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Evaluation of Sigma Metrics of Commonly Assayed Biochemical Parameters in a Clinical Laboratory

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Abstract

Objectives: Six Sigma is a quality management strategy to improve the quality of processes and lays emphases on identification and removal of defects. Implementation of Six Sigma across laboratory processes allows identification of errors and introduction of novel approaches towards cost reduction without sacrificing quality. Keeping this in view, the study laboratory aimed to gauge the process performance of 19 routinely assayed parameters on sigma scale–that will help in assessing the laboratory's performance and will enable in working out and choosing the correct approach towards improvement of problem analyte performance.

Methods: Quality Control data was harvested retrospectively from August 2019 to December 2019. Sigma metrics was calculated for 19 biochemical parameters tested on Vitros-5600 using Total Allowable Error (TEa), Coefficient of variation (CV%) and bias (%). Quality Goal Indices of the problem analytes were calculated to identify the cause of error.

Results: The following problem analytes were identified in this study having a sigma score of <3- Urea, ALT, ALP, Sodium, Calcium and Iron. QGI was calculated for these parameters to identify the area requiring improvement-imprecision, inaccuracy.

Conclusion: The study concluded that sigma metrics is a good quality tool to assess the analytical performance of a clinical chemistry laboratory and stringent internal QC rules need not be adopted for methods with sigma ≥ 6. Also, false rejections in such cases can be minimized by relaxing control limits to 3S. However, for a problem analyte with sigma metric below 3, root cause analysis should be performed along with improvement in method performance before it can be routinely used.

Keywords: Six sigma; Total allowable error; Bias; Coefficient of variation; Quality goal index.

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1. Introduction

Clinical laboratories are complex and dynamic organizations that unceasingly need to improve the quality of testing and meet stringent guidelines while trying to reduce the cost. Nowadays, laboratories are required to handle increased workloads with a broader spectrum of parameters with limited manpower and yet deliver consistent results with utmost quality within the defined turnaround time [1], in a cost-effective way.

Laboratory performance can be appraised with the application of six sigma in the laboratory functions [2]. Sigma metric analysis not only provides an objective assessment of analytical methods and instrumentation but also makes available critical design information needed for operational implementation.

Six Sigma is a quality management strategy to improve the quality of processes and lays emphases on identification and removal of defects. Quality is assessed on the sigma scale with 3 sigma as the minimum allowable sigma for routine performance and sigma of 6 being the world class quality goal [3]. It can be inferred that as the sigma value increases, the consistency and steadiness of test improves hence reducing the operational costs. Keeping in view the above, we aimed to gauge the process performance of some routinely assayed parameters on sigma scale– Cholesterol, Urea, Creatinine, Total Bilirubin, Uric Acid, Aspartate aminotransferase, Alkaline phosphatase, Alanine aminotransferase, Total Protein, Albumin, HDL, Triglyceride , Sodium, Potassium, Iron, Amylase, Calcium, Phosphorus and Glucose. Assessing the laboratory's performance on sigma scale will help in working out and choosing the correct approach towards improvement of target analyte performance and cost reduction.

2. Materials and Methods

The study was conducted in the Department of Biochemistry, in a Central Government Tertiary Care Hospital, New Delhi, which caters to samples received from different parts of India. Both internal and external Quality Control data were harvested retrospectively for a period of five months from August 2019 to December 2019 for the above-mentioned parameters. Sigma metrics was calculated for all the parameters using Total Allowable Error (TEa), Coefficient of variation (CV %) and bias (%). Two levels of clinical chemistry controls, both normal and pathological, Biorad Lyphocheck Assay Clinical Chemistry were used for each parameter and tested prior to release of patient reports on daily basis. All tests were run on Vitros 5600, Ortho clinical Diagnostics, a fully automated biochemistry analyser, as per the manufacturer's recommendations.

2.1 Statistical Analysis

Sigma value was calculated using the following formulas.

(Total Allowable Error) TEa, indicates the allowable difference from true values.

