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Application of Six Sigma tool as Quality Indicator for evaluation of analytical phase of sample processing

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Abstract
Introduction: In a Clinical Biochemistry Laboratory (CBL), the measures used to assess the QC are Internal QC (IQC) and EQAS. For Quality assessment in an objective and quantitative manner, sigma metrics have been used. Higher Sigma metric values represents few analytical; i.e. 3.4 defects per million opportunities. Based on the sigma metrics, appropriate QC rules are applied. The present study intends to evaluate the performance of Analytic phase of testing at Laboratory Services, GMERS Medical College & General Hospital Vadnagar in terms of Sigma metrics, and Quality Goal index for routine biochemical parameters.**Material Method:**We calculated (A) Sigma (σ) value and (B) Quality goal Index of 14 parameter. Sigma metrics were calculated using Total allowable goals as per i) Clinical Laboratory Improvement Amendments (CLIA) guidelines from US(2019) and ii) the biological variation database specifications. Microsoft Excel spreadsheet version 2016 was used for statistical analysis. Bias, CV, QGI and sigma metrics were calculated using the above formulae. Bias and CV were presented as percentages.**Result:**For 2 parameters; Urea and ALT sigma metrics was more than 6, which is a marker of world class quality. The lower performance of Total Bilirubin, Creatine, Cholesterol, HDL, Uric acid, Total Protein, Albumin in was however attributable to both lack of accuracy while for IQC norm and path.**Conclusion:**Sigma metrics is an excellent self-assessment tool for performance analysis of various test parameters in the laboratory. On applying the same to our routine biochemistry laboratory at Laboratory Services.
Key Words: Clinical Biochemistry Laboratory, Six Sigma, Quality Goal Index, Total allowable error

Introduction

Clinical laboratories play a major role in healthcare system[1]. Approximately, two-thirds of important clinical decisions on patient management are based on laboratory test results[2]. In a Clinical Biochemistry Laboratory (CBL), the measures used to assess the QC are Internal QC (IQC) and EQAS[3]. IQC is an important part of laboratory quality management whose products can determine the reliability of test results[4]. IQC is interpreted using the standard Westgard rules and is run daily, as per National Accreditation Board for Testing and Calibration Laboratories (NABL) guidelines. IQC keeps an eye continuously on the analytical system to check whether the results are reliable enough to be released or not. Contrarily, EQAS sample, which is supplied by an outside agency[5].

In clinical laboratories, for Quality assessment in an objective and quantitative manner, sigma metrics have been used[6]. The evolution of sigma metrics methodology by Bill Smith back in 1986[7]. Sigma metric is a composite measure of the total allowable error (method specific), bias (EQAS) and imprecision (CV% of IQC). Analysis of sigma metrics acts as a standardized scale for comparing the quality of test performance.

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Higher Sigma metric values represents few analytical errors with fewer questionable tests being accepted; to the tune that six sigma assay indicates 99.99966% of results being error free; i.e. 3.4 defects per million opportunities. Further, based on the sigma metrics, appropriate QC rules are applied[8–10].Sigma metrics can quantify the exact number of errors done in the analytical phase by the laboratory that cannot be gauged by running the internal and external QCs[11]. International Standard for Medical Laboratories Accreditation (ISO 15189: 2012) which recognizes the need to subdivide the Total Testing Procedure (TTP) into pre-examination, examination and post-examination procedures, commonly defined as pre, intra and post-analytical phases[12].

The present study intends to evaluate the performance of Analytic phase of testing at Laboratory Services, GMERS Medical College & General Hospital Vadnagar in terms of Sigma metrics, and Quality Goal index for routine biochemical parameters.

Material Method

This retrospective study was conducted at Clinical Chemistry laboratory, GMERS Medical College & General Hospital, Vadnagar. Study is approved by Institutional scientific committee.

The aim of our study was to quantify performance in the analytical phase of the testing process in Clinical Chemistry Laboratory using quality indicators and to compare our results with those reported in the literature.

We calculated (A) Sigma (σ) value and (B) Quality goal Index of following 14 parameter. The parameters included in the study were

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Glucose, Urea, Creatinine, Total Bilirubin, Total protein, Albumin, , Uric acid, Cholesterol, HDL, Triglycerides (TG), Aspartate Transaminase (AST), Alkaline Phosphatase (ALP), Alanine Transaminase (ALT), and Amylase for the period from January 2020 to December 2020.

For all these parameters, imprecision was estimated using CV% which is a measure of variability of an assay and indicator of random errors[13].

