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Original investigation

Evaluation of Analytical Process Performance by Six Sigma Method

Dilek İren Emekli[1], Nergiz Zorbozan[2], Zübeyde Erbayraktar[3]

[1]Erbayraktar Private Medical Laboratories, Department of Medical Biochemistry, Izmir, Turkey
[2]İzmir Kemalpaşa State Hospital, Department of Medical Biochemistry, Izmir, Turkey
[3]Dokuz Eylül University Faculty of Medicine, Department of Medical Biochemistry, Izmir, Turkey

Address for Correspondence: Dilek Iren Emekli, **E-mail:** dilekirenn@gmail.com
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ABSTRACT

Purpose: Clinical laboratories are responsible for producing reliable, reproducible and accurate test results. Should establish quality in their test analysis and evaluate process performance. Six sigma is a quality management strategy that evaluation of processes. The aim of our study is to evaluate the analytical process performance of routine tests in our laboratory with six sigma method.

Methods: Internal quality control (IQC) data of routine tests in our laboratory were obtained retrospectively. Mean, standard deviation and coefficient of variation (CV) values of the IQC data were calculated. Process sigma values were calculated using the formula "Total Allowable Error (TEa)%-Bias% /CV% ". TEa values were determined according to CLIA'88. Sigma value ≤3 low quality, between 3 and 6 good quality and ≥6 was recognized as world class quality.

Results: The sigma levels of all the tests we evaluated were >3. Sigma levels of albumin, creatinine, LDL, urea, chloride, total cholesterol, HDL, sodium for IQC 1; albumin, urea, UIBC, chloride, creatinine, potassium, sodium and direct bilirubin for IQC2 were between 3–6. The sigma levels of ALP, ALT, AST, CK, CKMB, iron, UIBC, phosphorus, GGT, glucose, calcium, LDH, magnesium, potassium, total protein, triglyceride, uric acid, amylase, lipase, direct bilirubin, total bilirubin, CRP for IQC 1; ALP, ALT, AST, CK, CK-MB, iron, phosphorus, GGT, glucose, calcium, total cholesterol, HDL, LDL, LDH, magnesium, total protein, triglyceride, uric acid, amylase, lipase, total bilirubin, CRP tests for IQC 2 were ≥6.

Conclusion: Six sigma methodology is an effective method for evaluating the analytical process performance of the laboratory. According to the results of our study, our laboratory performance is good or first class.

Key words: six sigma, total allowable error, quality control

INTRODUCTION

Clinical laboratories are responsible for producing reliable, reproducible and accurate test results. To achieve this goal, laboratories should establish quality in their test analysis and evaluate process performance (1–3). The total test process of the laboratories consists of pre-analytic (period from the physician's test order to analysis), analytical (period of test analysis) and post-analytic sub-processes (period in which the test result is reported and the clinician uses the test result for the benefit of the patient) (4–6). There are many assessment methods and tools defined according to the factors affecting the test results. These methods and tools vary according to the sub-processes of the total test process (1–3).

The process performance evaluation is performed according to the methods and criteria that the laboratories determine themselves. Evaluation should be done using scientifically accepted methods (7, 8). In this process, firstly, the performance targets should be determined. Processes are evaluated according to quality indicators, process sigma levels and statistical criteria such as trueness and precision (9, 10). Error percentages for the pre-analytic phase, trueness and precision measurement for the analytical phase (Bias, Standard deviation), panic value reporting and inappropriate turnaround times for the post-analytic phase are evaluated (12–14).

Six sigma, first used in 1986 to reduce differences in electronic manufacturing processes in the United State is a quality management strategy that enables processes to be evaluated, fault identified, and improved. It is based on statistical calculations, focuses on process variables and provides information about process performance. The application steps include defining, measuring, analysing, developing and controlling. These stages

are universal and can be applied in all sectors of industry, work and health (15–18).

In our country, the use of six sigma is very common in the industry, while the practices in medical laboratories are limited (18–20). Studies have been conducted to benefit from patient test results for quality control purposes and these studies are still ongoing (21–23).

According to the six sigma methodology, variability is accepted as the main source of errors. The main indicator is the process sigma level. Six sigma reveals a relationship between the number of product defects, wasted operating costs, and patient satisfaction. It can be concluded that with increasing sigma level, the consistency and stability of the test increases and thus the operating costs decrease. The sigma level can be easily calculated and interpreted by laboratories. In the six sigma methodology, process performance is evaluated according to the poor quality costs and the aim is to reduce these poor quality costs for improvement (1, 24). Costs of poor quality are shown as defects per million opportunities (DPMO) (7). Process sigma levels according to DPMO are shown in Table 1 (18).