Bias is the systematic difference between the results obtained from laboratory's test method and an accepted reference method. It was computed for each parameter from External Quality assurance records using the following formula.

$$\text{Bias\%} = \frac{\text{Lab EQAS Result- peer group mean (using same instrument and method)}}{\text{Peer group mean (using same instrument and method)}} \times 100$$

CV% (Coefficient of Variation) is the standard deviation expressed as a percentage and is the measure of the variability of an assay.

$$\text{CV\%} = \frac{\text{Standard Deviation}}{\text{Lab Mean}} \times 100$$

``Sigma metric for each parameter was calculated by using the formula-

$$\frac{\text{TEa-Bias}}{\text{CV\%}}$$

Quality Goal Index (QGI) Ratio- It signifies the relative extent to which bias and precision meet their corresponding quality goals [4]. The purpose of this is to analyse the reason for lower sigma values in the problem analytes, whether the problem is due to imprecision or inaccuracy or both.

QGI ratio has been calculated using the formula----

$$\text{QGI} = \text{Bias}/1.5 \times \text{CV\%}$$ [5]

The criteria for interpreting QGI of the problem analytes with low sigma performance is shown in the table below.

Table 1: Criteria for interpreting QGI Ratio

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

3. Results

Internal Quality Control and proficiency testing data for 19 clinical chemistry analytes were analysed retrospectively over a period of five months from August 2019 to December 2019. Process sigma was calculated for both QC levels using CV%, percentage bias and Total allowable error. Sigma metric (average of both quality control levels for five months) 3 has been taken as the minimum allowable sigma and parameters falling below this sigma scale has been termed as problem analytes. Quality goal index has been calculated for all the problem analytes to identify the possible source of error.

The following results were obtained.

Table 2:- Table showing CV% of both QC Levels (L1 and L2) over a period of five months from August to December 2019.

S. No.	Parameter	August CV%		September CV%		October CV%		November CV%		December CV%		Average CV%	
		L1	L2	L1	L2	L1	L2	L1	L2	L1	L2	L1	L2
1	Glucose	1.74	2.64	2.13	1.5	1.44	2.3	1.99	2.69	1.62	2.8	1.78	2.38
2	Urea	4.26	2.53	3.69	3.44	3.28	2.76	2.18	1.96	2.52	1.52	3.18	2.44
3	Creatinine	2.37	1.81	2.35	2.12	3.08	2.83	3.49	2.21	2.6	3.01	2.77	2.39
4	Uric acid	1.57	1.53	2.97	2.75	2.21	2.32	2.33	2.65	2.3	2.54	2.27	2.35
5	Total bilirubin	4.17	3.01	4.25	4.06	5.08	2.82	5.01	6.2	4.03	5.47	4.50	4.31
6	AST	3.71	3.82	2.97	2.16	2.52	2.59	3.75	2.89	4.55	2.94	3.5	2.88
7	ALT	8.72	4.9	7.17	3.34	11.3	4.2	18.8	8.65	3.5	4.96	9.89	5.21
8	ALKP	3.91	5.96	4.92	3.54	6.11	3.75	3.2	2.21	6.89	4.39	5.00	3.97
9	Total protein	2.15	3	1.88	2.12	1.55	2.75	2.48	2.69	1.44	2.05	1.9	2.52
10	Albumin	2.9	2.79	3.52	2.52	4.91	3.93	3.16	3.15	2.97	3.33	3.62	3.14
11	Cholesterol	1.72	2.34	2.01	1.96	1.71	2.35	3.16	2.29	1.67	3.48	2.15	2.48
12	HDL	3.01	3.24	3.33	3.24	2.93	3.56	5.08	6.17	2.59	3.02	3.46	3.84
13	Triglyceride	2.49	2.47	1.74	2.96	2.53	3.4	1.9	2.06	2.24	2.66	2.06	2.71
14	Sodium	1.78	1.38	1.06	1.16	1.43	1.93	1.09	1.61	1.94	1.01	1.59	1.41
15	Potassium	1.48	0.92	1.57	1.07	1.78	0.09	1.27	1.11	2.08	2.52	1.66	1.14
16	Calcium	1.13	1.23	1.52	1.6	1.61	0.19	1.38	1.62	0.88	1.07	1.51	1.14
17	Phosphorus	2.39	2.5	1.81	2.19	2.75	0.15	1.95	2.83	3.38	3.14	2.19	2.16
18	Iron	5.31	8.85	3.32	7.18	4.12	4.31	4.86	8.22	2.53	5.97	3.69	6.90
19	Amylase	7.36	3.66	3.58	5.89	8.47	5.31	10.42	4.18	9.05	5.22	6.64	4.85

Table 3:- Table showing Bias% of the parameters over a period of five months from August to December 2019.