(A)Sigma (σ) value

Sigma metrics were calculated using Total allowable goals as per i) Clinical Laboratory Improvement Amendments (CLIA) guidelines from US(2019) and ii) the biological variation database specifications. Sigma metrics was calculated as:

Sigma = TEa - Bias/ CV

Sigma was calculated using CV% for both levels of Internal Quality control (ERBA Norm & Path) using TEa targets from both CLIA guidelines and the biological variation database specifications[14,15]. Bias however is an indicator of accuracy and systematic errors in analysis. Bias % was calculated for each parameter by using the Monthly EQAS report from CMC, Vellore.

(B)Quality goal Index

The QGI ratio denotes the relative extent to which both bias and precision meet their respective quality goals [15]. The QGI ratio was calculated using the following formula[16].

QGI=Bias×CV%/1.5

QGI can be used to assess the reason for lower sigma (due to imprecision or inaccuracy or both) in some analytes [Table/Fig-1]. QGI ratio of <0.8 indicated imprecision, ratio of 0.8-1.2 indicated imprecision and inaccuracy and a ratio >1.2 indicated inaccuracy and was used in case test parameters fell short of six-sigma quality.

Table 1: Criteria for interpreting QGI ratio.	
QGI (Quality Goal Index)	Problem
<0.8	Imprecision
0.8-1.2	Imprecision and inaccuracy
>1.2	Inaccuracy

Statistical analysis

Microsoft Excel spreadsheet version 2016 was used for statistical analysis. Bias, CV, QGI and sigma metrics were calculated using the above formulae. Bias and CV were presented as percentages.

Result

Table 2 and 3 represents the CV% for all analytes for IQC - Norm and Path from January 2020 to December 2020 along with the mean value of CV%

Table 2: CV% for all analytes for IQC - Path

Parameter -Norm	January	February	March	April	May	June	July	August	September	October	November	December	Average
Glucose	3.25	2.3	3.1	2.6	3.5	1.9	3.2	4.1	3.2	3.6	2.8	1.4	**2.91**
Urea	3.5	1.9	3.3	3.6	2.5	2.8	2.7	3	1.9	3.8	4.1	2.9	**3.00**
Creatinine	1.5	2.5	1.6	2.8	2.9	3.5	1.8	2.5	2.4	2.7	2.9	2.7	**2.48**
Bilirubin	3.9	4.1	3.9	4.9	5.2	5.6	4.3	4.7	5.6	6.7	7.2	7.9	**5.33**
Protein, Total	3.6	4.3	4.37	3.6	3.9	1.8	2.9	3.5	3.7	3.8	3.7	3.2	**3.53**
Albumin	3.6	3.7	4.2	3.9	2.5	2.8	1.9	2.8	3.9	1.4	1.9	4.9	**3.13**
Uric Acid	4.5	5.9	3.8	4.7	5.3	4.8	4.9	4.6	4.7	5.3	7.2	5.2	**5.08**
Cholesterol	10.2	7.2	6.3	5.8	7.2	7.1	7.8	6.8	5.2	5.7	6.7	6.3	**6.86**
Triglyceride	14.2	14.3	14.9	15.6	11.1	12.3	10.3	13.1	15.6	9.8	10.1	9.7	**12.58**
HDL Cho	17.6	14.3	12.6	14.6	17.3	17.6	14.6	15.4	16.3	14.6	17.6	14.6	**15.59**
AST (SGOT)	4.1	5.2	3.9	3.7	4.2	5.2	3.9	4.7	4.2	3.4	6.2	5.1	**4.48**
ALT (SGPT)	2.6	3.5	4.2	3.1	3.7	4.2	3.5	3.7	4.6	5.1	4.9	6.7	**4.15**
ALP	8.3	10.3	11.4	9.8	7.8	8.3	5.9	11.2	10.4	9.2	8.4	7.2	**9.02**
Amylase	8.3	10.6	7.2	4.1	6.9	4.5	5.8	4.2	7.2	4.9	5.2	7.2	**6.34**