In this context, the aim of our study is to evaluate the analytical process performances of routine tests in our laboratory according to six sigma methodology.

METHODS

The study was conducted between June 1, 2018 and September 30, 2018 in Erbayraktar Special Clinical Laboratories, Izmir.

Samples and Test Methods

Albumin, alkaline phosphatase (ALP), alanine amino transferase (ALT), aspartate amino transferase (AST), urea, creatine kinase (CK), CKMB, iron, unsaturated iron binding capacity (UIBC), phosphorus, gamma glutamyl transferase (GGT), glucose, calcium, chloride, total cholesterol, HDL cholesterol, LDL cholesterol, creatinine, lactate dehydrogenase (LDH), magnesium, potassium, sodium, total protein, triglyceride, uric acid, amylase, lipase, total bilirubin, direct bilirubin and CRP tests were performed on Roche Cobas c501 analyser (Roche Diagnostics GmbH, Mannheim, Germany) in our laboratory. Principle of tests was shown in Table 2. The internal quality control (IQC) of these tests was routinely performed at the beginning of each working day using IQC 1 (expected value) and IQC 2 (pathological value) materials (PCC1 and PCC2) provided by the manufacturer. The analyser and reagents were used according to the manufacturer's instructions and calibrated

Table 1. Process sigma levels according to defects per million opportunities

Sigma Levels	Defects per million opportunities
1	691462
2	308538
3	66807
4	6210
5	233
6	3.4

Table 2. Test principles of analytes

Analytes	Principle of Tests
Albumin	Colorimetric assay
Alkaline phosphatase	Colorimetric assay in accordance with a standardized method.
Alanine amino transferase	Determination with pyridoxal phosphate (Assay follows the recommendations of the IFCC, but was optimized for performance and stability)
Aspartate amino transferase	Determination without pyridoxal phosphate (Assay follows the recommendations of the IFCC, but was optimized for performance and stability)
Urea	Kinetic test with urease and glutamate dehydrogenase
Creatine kinase	UV-test
CKMB	Immunological UV assay
Iron	Colorimetric assay
Unsaturated iron binding capacity	Direct determination with FerroZine
Phosphorus	Molybdate UV
Gamma glutamyl transferase	Enzymatic colorimetric assay
Glucose	UV test, enzymatic reference method with hexokinase
Calcium	Method according to Schwarzenbach with o-cresolphthalein complexone
Chloride	Ion-Selective Electrode
Total cholesterol	Enzymatic, colorimetric method
HDL cholesterol	Homogeneous enzymatic colorimetric
LDL cholesterol	Homogeneous enzymatic colorimetric
Creatinine	Buffered kinetic Jaffé reaction without deproteinization
Lactate dehydrogenase	UV assay
Magnesium	Colorimetric assay
Potassium	Ion-Selective Electrode
Sodium	Ion-Selective Electrode
Total protein	Colorimetric assay
Triglyceride	Enzymatic colorimetric
Uric acid	Enzymatic colorimetric
Amylase	Enzymatic colorimetric
Lipase	Enzymatic colorimetric assay with 1.2-O-Dilauryl-rac-glycero-3-glutaricacid-(6-methyl-resorufin) ester
Total bilirubin	Colorimetric assay
Direct bilirubin	Diazo method
CRP	Particle enhanced immunoturbidimetric assay

Table 3. Mean, standard deviation, coefficient of variation%, bias% values of internal quality controls calculated in our laboratory and declared in the manufacturer's package insert and Tea% values