S. No	Parameter	Tea	August BIAS%	September BIAS%	October BIAS%	November BIAS%	December BIAS%	Average BIAS%
1	Glucose	10	0.74	2.8	3.86	-1.39	2.75	1.75
2	Urea	9	4.5	-2.28	3.3	0.23	0	1.15
3	Creatinine	15	5.7	-2.59	-5.2	-2.9	-1.4	-1.28
4	Uric Acid	12	-1.06	-3.1	0	-1.75	-0.34	-1.25
5	BIL-T	20	4.1	4.47	2.51	11.8	-23	-0.02
6	AST	20	0	-6.41	-3.25	5.05	3.44	-0.23
7	ALT	12	0.9	-4.32	-1.21	-14	-11.69	-6.06
8	ALKP	12.04	-3.8	4.93	-10.18	-4.38	9.15	-0.85
9	Total Protein	10	-0.1	1.06	1.44	-5.33	-10.3	-1.31
10	Albumin	10	1.9	3.96	6.31	-3.5	-8.6	0.01
11	Cholesterol	10	-4.9	4.48	2.86	-6.8	5.55	0.24
12	HDL	11.63	-4.9	2.07	-19.5	-6.88	-18.86	-9.61
13 (03+6)	Triglyceride	15	-7.9	-2.73	2.35	-4.02	-7.07	-3.87
14	Sodium	0.73	-1.5	-2.69	-3.08	-2.8	-1.33	-2.28
15	Potassium	5.61	-3.9	-0.24	-1.61	-1	-4.17	-2.18
16	Calcium	2.55	-1.5	0	-0.55	-1.02	1.63	-0.28
17	Phosphorus	10.7	0	-0.22	3.8	-1.09	-5.3	-0.375
18	Iron	20	0	1.76	-0.89	-1.38	-0.43	-0.19
19	Amylase	14.6	-4.7	-34.59	-3.27	-14.7	13	-8.85

Table 4:- Table showing Sigma values obtained for both levels of QC of the parameters over a period of five months from August to December 2019.

S. No.	Parameter	August		September		October		November		December		Average	
		L1	L2	L1	L2	L1	L2	L1	L2	L1	L2	L1	L2
1	Glucose	5.32	3.5	3.38	4.8	4.26	2.66	5.72	4.23	4.47	2.58	4.63	3.55
2	Urea	1.05	1.8	3.05	3.27	1.73	2.06	4.02	4.47	3.57	5.92	2.68*	3.50
3	Creatinine	3.92	5.1	7.48	8.29	6.5	7.13	5.12	8.09	6.3	5.44	5.86	6.81
4	Uric Acid	8.31	8.53	5.08	5.49	5.42	5.17	5.9	5.18	5.36	4.85	6.01	5.84
5	BIL-T	3.81	5.28	3.65	3.82	3.44	6.2	1.63	1.32	10.6	7.86	4.63	4.89
6	AST	5.39	5.23	8.89	10.11	9.22	8.97	3.98	5.17	3.63	5.63	6.22	7.02
7	ALT	1.27	2.26	2.27	4.88	1.16	3.14	1.38	3	6.76	4.77	2.56*	3.61
8	ALKP	2.65	3.6	1.44	2	3.6	5.92	5.13	7.42	0.41	0.65	2.64*	3.91
9	Total Protein	4.69	3.36	4.75	4.21	5.52	3.11	6.18	5.69	14.1	9.9	7.04	5.25
10	Albumin	2.79	2.9	1.71	2.39	0.75	0.93	4.27	4.28	6.26	5.58	3.15	3.21
11	Cholesterol	8.19	6.02	2.74	2.81	4.17	3.03	5.31	7.33	2.66	1.27	4.61	4.09
12	HDL	5.49	5.1	2.87	2.95	10.6	8.74	3.64	3	11.7	10.09	6.87	5.97
13	Triglyceride	12.8	9.27	10.1	5.98	5	3.72	10.0	9.23	9.85	8.29	9.55	7.29
14	Sodium	1.25	1.61	2.29	2.94	2.6	2.42	3.23	2.19	1.06	2.03	2.08*	2.23*
15	Potassium	6.42	10.3	3.72	5.46	4.05	4.75	5.2	5.95	4.89	3.88	4.85	6.06
16	Calcium	3.58	3.29	1.67	1.59	1.92	1.89	2.58	2.2	1.04	0.85	2.15*	1.96*
17	Phosphorus	4.47	4.28	6.03	4.98	2.5	3.25	6.04	4.16	4.73	5.09	4.75	4.35
18	Iron	3.76	2.25	5.49	2.54	5.07	2.88	4.39	2.6	8.07	3.42	5.35	2.73*
19	Amylase	2.6	5.36	8.3	15.8	2.1	7	2.81	7	0.17	0.3	3.2	7.09

