CV.[9] Interpretation criteria for the analysis of the analytes which fall short of six-sigma quality are shown in the Table 2.

## RESULTS

Calculated CV, percentage bias and TEa values from the CLIA guidelines for both levels of control (L1 and L2) used are shown in Table 3 which indicates that bias and CV of parameters like urea, creatinine, albumin, total cholesterol, alkaline phosphatase and magnesium are high enough that resulted in computation of low sigma value. AST, total cholesterol and alkaline phosphatase have comparable bias and CV from both analyzers for both L1 and L2 which resulted in similar sigma score for them as shown in Table 4 and 5. Sigma values and quality goal index (QGI) for each clinical analytes for both levels of control from both analyzers were calculated and summarized in Tables 4 and 5.

It showed that in BT1500 both levels of control for ALT had the sigma value greater than 6. Control level L1 of glucose, uric acid and AST scored sigma value between 3 and 6 whereas both the levels of control for urea, creatinine, albumin, total cholesterol, triglyceride, alkaline phosphatase and magnesium showed the unacceptable sigma values below 3. Along with this parameters that performed poorly on sigma scale like urea, creatinine, triglyceride and magnesium showed the problem to be both imprecision and accuracy. Glucose, AST, total protein, albumin and total cholesterol pointed towards imprecision whereas uric acid and ALP had the problem of inaccuracy as shown by their QGI score in Table 4.

*Table 3. TEa, CV%, and Bias% obtained for various parameters from BT 1500 and BT3500*

| Parameters | TEa | BT1500 | | | | BT3500 | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Bias% L1 | CV% L1 | Bias% L2 | CV% L2 | Bias% L1 | CV% L1 | Bias% L2 | CV% L2 |
| Glucose | 10 | 1.63 | 1.97 | 2.27 | 2.58 | 0.81 | 3.92 | 2.61 | 2.38 |
| Urea | 9 | 29.37 | 8.98 | 3.17 | 6.19 | 11.31 | 7.54 | 6.88 | 3.99 |
| Creatinine | 15 | 10.61 | 5.16 | 2.43 | 4.20 | 13.81 | 3.49 | 2.84 | 13.50 |
| Uric acid | 17 | 2.92 | 2.66 | 14.59 | 2.91 | 1.02 | 2.98 | 10.78 | 3.80 |
| AST | 20 | 4.11 | 3.18 | 0.20 | 1.89 | 4.11 | 3.26 | 0.18 | 2.14 |
| ALT | 20 | 1.67 | 2.70 | 4.48 | 2.38 | 4.97 | 5.06 | 0.15 | 4.04 |
| Total protein | 10 | 3.35 | 3.65 | 1.75 | 2.37 | 4.62 | 3.47 | 3.10 | 3.12 |
| Albumin | 10 | 8.64 | 7.21 | 6.02 | 3.81 | 3.25 | 5.12 | 4.04 | 3.66 |
| Total cholesterol | 10 | 7.39 | 5.81 | 5.09 | 2.88 | 7.98 | 6.75 | 7.04 | 3.23 |
| Triglyceride | 25 | 2.91 | 9.15 | 12.29 | 4.37 | 5.82 | 6.23 | 8.19 | 3.03 |
| ALP | 30 | 27.88 | 7.16 | 26.15 | 6.09 | 30.58 | 4.88 | 26.97 | 5.73 |
| Magnesium | 25 | 5.38 | 10.58 | 17.74 | 5.98 | - | - | - | - |

*Table 4. Calculated sigma values and quality goal index (QGI) ratio for each parameters from BT1500*

| Parameters | Six-sigma (6σ) Values | | Quality Goal Index (QGI) Ratio | | |
|---|---|---|---|---|---|
| | L1 | L2 | L1 | L2 | Problem |
| Glucose | 4.24 | 2.99 | 0.5 | 0.5 | Imprecision |
| Urea | -2.26 | 0.94 | 2.2 | 0.3 | Imprecision and Inaccuracy |
| Creatinine | 0.85 | 2.99 | 1.4 | 0.4 | Imprecision and Inaccuracy |
| Uric acid | 5.29 | 0.82 | 0.7 | 3.3 | Inaccuracy |
| AST | 4.99 | 10.47 | 0.8 | 0.07 | Imprecision |
| ALT | 6.78 | 6.52 | 0.4 | 1.2 | None |
| Total protein | 1.82 | 4.48 | 0.6 | 0.5 | Imprecision |
| Albumin | 0.19 | 1.04 | 0.8 | 1.0 | Imprecision |
| Total cholesterol | 0.44 | 1.70 | 0.8 | 1.1 | Imprecision |
| Triglyceride | 2.41 | 2.90 | 0.2 | 1.8 | Imprecision and Inaccuracy |
| ALP | 0.30 | 0.63 | 2.5 | 2.8 | Inaccuracy |
| Magnesium | 1.85 | 1.21 | 0.3 | 1.9 | Imprecision and Inaccuracy |