Test (Unit)	IQC Levels	Target Mean	Target SD	Target CV%	TEa% (CLIA'88)	Laboratory Mean	Laboratory SD	Laboratory CV%	Laboratory Bias%
Albumin (mg/dL)	IQC1	3.17	0.19	6	10	3.1	0.09	2.9	-2.5
	IQC2	4.76	0.29	6	10	4.7	0.1	2.1	-2.1
ALP (IU/L)	IQC1	104	6	6	30	98	3.3	3.4	-6.1
	IQC2	226	14	6.2	30	221	4.6	2.1	-2.4
ALT (IU/L)	IQC1	45.6	2.7	5.9	20	45	0.9	2	-1.8
	IQC2	121	7	6	20	113	2.2	1.9	-6.4
AST (IU/L)	IQC1	45.4	2.7	5.9	20	45	1.2	2.7	-0.4
	IQC2	141	8	5.7	20	143	4	2.8	1.4
Urea (mg/dL)	IQC1	39	2	5.1	9	38.72	1.01	2.6	-0.7
	IQC2	117	6	5	9	114	2.24	2	-2.7
CK (IU/L)	IQC1	150	9	6	30	147	2.5	1.7	-1.9
	IQC2	296	18	6.1	30	289	4.7	1.6	-2.2
CK-MB (U/L)	IQC1	42.7	3.4	8	30	40	1.04	2.6	-6.8
	IQC2	95.4	7.6	8	30	92	0.86	0.9	-4.0
Iron (ug/dL)	IQC1	106	6	6	20	109	1	0.9	2.5
	IQC2	242	15	6.2	20	248	4.5	1.8	2.5
UIBC (ug/dL)	IQC1	220	15	7	20	213	6.6	3.1	-3.3
	IQC2	293	21	7.2	20	294	10.3	3.5	0.2
Phosphorus (mg/dL)	IQC1	4	0.2	5	15	4.1	0.06	1.5	1.5
	IQC2	8.09	0.4	4.9	14.8	8.3	0.09	1.1	2
GGT (U/L)	IQC1	57	3.4	6	17.9	56	1.6	2.8	-1.1
	IQC2	241	14	5.8	17.4	240	1.9	0.8	-0.3
Glucose (mg/dL)	IQC1	102	5	4.9	10	102	1.7	1.7	0.0
	IQC2	240	12	5	10	238	3.3	1.4	-0.7
Calcium (mg/dL)	IQC1	8.86	0.35	4.0	11.3	8.7	0.14	1.6	-2.3
	IQC2	13.6	0.5	3.7	7.4	13.3	0.11	0.8	-2.1
Chloride (mmol/L)	IQC1	80	2.4	3	5	79.03	1.1	1.4	-1.2
	IQC2	108	3	2.8	5	107	1.8	1.7	-1.3
Total Cholesterol (mg/dL)	IQC1	64.9	3.2	4.9	10	65	1.41	2.2	-0.1
	IQC2	167	8	4.8	10	164	1.6	1	-1.6
HDL (mg/dL)	IQC1	21.5	1.7	7.9	30	21	1.2	5.7	-1.4
	IQC2	66.5	5.3	8	30	65	1	1.5	-2.9
LDL (mg/dL)	IQC1	42.9	3.4	7.9	20	41	2.91	7.2	-5.5
	IQC2	100	8	8	20	93	1.06	1.1	-7.3
Creatinine (mg/dL)	IQC1	1.09	0.07	6.4	15	1.1	0.04	3.6	1.8
	IQC2	3.86	0.23	6	15	4.0	0.09	2.3	2.6
LDH (U/L)	IQC1	163	10	6.1	20	157.9	2.2	1.4	-3.1
	IQC2	302	18	6	20	294.3	3.8	1.3	-2.5
Magnesium (mg/dL)	IQC1	2.12	0.08	3.8	25	2.1	0.08	4	-1.4
	IQC2	3.47	0.14	4	25	3.4	0.07	2.1	-2
Potassium (mmol/L)	IQC1	3.61	0.11	3	13.9	3.6	0.08	2.1	-0.7
	IQC2	7.14	0.21	3	7	7.0	0.11	1.6	-1.4
Sodium (mmol/L)	IQC1	111	3	2.7	3.6	110.8	1	0.9	-0.2
	IQC2	137	4	2.9	2.9	136	1	0.7	-0.7
Total Protein (g/dL)	IQC1	4.71	0.19	4	10	4.7	0.05	1	-0.2
	IQC2	7.47	0.3	4	10	7.5	0.09	1.3	0.5
Triglyceride (mg/dL)	IQC1	117	6	5.1	25	117	2.3	2	0.2
	IQC2	219	11	5	25	219	6	2.7	0.0
Uric acid (mg/dL)	IQC1	4.72	0.24	5.1	17	4.8	0.09	1.9	0.8
	IQC2	10.4	0.5	4.8	17	10.5	0.15	1.4	0.7
Amylase (U/L)	IQC1	82	4.9	6	30	82.2	0.9	1.1	0.2
	IQC2	200	12	6	30	197.4	1.1	0.6	-1.3
Lipase (U/L)	IQC1	43.7	2.6	5.9	30	45	1.3	2.9	3
	IQC2	102	6	5.9	30	95.8	2.8	2.9	-6.1
Direct Bilirubin (mg/dL)	IQC1	1.02	0.08	7.8	20	1.0	0.03	2.5	-1.9
	IQC2	2.69	0.22	8.2	20	2.6	0.11	4.4	-2.8
Total Bilirubin (mg/dL)	IQC1	1.05	0.06	5.7	20	1.0	0.03	3.1	-0.4
	IQC2	4.04	0.24	5.9	20	3.9	0.12	3.1	-3.2
CRP (mg/dL)	IQC1	0.892	0.059	6.6	30	0.9	0.03	2.9	-2.9
	IQC2	4.31	0.29	6.7	30	4.0	0.04	0.9	-6.2