***Significant Observation= < 3 SIGMA**
Level 1 QC=Urea, ALT, ALKP, Sodium, Calcium
Level 2 QC= Sodium, Calcium, Iron

Out of the 19, only six analytes (urea, ALT, alkaline phosphatase, sodium, calcium and iron) were found to have an average sigma value <3.

Figure 1 and Figure 2 shows the sigma metric scale obtained for each analyte for both levels of quality controls on a method decision chart.

Figure-1: Method Decision Chart for Quality Control Level 1

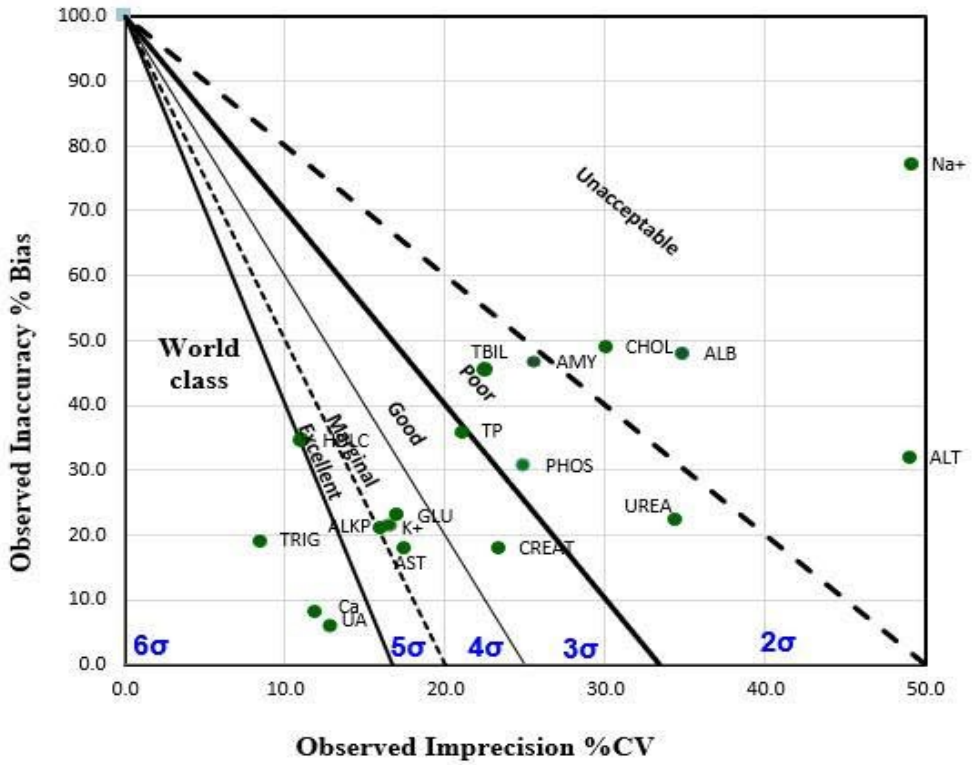


Figure-2: Method Decision Chart for Quality Control Level 2

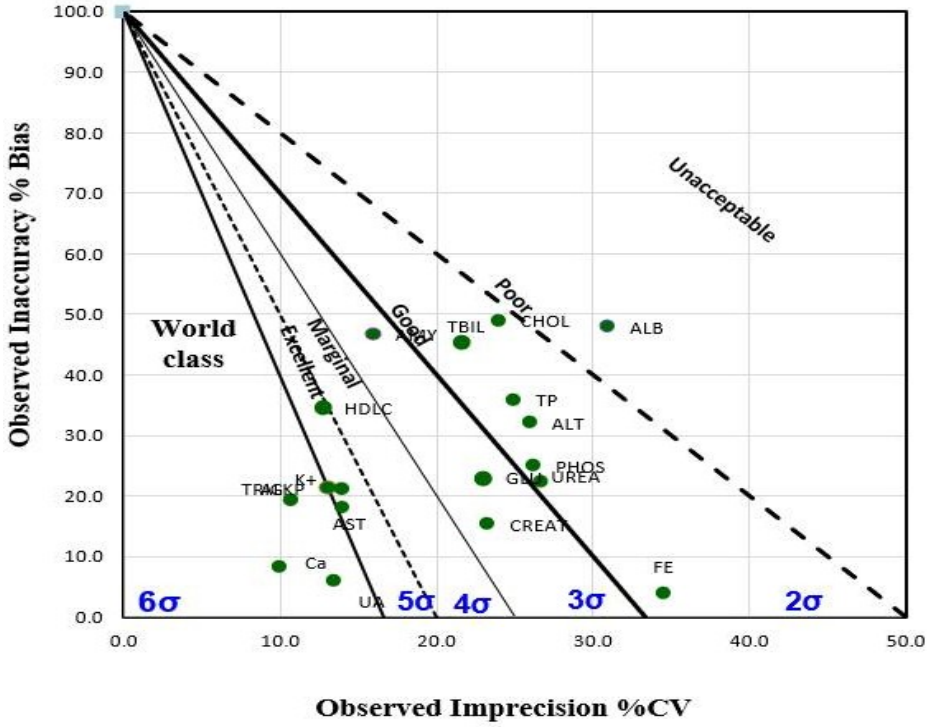


Table 5: Table showing average coefficient of variation percentage, bias percentage and sigma value of the problem analytes and quality goal index ratio calculation for problem identification.

Analytes	CV%		BIAS%	SIGMA		QGI Ratio		Problem	
	Level 1	Level 2		Level 1	Level 2	Level 1	Level 2	Level 1	Level 2
Urea	3.18	2.44	5.75	2.68	3.50	1.2	1.5	Imprecision and Inaccuracy	Inaccuracy
ALT	9.89	5.21	-6.06	2.56	3.61	0.4	0.7	Imprecision	Imprecision
ALKP	5.0	3.97	0.66	2.64	3.91	0.08	0.1	Imprecision	Imprecision
Sodium	1.46	1.41	1.68	2.08	2.23	0.7	0.8	Imprecision	Imprecision and Inaccuracy
Calcium	6.52	1.14	0.31	2.15	1.96	0.03	0.2	Imprecision	Imprecision
Iron	4.02	6.9	0.17	5.35	2.73	0.02	0.01	Imprecision	Imprecision

4. Discussion

Providing better diagnosis and improving the quality credentials along with cost reduction is a unremitting challenge for the diagnostic and healthcare industry. The effects incurred by operational inefficiencies can have a significant impact on quality of reporting and on laboratory's budget. Identification of the bottleneck points is thereby crucial for improving operational productivity.

Implementation of Six Sigma across laboratory processes allows identification of errors and introduction of novel approaches towards cost reduction without sacrificing quality.

In general, laboratories design their QC (Quality Control) protocol for both frequency and the number of levels of daily IQC runs based on guidelines of accreditation bodies. However, Good Laboratory Practice (GLP) requires every individual laboratory to design their own Individualized Quality Control Plan (IQCP) based on Sigma metric analysis [6], which prevents unnecessary repeated QC runs that leads to wastage and incurs more operational costs on the institution.

Employing Six Sigma in laboratory involves quantifying the performance of the test using standard quality control methods, specifying the quality requirements for the test (TEa), analyzing the data and computing a sigma value; recovering the process based on results of analysis which is then closely followed up. [7]

In the present study, retrospective evaluation of sigma metrics for the analytical phase revealed glitches associated with six analytes (urea, ALT, alkaline phosphatase, sodium, calcium and iron) with an average sigma value <3.Variations in the sigma values obtained may be attributed to the difference in instrumentation, quality control material used and other pre and post analytical conditions.

