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Sigma metrics in clinical chemistry laboratory – A guide to quality control

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Abstract: *Background:* Six sigma is a process of quality measurement and improvement program used in industries. Sigma methodology can be applied wherever an outcome of a process is to be measured. A poor outcome is counted as an error or defect. This is quantified as defects per million (DPM). Six sigma provides a more quantitative frame work for evaluating process performance with evidence for process improvement and describes how many sigma fit within the tolerance limits. Sigma metrics can be used effectively in laboratory services. The present study was undertaken to evaluate the quality of the analytical performance of clinical chemistry laboratory by calculating sigma metrics. *Methodology:* The study was conducted in the clinical biochemistry laboratory of Karwar Institute of Medical Sciences, Karwar. Sigma metrics of 15 parameters with automated chemistry analyzer, transasia XL 640 were analyzed. The analytes assessed were glucose, urea, creatinine, uric acid, total bilirubin (BT), direct bilirubin (BD), total protein, albumin, SGOT, SGPT, ALP, Total cholesterol, triglycerides, HDL and Calcium. *Results:* We have sigma values <3 for Urea, ALT, BD, BT, Ca, creatinine (L1) and urea, AST, BD (L2). Sigma lies between 3-6 for Glucose, AST, cholesterol, uric acid, total protein(L1) and ALT, cholesterol, BT, calcium, creatinine and glucose (L2).Sigma was more than 6 for Triglyceride, ALP, HDL, albumin (L1) and TG, uric acid, ALP, HDL, albumin, total protein(L2). *Conclusion:* Sigma metrics helps to assess analytical methodologies and augment laboratory performance. It acts as a guide for planning quality control strategy. It can be a self assessment tool regarding the functioning of clinical laboratory.

Keywords: Total allowable error, Bias, CV%, sigma

Introduction

Six Sigma is a management strategy that seeks to improve the quality of process outputs by identifying and removing the causes of defects (errors) and minimizing variability in manufacturing and business processes. Sigma metrics places analytical characteristics within the framework of clinical requirements. The six sigma idea asserts an association between the numbers of product defects, wasted operating costs and levels of customer satisfaction. It can be inferred that as sigma increases, the consistency and steadiness of the test improves, thereby reducing the operating costs.

The Sigma scale is easily interpreted and appreciated by laboratories. Sigma values can be calculated for both qualitative and quantitative assays. The Sigma scale provides guidelines for assay improvement and monitoring. Total testing process is a multistep process that begins and ends with the needs of the patient [1]. The number of steps may vary according to test types and laboratory organisation. We can describe nine activity steps in laboratory medicine, test selection and ordering a laboratory test request, collecting the sample (seum, plasma, urine and so on), identification, transport the sample to laboratory, preparation of the sample, analysis, reporting test results, interpretation of test results, action. Historically in clinical laboratories, the total testing process was assumed to consist of only three phases:

1. Pre-analytical phase
2. Analytical phase
3. Post-analytical phase

Further, the pre-analytical phase contain two sub-phases:

a. Outside the laboratory
b. Within the laboratory

The errors can occur in any of the above mentioned steps. To overcome the serious errors originating in clinical laboratories, a new perspective and approach seem to be essential. All laboratory procedures are prone to errors because in many tests, the rate of human intervention is higher than expected. It appears that the best solution for analyzing problems in clinical laboratories is the application of Six Sigma methodology. Bill Smith, the father of Six Sigma, decided to measure defects per *million* opportunities.

Total quality management was popular by the 1990s, and it application in clinical laboratories is well documented [2-4]. The generic TQM model is called "PDCA": plan, do, check, and act. First, one must *plan* what to do, and then *do* it. The next step is to *check* the data, and in the last step, *act* on the results. If this does not achieve a satisfactory result, one must *plan* again and follow the remaining steps. This procedure continues until the desired result is obtained. Six Sigma methodology represents an evolution in quality assessment and management that has been implemented widely in business and industry since the mid-1980s. Six Sigma methodology was developed by Motorola, Inc. to reduce the cost of products, eliminate defects, and decrease variability in processing. It consists of five steps: define, measure, analyze, improve, and control (DMAIC) [2, 5-6]. These steps are universal and could be applied to all sectors of industry, business, and healthcare. The sigma value indicates how often errors are likely tooccur; the higher the sigma value, the less likely it is that the laboratory reports defects orfalse test results.