*Table 4. Calculated sigma values and quality goal index (QGI) ratio for each parameters from BT3500*

| Parameters | Six-sigma (6σ) Values | | Quality Goal Index (QGI) Ratio | | |
|---|---|---|---|---|---|
| | L1 | L2 | L1 | L2 | Problem |
| Glucose | 2.34 | 3.10 | 0.1 | 0.7 | Imprecision |
| Urea | 0.30 | 0.53 | 1.0 | 1.1 | Imprecision and Inaccuracy |
| Creatinine | 0.34 | 0.90 | 2.6 | 0.1 | Imprecision and Inaccuracy |
| Uric acid | 5.36 | 1.64 | 0.2 | 1.9 | Inaccuracy |
| AST | 4.87 | 9.26 | 0.8 | 0.05 | Imprecision |
| ALT | 2.97 | 4.91 | 0.6 | 0.02 | Imprecision |
| Total protein | 1.55 | 2.21 | 0.8 | 0.5 | Imprecision |
| Albumin | 1.31 | 1.62 | 0.4 | 0.7 | Imprecision |
| Total cholesterol | 0.30 | 0.91 | 0.7 | 1.4 | Imprecision and Inaccuracy |
| Triglyceride | 3.07 | 5.54 | 0.6 | 1.8 | Imprecision and Inaccuracy |
| ALP | -0.11 | 0.52 | 4.1 | 3.1 | Inaccuracy |

In BT3500 sigma value greater than 6 was found only for control level L2 of AST. Control level L1 of AST and uric acid; control level L2 of glucose and ALT, along with both levels of control for triglyceride showed the acceptable sigma values between 3 and 6. Beside these, unacceptable sigma values of less than 3 were obtained for urea, creatinine, total protein, albumin, total cholesterol and alkaline phosphatase for both levels of control. Similarly urea, creatinine, total cholesterol and triglyceride showed the problem with both imprecision and inaccuracy. Glucose, AST, ALT, total protein, albumin had difficulties with imprecision only whereas uric acid and ALP showed inaccuracy as depicted by QGI ratio in Table 5. Thus, it can be observed that there is not much performance difference in both the BT analyzers used in TUTH biochemistry laboratory.

IQC for magnesium was performed only in the automated biochemistry analyzer BT1500.

## DISCUSSION

Evaluation of the performance of clinical laboratory is very important to provide the reliable test reports to the patients. Being an emerging tool in the developing countries six-sigma has not been adopted currently in clinical laboratory setting. The six-sigma includes bias and CV which accounts for the systemic and random errors of the laboratory respectively, thereby, exclusively guiding the quality management of the laboratory while analyzing the possible causes of error, finding better solutions to assure quality result and rescheduling the quality control (QC) time.[8]

The sigma value of some of the parameters in this study such as urea, creatinine, albumin, alkaline phosphatase, magnesium, total protein and cholesterol showed considerable variation among different studies as shown in Table 6. These variations are due to use of different types of biochemistry analyzers, reagents and quality control materials. Along with these factors pre-analytical and analytical conditions also played major role in results variation.[3] Even though TEa values were attributed from the same source (CLIA), the bias calculation was major contributing process towards sigma value calculation.[7] Other studies included the external quality control (EQC) samples for bias calculation but present study used the internal quality control samples (IQC) samples as the EQC samples are not frequently available in our laboratory so the calculated bias is relative.[7] Also, the duration of the study contributed to the coefficient of variation (CV). Longer duration studies with large sample size have less CV compared to the short duration studies.[8]

More interestingly, wide variation among the sigma value of same analyte for two control levels was found such as for total protein, AST, uric acid, triglycerides and ALT in current analyzers. This situation was not limited only to this study but similar results were also found among other studies too. Inconsistency among these studies may be due to methodology used which results in performance difference with normal and abnormal concentration in QC material.