Table 3: CV% for all analytes for IQC -Path

Parameter -Path	January	February	March	April	May	June	July	August	September	October	November	December	Average
Glucose –	1.8	2.5	1.9	1.7	2.6	2.4	2.9	2.4	2.7	3.1	2.4	1.2	**2.30**
Urea -	3.2	3.2	2.4	3.6	3.4	2.4	1.3	2.5	1.7	3.5	3.9	4.2	**2.94**
Creatinine	2.3	5.2	4.7	4.6	4.2	4.7	3.4	3.7	2.8	1.9	2.5	3.8	**3.65**
Bilirubin –	4.2	3.6	3.7	4.2	5.1	2.7	2.9	2.5	2.7	5.2	4.7	3.5	**3.75**
Protein, Total	1.8	3.7	3.8	2.4	4.1	2.4	1.9	2.4	3.8	3.9	4.1	3.1	**3.12**
Albumin	3.2	3.3	4.2	4.7	3.2	3.6	3.7	3.5	4.2	4.7	4.6	7.2	**4.18**
Uric Acid	4.6	10.3	8.2	8	7.1	4.6	5.7	7.1	7.6	4.1	4.7	5.1	**6.43**
Cholesterol	4.3	5.3	4.1	5.2	7.1	4.5	7.2	2.8	3.5	4.6	4.7	4.9	**4.85**
Triglyceride	11.3	9.8	9.7	8.8	7.6	10.3	11.6	8.7	7.2	7.6	13.5	14.6	**10.06**
HDL Cho	15.3	17.3	15.6	14.6	15.6	14.6	14.6	17.6	15.6	18.6	14.9	18.6	**16.08**
AST (SGOT)l	1.5	2.6	3.1	1.7	2.3	1.8	2.4	3.7	1.5	4.7	5.6	4.9	**2.98**
ALT (SGPT) –	4.2	10.3	3.4	3.9	4.2	3.4	4.3	3.1	2.9	3.5	4.2	3.2	**4.22**
ALP	11.3	10.4	11.3	12.2	9.5	10.4	14.3	11.3	7.3	8.7	14.3	7.2	**10.68**
Amylase	5.9	6.8	7.1	7.2	6.9	9.5	6.7	8.4	7.2	9.5	8.2	8.3	**7.64**

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Table 4 summarizes Bias % obtained from EQAS report by CMC Vellore for all analyte from January 2020 to December 2020 along with the mean value of Bias%.

Parameter	January	February	March	April	May	June	July	August	September	October	November	December	Ave
Glucose	-2.64	-0.55	0.35	2.45	0.47	0.77	-0.85	-1.54	-1.54	-2.3	-0.03	-0.38	**-0.48**
Urea	-0.12	-1.93	-1.33	-0.85	-1.92	-2.38	-2.13	6.04	2.3	0.69	2.59	-0.32	**0.05**
Creatinine	0.11	1.64	0.98	-0.06	0.3	-0.2	2.02	0.24	1.33	-0.25	0.98	0.26	**0.61**
T. Bilirubin	1.11	1.29	2.25	-0.56	1.59	1.51	1.99	0.66	1.47	1.02	0.57	7.92	**1.74**
T. Protein	0.44	1.1	1.27	4.01	-0.32	2.17	3.85	1.15	0.32	-0.02	0.73	0.16	**1.24**
Albumin	-1.32	0.24	0	2.49	0.84	0.6	2.96	-1.04	0.83	5.73	-2.32	2.36	**0.95**
Uric Acid	1.28	1.1	-1.37	0.6	-1.36	3.38	-0.5	2.42	1.92	-0.04	-0.06	3.46	**0.90**
Cholesterol	-1.39	1.21	2.56	1.61	0.33	0.24	0.32	-0.17	1.02	8.59	0.96	1.33	**1.38**
Triglyceride	-1.59	0.02	3.82	0.47	-1.73	-0.82	0.48	-1.29	-1.39	0.45	1.02	0.34	**-0.02**
HDL CHO	2.26	-----	4.85	2.75	2.31	3.74	4.73	3.63	5.12	4.44	2.85	1.78	**3.50**
AST	0.45	0.43	-1.57	-0.89	-1.95	-0.94	0.12	0	0.44	-0.99	1.69	0.72	**-0.21**
ALP	----	----	-0.69	-54	4.26	0.52	-0.62	-0.34	-1.08	-0.34	0.91	-0.13	**-5.15**
ALT	-0.48	1.24	----	-1.98	-2.28	-2.69	-0.82	1.04	-0.12	-0.61	-1.27	-1.14	**-0.83**
Amylase	-0.56	-0.7	-0.12	-0.58	-2.72	-1.12	0.03	-0.32	0.35	0.43	2.48	1.42	**-0.12**

Table 5 indicates the sigma metrics and QGI ratio for all analytes for IQC - Norm and Path using Average of CV%, Bias % and TEa values from CLIA guidelines and biological Variation database specifications