The Six Sigma model is similar to TQM. The basic scientific model is "DMAIC": define, measure, analyze, improve, and control. In comparison with TQM's PDCA, we can say that define corresponds to the *plan* step, measure to the *do* step, analyze to the *check* step, and *improve*to the act step. The Six Sigma model has an extra step, *control*, which is important in modern quality management. With this step, we intend to prevent defects from returning to the process. There are a few studies done on sigma metrics in laboratory medicine [7-9].

Aim of our study was to: (i) study sigma metrics of clinical chemistry analytes and plan the quality control strategy. (ii) calculate the total allowable error in our laboratory and compare it with that of CLIA guidelines, thereby evaluate the functioning of the instrument as well as adequacy of the methodology being followed.

Material and Methods

The study was conducted in the clinical biochemistry laboratory of Karwar Institute of Medical Sciences, Karwar. This is a 400 bedded, tertiary care center in which department of biochemistry was newly established. Aim of our study was to measure the sigma metrics of our laboratory and to assess the errors associated with it. We analyzed sigma metrics of 15 parameters with automated chemistry analyzer, XL 640. The study protocol was approved by institutional human ethics committee.

Internal quality control (IQC) data of 15 analytes were analyzed retrospectively over a period of 6 months from March 2015 to August 2015 with XL 640. Both normal (L1) and pathological (L2) levels of QC materials were assayed before commencing reporting of patient samples every day. The instruments was calibrated regularly. The analytes assessed were glucose, urea, creatinine, uric acid, total bilirubin, direct bilirubin, total protein, albumin, SGOT, SGPT, ALP, Total cholesterol, triglycerides, HDL and Calcium.

Sigma value was calculated with the following formulas:

Total allowable error: It is the total allowable difference from accepted reference value seen in the deviation of single measurement from the target value. TE_a values of various parameters were taken from Clinical Laboratories Improvement Act (CLIA) guidelines [10].

Bias: Bias is the systematic difference between the expected results obtained by the laboratory's test method and the results that would be obtained from an accepted reference method. Bias was derived as follows;

$$\text{Bias (\%)} = \frac{\text{Mean of all laboratories using same instrument and method} - \text{our mean}}{\text{Mean of all laboratories using same instrument and method}} \times 100$$

CV% is the analytical coefficient of variation of the test method. Coefficient of variance (CV) were calculated as follows.

$$CV\% = \frac{Standarddeviation}{LaboratoryMean} X\ 100$$

Sigma metrics were calculated from CV, percentage bias and total allowable error for the parameters by the following formula:

$\Sigma\ (\sigma) = (TE_a - \text{bias}) / CV\%$

[TE_a - total allowable error, CV% - Coefficient of variance]

TE_a observed in our assay was calculated using the formula,

TE_a observed **= bias + %CVx 2**

Thus observed TE_a is compared with that obtained by CLIA guidelines.

Results

We have calculated mean, SD, CV%, bias, TEa and sigma values for all the 15 analytes. Results are given in the following tabulated columns.

Table-1: Mean, SD& CV of five analytes from March 2015-May 2015

Analyte	March			April			May		
	Mean	SD	CV%	Mean	SD	CV%	Mean	SD	CV%
AST	158.72	2.42	1.52	166.8	19	11.3	50.68	1.17	0.23
CHOL	206	2.76	1.3	210.6	8.9	4.4	166.3	3.8	2.2
GLU	255.6	3.65	1.4	261.63	9.94	3.7	99.57	2.67	1.64
TRIG	191.9	2.59	1.34	194.3	3.7	1.90	96.02	1.88	1.95
UREA	156.8	4.28	6.72	173.5	14.03	8.08	40.31	0.865	2.14

Table-2: Mean, SD& CV of five analytes from June 2015-August 2015

Analyte	June			July			August		
	Mean	SD	CV%	Mean	SD	CV%	Mean	SD	CV%
AST	50.8	2.44	4.72	49.75	1.12	2.25	154.9	2.08	1.34
CHOL	163.76	2.18	1.33	138.5	1.38	0.87	196.6	12.55	6.38
GLU	101.5	3.022	1.7	97	0.422	0.435	249.4	2.7	1.08
TRIG	94.14	2.61	2.77	94.2	1.87	1.98	195.4	1.18	0.603
UREA	41.56	1.16	2.79	40.61	1.35	3.3	168.32	3.89	2.31