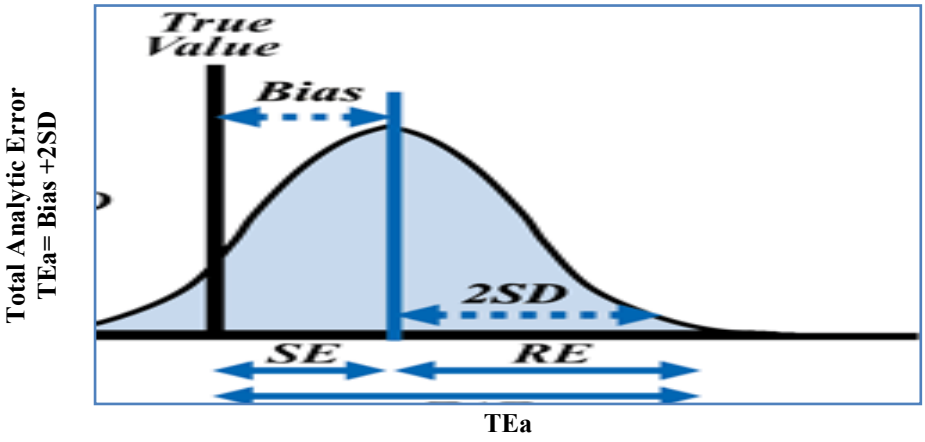
Quality Index Ratio was calculated for all the six to determine the cause of errors. The problem was identified to be imprecision for ALT, alkaline phosphatase, sodium, calcium and iron, while both imprecision and inaccuracy was the cause of error for urea.

Similar studies were done by Singh *et al*, Nanda *et al*, Chaudhary *et al*, Adiga *et al*. [8-11].

Total allowable error refers to the amount of error that is acceptable without invalidating the medical usefulness of the test result.

It is used to define acceptable analytical performance for assessment of an individual instrument's analytical performance, quality control validation and as a measure of agreement or comparability of results for analytes measured on different systems [12]. It sets the limit for both combined imprecision (random error) and bias/inaccuracy (systematic error) that is permissible in a single test result to ensure clinical utility. (Figure: 1) Having a preset quality specification also ensures uniformity across multiple analysers in the laboratory.

Figure-3: Concept of Total Allowable Error



In the current study, total allowable error (Tea) for the analytes were taken from different industry standards in the current study. This permitted allowable error limits that is neither too stringent to give rise to false outlier alarms not too broad to miss out on the latent errors. The table below illustrates the different sources of total allowable error limits for the parameters included in the study.

Table 6:- Table showing total allowable error for each parameter and different industry standards from which it has been taken.

S. No.	Parameter	TEA	Sources
1	Glucose	10	CLIA*
2	Urea	9	CLIA
3	Creatinine	15	CLIA
4	Uric Acid	12	CFX**
5	BIL-T	20	CLIA
6	AST	20	CLIA
7	ALT	12	RCPA***
8	ALKP	12.04	BV****
9	Total Protein	10	CLIA
10	Albumin	10	CLIA
11	Cholesterol	10	CLIA
12	HDL	11.63	BV
13	Triglyceride	15	NCEP*****
14	Sodium	0.73	BV
15	Potassium	5.61	BV
16	Calcium	2.55	BV
17	Phosphorus	10.7	CAP******
18	Iron	20	CLIA
19	Amylase	14.6	BV

*Clinical Laboratory Improvement Amendments
**Canadian Fixed limits from the College of Physicians and Surgeons of Saskatchewan.
***Royal College of Physicians of Australasia (RCPA) Quality Assurance Program
****Desirable specifications for allowable total error, based on biological variability (BV)-Ricos
*****National Cholesterol Education Program recommendations for triglyceride measurement [13]

Our study finally concluded that sigma metrics is a good quality tool to assess the analytical performance of a clinical chemistry laboratory and stringent internal QC rules need not be adopted for methods with sigma ≥ 6. Also, false rejections in such cases can be minimized by relaxing control limits to 3S. However, for a problem analyte with sigma metric below 3, root cause analysis should be performed along with improvement in method performance before it can be routinely used [14] Poor sigma performance (<3) also calls for adoption of a newer and better method as the quality of the test in such cases cannot be assured even after repeated QC runs.

The strength of the study lies in its ability to integrate both the internal and external quality control performances, both of which are paramount tools for evaluating the analytical system quality and stability.

The study also recommends the application of sigma metrics to all segments of laboratory process to gauge their performance on sigma scale.

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