PARAMETER	Total allowable error	CV% Norm	CV% Path	Bias %	Bias %	TaE BVD	Sigma CLIA-N	Sigma CLIA-P	Sigma BVD-N	Sigma BVD-P	QGI-N	QGI-p	Problem-N	Problem-P
Glucose	8.00	2.91	2.30	-0.48	-0.48	6.69	2.91	3.69	2.46	3.12	-0.94	-0.74	Imprecision	imprecision
Urea	9.00	3.00	2.94	0.05	0.05	15.55	2.98	3.04	5.17	5.27	0.11	0.10	Imprecision	imprecision
Creatinine	10.00	2.48	3.65	0.61	0.61	8.87	3.79	2.57	3.33	2.26	1.01	1.49	Inaccuracy	inaccuracy
Bilirubin, Total	20.00	5.33	3.75	1.74	1.74	26.94	3.43	4.87	4.73	6.72	6.17	4.34	Inaccuracy	inaccuracy
T.Protein	8.00	3.53	3.12	1.24	1.24	3.63	1.92	2.17	0.68	0.77	2.91	2.58	Inaccuracy	inaccuracy
Albumin	8.00	3.13	4.18	0.95	0.95	4.07	2.25	1.69	1.00	0.75	1.98	2.64	Inaccuracy	inaccuracy
Uric Acid	10.00	5.08	6.43	0.90	0.90	11.97	1.79	1.41	2.18	1.72	3.06	3.87	Inaccuracy	inaccuracy
Cholesterol	10.00	6.86	4.85	1.38	1.38	9.01	1.26	1.78	1.11	1.57	6.33	4.48	Inaccuracy	inaccuracy
Triglyceride	15.00	12.58	10.06	-0.02	-0.02	25.99	1.19	1.49	2.07	2.59	-0.15	-0.12	Imprecision	imprecision
HDL Cho	20.00	15.59	16.08	3.50	3.50	11.63	1.06	1.03	0.52	0.51	36.34	37.48	Inaccuracy	inaccuracy
AST	15.00	4.48	2.98	-0.21	-0.21	16.69	3.39	5.10	3.77	5.67	-0.62	-0.41	Imprecision	imprecision
ALT	15.00	4.15	4.22	-5.15	-5.15	27.48	4.86	4.78	7.86	7.73	-14.25	-14.49	Imprecision	imprecision
ALP	20.00	9.02	10.68	-0.83	-0.83	12.04	2.31	1.95	1.43	1.20	-4.98	-5.90	Imprecision	imprecision
Amylase	10.00	6.34	7.64	-0.12	-0.12	14.60	1.60	1.32	2.32	1.93	-0.50	-0.60	Imprecision	imprecision

Table 5 indicates the performance of various analytes in terms of sigma metrics using Total Allowable error targets from CLIA and Biological variation database guidelines.

For IQC-Norm, average CV% ranged from 2.48 (Creatinine) to 15.59 (HDL) while for IQC - Path it ranged from 2.30 (Glucose) to 16.48 (HDL).

IQC Norm analysis revealed CV% less than 6% for all analytes except for 5 parameters: Cholesterol, TG, HDL, ALP and Amylase whereas for IQC Norm, CV% for all analytes was less than 6% for all analytes except for Uric acid, TG, HDL, ALP and Amylase.

Poor precision for these analytes was due to temperature fluctuations affecting the performance of enzymatic reagents used for assay, due to other random errors in reconstitution, pipetting of reagent and sample. Elevated bias (poor accuracy) observed in ALP, Amylase and HDL is due to significant difference between expected range of the Internal Quality control samples and reported value of EQAS.

The Sigma metrics analysis for **IQC- Norm** showed sigma value <**3** for Glucose, Urea, Total protein, Albumin, Cholesterol, TG, HDL, ALP and Amylase using CLIA guidelines indicating failure to perform minimum sigma quality performance.

In contrast, while using biological variation database specifications, sigma value lesser than 3 was observed for all parameters except for Total Bilirubin, Urea, AST and ALT.

For 2 parameters; Urea and ALT sigma metrics was more than 6, which is a marker of world class quality.

Similarly, sigma metrics for **IQC Path** also revealed sigma values < 3 for Creatinine, Total Protein, Albumin, Cholesterol, TG, HDL, ALP and Amylase using CLIA guidelines. AST and ALT evaluation by using biological variation database specifications also showed sigma value > 6.

Marginal performance i.e. sigma metrics between 3-6 was noted for 5 parameters namely Glucose, Urea, Total Bilirubin, ALT & AST.

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Sigma value < 3 was observed Creatinine, Total Protein, Cholesterol, TG, ALP and Amylase using CLIA guidelines indicating failure to perform minimum sigma quality performance.

For parameters with sigma metrics < 3, the reason behind their poor performance was evaluated and it showed that the main problem was imprecision for Total protein, Glucose, Urea, TG, AST, ALT, ALP and Amylase.