Table-3: Mean, SD& CV of Nine analytes from May 2015 - August 2015

Analyte	May			June			July			August		
	Mean	SD	CV%	Mean	SD	CV%	Mean	SD	CV%	Mean	SD	CV%
ALB	4.25	0.057	1.34	4.21	0.051	1.21	4.08	0.036	0.88	4.69	0.02	0.511
ALP	64.8	0.74	1.1	63.64	1.73	2.71	65.66	1.1	1.67	186	3.26	1.75
ALT	42.13	3.4	8.07	51.13	4.45	8.7	40.18	2.34	5.8	113.0	3.2	2.83
BT	1.21	.080	6.6	1.34	.027	2.0	1.28	.0097	.75	4.42	.065	1.47
BD	.431	.013	3.0	.46	.031	6.7	.49	.0074	1.5	1.83	.061	3.33
Ca+2	9.32	.56	6.0	8.83	1.24	.14	8.3	.244	2.94	9.25	.15	1.62
Creati	1.704	.038	2.2	1.42	.33	21.12	1.65	.042	2.5	3.67	.065	1.78
HDL	53.9	.96	1.78	52.86	1.33	2.51	51.98	.49	.94	63.1	.75	1.1
TP	6.56	.099	1.55	6.51	.126	1.93	6.45	.10	1.55	8.08	.105	1.29
UA	7	.33	4.7	6.8	.24	3.5	6.47	.088	1.36	10.23	.047	.45

Table-4: Month wise bias from March 2015-May 2015						
	March L2	**April L2**	**May L1**	**June L1**	**July L1**	**August L2**
Albumin	*	*	.23	.68	3.77	6.57
ALP	*	*	5.19	3.31	6.59	9.4
ALT	*	*	8.4	11.1	12.6	8.8
AST	3.8	1.09	5.27	5	7	6.12
BIL-Total	*	*	14.7	6.06	9.8	17.8
BIL-D	*	*	20.18	14.8	9.25	6.15
Calcium	*	*	7.8	2.19	3.9	4.9
Cholesterol	2.8	.66	.78	.75	3.9	7.26
Creatinine	*	*	13.6	5.3	10	6.37
Glucose	2.4	.15	3.8	5.8	1.1	4.8
HDL	*	*	5.27	3.24	1.52	2.32
TP	*	*	.92	.15	.76	.24
TG	2.62	3.9	2.14	.14	.21	4.49
UA	*	*	9.37	6.25	1.0	3.49
UREA	7	3.2	1.28	4.4	2.03	.19
*bias value not available						

Table-5: Sigma metrics of automated chemistry analyzer						
Parameter	**XL 640**					
	TEa	**BIAS%**	**CV% (L1)**	**CV%(L2)**	**SIGMA(L1)**	**SIGMA(L2)**
ALBUMIN	10	2.81	1.15	0.511	6.25	14.07
ALP	30	6.12	1.84	1.75	12.98	13.64
ALT	20	10.22	7.62	2.83	1.28	3.46
AST	20	5.59	3.11	4.87	4.63	2.96
BIL TOTAL	20	12.09	3.125	1.47	2.53	5.38
BIL–D	20	12.59	28	3.33	0.26	2.22
CALCIUM	11	4.69	7.71	1.62	0.82	3.89
CHOL	10	2.69	1.5	2.1	4.87	3.48
CREAT	15	8.81	8.2	1.77	0.75	3.5
GLU	10	3.0	1.25	2.12	5.6	3.3
HDL	30	3.08	1.76	1.19	15.73	23.3
TP	10	0.51	1.68	1.299	5.65	7.3
TRIG	25	2.25	2.23	1.28	10.2	17.8
UA	17	5.02	3.25	0.45	3.68	26.6
UREA	10	3.01	2.75	4.45	2.54	1.57

Table-6: Sigma metrics of various parameters		
Sigma metrics	**L1**	**L2**
<3	Urea, ALT, BD, BT, Ca,Creatinine	Urea, AST, BD
3-6	Glucose, AST, cholesterol, uric acid, total protein	ALT, cholesterol, BT, calcium, creatinine, glucose
>6	Triglyceride, ALP, HDL, albumin	TG, uric acid, ALP, HDL, albumin, total protein

Table-7: Comparison of observed TEa to CLIA guidelines			
Analyte	TEa observed		TEa as per CLIA
	L1	L2	
ALBUMIN	5.11	3.83	10
ALT	25.46	15.88	20
ALP	9.8	9.62	30
AST	11.81	15.33	20
BD	68.59	19.25	20
BT	18.34	15.03	20
Ca+2	20.11	7.93	11
CHOLESTEROL	5.69	6.89	10
CREATININE	25.01	12.35	15
GLUCOSE	5.5	7.24	10
HDL	6.6	5.46	20
TG	6.71	4.81	25
TP	3.87	3.11	10
UA	11.52	5.92	17
UREA	8.51	11.91	10