Internal quality control (IQC) process is regularly needed to be performed in clinical laboratory setting before dispatching reports. So obtained IQC results are plotted in Leavy-jennings chart to monitor the quality control with westgard rules. In this study in BT1500 only ALT had sigma value of above 6, so only one QC rule 13s needed to be followed. Similarly, analytes with sigma value ≥5, 13s/22s/R4s rules must be followed and with sigma value ≥4, 13s/22s/R4s/41s rules are required.[10] Most of the other parameters in both analyzers like total protein, albumin, urea, creatinine and magnesium performed poorly with sigma value below 3. Thus, improvement in testing methodology becomes the only option to obtain desired quality.[10,11]

*Table 6. Comparison of our study with various other studies based on sigma scale*

| Parameters | Shao et al[10] | Singh et al[12] | Kumar et al[13] | Patel et al[5] | Present study |
|---|---|---|---|---|---|
| Total analytes | 20 | 15 | 10 | 12 | 12 |
| Study period | 5 months | 6 months | 4 months | 12 months | 3 months |
| Instruments | Beckman-coulter AU 5800 | Olympus biochemistry analyzer | ILAB-650 auto-analyzer | Cobas-integra-400 plus auto-analyzer | BT 1500 and BT 3500 auto-analyzer |
| QC levels | 2 | 2 | 2 | 2 | 2 |
| IQC sample | Bio-rad | Randox | Bio-rad | Bio-rad | Giesse |
| TEa guidelines | CLIA | CLIA | CLIA | CLIA | CLIA |
| Six-sigma value | | | | | |
| >6 | Amylase, HDL, TG, AST, ALP, uric-acid | HDL, ALP, Bilirubin, creatinine | - | ALP, AST, ALT, TG, uric-acid, glucose | ALT (L1), AST (L2) |
| 3-6 | Total protein, CK, glucose, albumin, CHOL | Glucose, urea, AST, ALT, CK, amylase | Glucose, ALP, total protein, TG, HDL, uric-acid | Albumin, CHOL, Bilirubin, total protein | Glucose (L1), uric-acid, TG, total protein |
| <3 | Urea, sodium | CHOL, TG, Protein | AST, ALT, CHOL | Urea, creatinine | CHOL, ALP, Mg, urea, creatinine, albumin |

Additionally, quality goal index (QGI) was also calculated for all the analytes scoring sigma value below 6 to find the problem is either imprecision, inaccuracy or both. All the analytes below sigma value 6 showed QGI of <0.8 indicating the need of improvement to be imprecision except ALP whose QGI was >1.2 requiring the improvement in the area of inaccuracy. Some of the analytes like urea, creatinine, total cholesterol, magnesium and triglycerides scored QGI between 0.8 and 1.2 which requires the monitoring in both the areas of imprecision and inaccuracy.

Calculating the sigma values for each parameter had become useful for accessing the performance of the laboratory analyzers. Necessary quality controls rules can be implemented for the needed analytes to reduce the errors produced by the applied method and save the time and cost of the laboratory, establishing the total quality management.[14] This study was done to analyze the performance of routine biochemical parameters based on six-sigma and quality goal index (QGI). Overall, use of six-sigma methodology as a tool for quality control in our laboratory has revealed the need towards requirement of more advanced and accurate analyzers in today's competitive healthcare system.

## CONCLUSION

Sigma value for ALT was found to be more than 6 in BT1500 for both levels of control whereas sigma level of 3-6 was found for glucose, uric acid, AST and triglycerides. All other analytes were below 3 sigma value in both analyzers. The use of six-sigma methodology showed the performance of the automated clinical chemistry analyzers used with no significant difference in present context. On the other hand QGI ratio for the analytes below sigma value six helped to identify the problem to be either imprecision, inaccuracy or both. Thus, application of six-sigma rule has become one of the necessities to laboratories in the today's competitive world as it helps to design the protocol for IQC, point out the poor assay performance and maintain the efficiency of the laboratory process.

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## CONFLICT OF INTEREST

None declared.

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