The lower performance of Total Bilirubin, Creatine, Cholesterol, HDL, Uric acid, Total Protein, Albumin in was however attributable to both lack of accuracy while for IQC norm and path.

Using biological variability data, σ metrics ranged from 0.51 to 7.86 for NORM and from 0.52 to 7.73 for PATH. Performance analysis for 14 parameters revealed σ < 3 (poor performance) for 7 parameters of NORM IQC (ALP, TOTAL PROTEIN, ALBUMIN, URIC ACID, CHOLESTEROL, TG, HDL), 7 analytes of PATH IQC (UREA, ALP, TOTAL PROTEIN, ALBUMIN, URIC ACID, CHOLESTEROL, HDL) using TEa values as per using Biological Variability data guidelines.

Discussion

The assay performance of any analyte can be evaluated in terms of sigma metrics with σ value ≥ 6 indicating excellent performance, σ value ≥ 5 as excellent performance, σ value ≥ 4 as good, σ ≥ 3 as marginal, σ value ≥ 2 as poor and σ < 2 as unacceptable performance. In the present study, we evaluated the performance of 14 routine chemistry parameters being carried out on MICROLAB RX-50 at clinical biochemistry laboratory at GMERS Medical College & Hospital Vadnagar in terms of sigma metrics. The previous studies undertaken by scientists across the country evaluated sigma metrics using TEa goals from CLIA[13,17-21].

In the present study, we used TEa goals from two sources CLIA and biological variability database as undertaken by Hens K et al from Belgium and Xia J et al from China[20, 21].

Further, for analytes showing poor performance in terms of σ < 3, the cause for poor performance was evaluated using QGI index similar to study preformed by Verma M et al from Rohtak and Kumar BV et al[5, 13]. Sigma metric analysis using TEa specifications as per CLIA guidelines revealed that for 2 parameters (ALT and T.Bilirubin) σ value was > 6 similar to the observation by Vijatha Thomas et al[17].For AST, σ value was > 5 in IQC PATH but in IQC NORM it was 3.39. Similarly, for ALT; σ value was > 4 in IQC NORM and PATH. Glucose, Urea, Creatinine and Total Bilirubin exhibited marginal performance (σ 3- 6) in both levels of IQC indicating a scope for improvement[13, 18, 19].

Root cause analysis in terms of Quality Goal Index for poor performers (AST, ALT, ALP, Amylase, Glucose, Urea, TG) in IQC NORM and IQC PATH revealed imprecision as the cause for poor performance[22]. In the present study we noted that significantly different σ values were obtained using same bias and CV% but different Total Allowable error targets from CLIA and Biological Variability data similar to the observations by Hens K et al and Xia J et al[20,21].

Table: 6 Comparison of Six sigma value in various studies.

	Nanda et al[14]	Singh et al[15]	B.Vinod et al[22]	Carl Garber [23]	Present Study
Six Sigma		TG, HDL-C	ALP, Magnesium, TG, HDL-C (Both level QC)	Creatinine 6	AST, ALT and Bilirubin Total, Urea
	Creatinine 3.1	ALP 3.2-3.4	Creatinine 5-6 for both levels		

The discrepancy observed in the evaluation of various analytes in terms of sigma metrics can be attributed to a combinational of multiple factors ranging from different methodology used, differences in IQC material, differences in the reported bias % by the different Proficiency test providers[19].

Further after considering the results of sigma metrics and QGI for poor performers (of Creatinine, Albumin, Total Protein, Cholesterol, HDL) in IQC NORM and IQC PATH, laboratory tried to improve the performance by adopting NABL for better quality achievement. Standardization of present method for reconstitution, handling and storing the QC material. Temperature fluctuation was found to be a major culprit as we used enzymatic reagents. Further as a result strict temperature monitoring (Charts) was undertaken for the lab and the refrigerator where the kits were stored and also technician trained at regular interval by competency testing, direct observation of routine work and handling of instrument.

Conclusion

Sigma metrics is an excellent self-assessment tool for performance analysis of various test parameters in the laboratory. On applying the same to our routine biochemistry laboratory at Laboratory Services, GMERS Medical College & General Hospital, Vadnagar, we observed that Total Bilirubin, Urea, AST and ALT showed world class/excellent performance. Glucose and Creatinine exhibited marginal performance (σ 3–6) in both levels of IQC indicating a scope for improvement. However, for Albumin, Total Protein, Cholesterol, TG and HDL σ < 3 was obtained for both levels of IQC indicating poor performance due to lack of precision and lower accuracy**.**

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