Discussion

We have analyzed 15 analytes over a period of 6 months (March – August 2015) and assessed for sigma metrics. Similar studies were done by Bhavna sing et al, Sunil Nanda et al, Nitinkumar et al [7-9] etc. Variations in sigma values between our study and others can be attributed to the difference in the instrument used, quality control material used and other pre & post analytical conditions. In order to calculate sigma, we have calculated mean, standard deviation (sd), coefficient of variation (cv) and bias. SD quantifies how close numerical values are in relation to each other. Since SD typically increases as the concentration of analyte increases, CV can be regarded as statistical analyzer. Since CV is the ratio of two, it cancels that effect. CV is therefore standardiztion of the SD that allows comparison of variability estimates regardless of analyte concentration. CV is dimensionless and does not vary with changes in measurement units. We have obtained higher CV for SGPT, creatinine and calcium in L1, for urea and SGOT in L2 compared to other parameters. CV is correlated to precision. Precision is closeness of agreement between independent, repeated results obtained from the same sample under specific conditions. Lesser the CV, better is the precision. This suggests that precision is low for above mentioned parameters.

Bias is the difference between the measured result and actual value. It is used to describe the inaccuracy of the method. In our study we have obtained a higher bias value for SGPT, creatinine, BD & BT. Lower the bias more is

the accuracy. This suggests the chances of inaccuracy in the methods for measurement of above mentioned analytes which need evaluation. The Six Sigma scale typically runs from zero to six, but a process can actually exceed Six Sigma, if variability is sufficiently low as to decrease the defect rate. In industries outside healthcare, 3 Sigma is considered the minimal acceptable performance for a process. When performance falls below 3 Sigma, the process is considered to be essentially unstable and unacceptable [11]. We have sigma values <3 for Urea, ALT, BD, BT, Ca (L1) and Glucose, urea, AST,BD (L2).

We have sigma values <3 for Urea, ALT, BD, BT, Ca and creatinine(L1) and urea, AST,BD (L2).A very stringent internal QC has to be followed for these parameters, and the frequency of internal QC (n) should be increased and corrective action should be taken for these parameters. Upgraded analyzers and better methodologies may help in achieving sigma values. For less than 3 sigma, method performance must be improved before the method can be used for routine production [2]. For a method with sigma below 3 calls for improvement in the method as quality of the test cannot be assured even after repeated QC runs [12].Thus sigma metrics values are useful in setting the internal QC acceptability criteria.

We have obtained our sigma value between 3-6 for Glucose, AST, cholesterol, uric acid, total protein (L1) and ALT, cholesterol, BT, calcium, creatinine and glucose (L2). For a 3 sigma process, use a multi rule procedure with number of QC of 6 or 8 have to be used. For a 4 sigma process, use 2.5 SD control, limits or a multi rule procedure with n=4 have to be used. For a 5 sigma process, use 3.0 SD control limits with n=2 have to be used. For a 6 sigma process (or higher), use 3.5 SD control limits with N (number of controls to be run per day)=2 have to be used. That is QC should be run at higher frequency need to be run for analytes attaining sigma between 4-5 and 3-4 respectively.

Sigma was more than 6 for Triglyceride, ALP, HDL, albumin (L1) and TG, uric acid, ALP, HDL, albumin, total protein (L2).Less stringent QC rules can be followed in this case. In such cases, false rejections can be minimized by relaxing control limits up to 3 s [12].

Functioning at the 3-sigma level is regarded as the minimum acceptable level of quality. The six sigma idea asserts an association between the numbers of product defects, wasted operating costs and levels of customer satisfaction. It can be inferred that as sigma increases, the consistency and steadiness of the test improves, thereby reducing the operating costs. As sigma increases, the consistency, reliability, steadiness and overall performance of the test improves, thereby decreasing the operating costs [13].

The rule is, strive for 6 sigma, >4 sigma is ideal, <3 sigma cannot be controlled with statistical QC protocols.

So ultimately the rule is;

- >6σ –excellent tests - evaluate with 1 QC/day.(alternating levels between days) and 1:3.5 s rule.
- 4 σ - 6 σ -suited for purpose –evaluate with two levels of qc /day,1:2.5 s rule
- 3 σ - 4 σ –poor performers-use a combination of rules with 2 levels of qc/day.
- <3 σ – problems- max qc, 3 levels, 3 times a day. Consider testing specimens in duplicate. Total quality management works on plan, do, check and act rules where as sigma metrics works on define, measure, analyze, improve, control.

When process performance is validated against Westgard rules or any other quality criteria for acceptability of control data, probability for rejection and probability of error detection are of paramount importance [14].The term probability of false rejection (Pfr) is used to describe a situation where there are no analytical errors present except for the inherent imprecision or random error of the method. Probability of error detection (Ped) is the term used to describe where an analytical error occurs in addition to the inherent random error. For achievement of world class quality it is desirable to have a high probability of error detection and a low probability of false rejection [15]. We have also calculated total allowable error (TE_a) for all the 15 analytes and compared it with the total allowable error as per CLIA guidelines

(Table VII). As per rule, TE_a observed $<TE_a$ (CLIA) or closeto it, the quality requirement is met and instrument is suitable for measurement of analyte. Only analytes for which TE_a observed $>TE_a$ (CLIA) were ALT, BD, Ca+2,creatinine (L1) suggesting that respective methodologies need a thorough evaluation. Otherwise the results were excellent suggesting that ideal methodologies are being used. Even though our clinical biochemistry lab is a newly established laboratory narrow SD and CV values ensure precision, bias values ensure accuracy for majority of the analytes. We have derived quality control strategy from our sigma values. TE_avalues assure us the use of correct methodologies for all the analytes.

Conclusion

The six sigma motive is to minimize both variance and quality control processes to guarantee compliance with the critical specifications. Sigma metrics will also facilitate the inculcation of ideal analytical methodologies in order to augment laboratory performance. Each and every laboratory can use sigma metrics as guideline for quality control strategy and plan their QC frequency accordingly. It can be a self assessment tool regarding the functioning of clinical laboratory.

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References

1. Barr JT, Silver S. The total testing process and its implications for laboratory administration and education. *Clin Lab Manage Rev,* 1994; 8:526-42.
2. Westgard JO. Six sigma quality design and control, 2nd ed. *Madison WI:Westgard QC Inc.,* 2006; 338**.**
3. Westgard JO, Barry PL, Tomar RH. Implementing total quality management (TQM) inhealtcare laboratories. *CLMR* 1991; 5:353-70.
4. Berwick DM, Godfry AB, Roessner J. Curing helath care: New strategies for quality improvement. *San Fransisco, Jossey-Bass Publishers,* 1990; 23-28.
5. Westgard JO, Klee GG. Quality management. In: Burtis CA, Ashwood ER, Bruns DE, editors. Tietz textbook of clinical chemistry and molecular diagnostics. *St Louis, MO: Elsevier Saunders Inc.* 2006; 485-529.
6. Brussee W. Statistics for Six Sigma made easy. *New York: McGraw-Hill* 2004; 229.
7. Singh B & Goswami B. Application of Sigma Metrics for the Assessment of Quality Assurance in Clinical Biochemistry Laboratory in India: A Pilot Study. *Ind J ClinBiochem* 2011; 26(2):131-135.
8. Nanda SK, Ray L. Quantitative Application of Sigma Metrics in Medical Biochemistry. *J of Clinical and Diagnostic Res.* 2013; 7(12):2689-2691.
9. Chaudhary NG, Patani SS, Sharma H, Maheshwari A, Jadhav PM, Maniar MG. Application of six sigma for the quality assurance in clinical biochemistry laboratory – a retrospective study. *Int J Res Med.* 2013; 2(3):17-20.
10. U.S. Department of health and human services. Clinical Laboratory Improvement Amendments of 1988. Final rules and notice. 42 CFR Part 493. *Federal Register* 1992; 57:7188-288.
11. Westgard, Sten, and QC Westgard. Six Sigma metric analysis for analytical testing processes. *Abbott MS-09,* 2009; 04:7907.
12. Westgard JO, Quality control. How labs can apply six sigma principles to quality control planning. *Clin Lab News* 2006; 32:10-12.
13. Tetrault G. Evaluating laboratory performancewith the six sigma scale. *Arch Pathol Lab Med.* 2000; 124(12):1748-9.
14. Westgard JO. Internal quality control: planningand implementation strategies. *Ann Clin Biochem.* 2003; 40:593-611.
15. Westgard JO, Groth T, Aronsson T, Falk H, De Verdier CH. Performance characteristics of rules for internal quality control: probabilitiesfor false rejection and error detection. *Clin Chem.* 1977; 23: 1857-67.

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