IQC, internal quality control; SD, standard deviation; CV, coefficient of variation; TEa, total allowable error; CLIA'88, clinical laboratory implementation amendments 1988.

according to routine standard operating procedures before any control analysis.

IQC 1 (n=80, for each test) and IQC 2 (n=80, for each test) data of the evaluated tests (June-September 2018) were obtained from the laboratory information system. Control data that were not accepted due to random and technique errors were excluded from the study. CV%, bias% and sigma values of the tests were calculated. The target mean, standard deviation (SD) and coefficient of variation (CV)% values of the IQC material declared by the manufacturer were obtained from the IQC package insert (Table 3).

Calculations

CV%

CV is the percentage of SD to the mean. The CV%, defined as the precision criterion, is calculated with the mean and standard deviation obtained from the IQC data.

CV%=(SD/IQC mean) × 100

Bias

The bias was calculated as the difference between the mean value of the observed results and the target value declared in the company inserts.

Bias%=[(Laboratory mean of IQC-Target average of IQC)/Target average of IQC] × 100

Total allowable error (TEa)

The total acceptable error can be determined according to guidelines such as Clinical Laboratory Implementation Amendments 1988 (CLIA'88) and RiliBÄK (17). The maximum error limits that are legally appropriate for the substance to be measured are defined in the CLIA'88 criteria. In our study, target TEa levels were determined according to CLIA'88 total error criteria. CLIA is regularly updated and can be freely accessed through http://www.westgard.com. The TEa values of the tests we evaluated in our study are shown in Table 3.

Sigma calculation

Sigma was calculated using CV% and bias% obtained from IQC data and TEa%.

Sigma=(TEa%-Bias%)/CV%

A sigma level of <3 indicates a poor performance indicator. >3 sigma levels can be considered good performance (1). The calculated sigma values of tests are shown in Table 4.

Statistical Methods

Calculations were performed using the SPSS software package (version 20.0; SPSS, Inc., Chicago, IL, USA) and Microsoft Excel program.

RESULTS

Mean, SD, CV% and bias values of the tests for IQC1 and IQC2 are shown in Table 3. According to the calculated process sigma levels of our tests, sigma value was not less than 3. For the IQC1, sigma level of ten tests (albumin, creatinine, LDL cholesterol, urea, chloride, total cholesterol, HDL cholesterol, sodium) and for the IQC2, sigma levels of eight tests (albumin, urea, UIBC, chloride, creatine, potassium, sodium and direct bilirubin) were between 3 and 6.

Sigma levels of ALP, ALT, AST, CK, CKMB, iron, UIBC, phosphorus, GGT, glucose, calcium, LDH, magnesium, potassium, total protein, triglyceride, uric acid, amylase, lipase, direct bilirubin, total bilirubin, CRP tests for the IQC1; sigma levels of ALP, ALT, AST, CK, CKMB, iron, phosphorus, GGT, glucose, calcium, total cholesterol, HDL cholesterol, LDL cholesterol, LDH, magnesium, total protein, triglyceride, uric acid, amylase, lipase, total bilirubin, CRP tests for the IQC2 showed an ideal performance (≥6 sigma) (Table 4, Table 5).

Table 4. Process sigma levels of the analytes

	Sigma Level	
Analyte (unit)	IQC1	IQC 2
Albumin (mg/dL)	4.30	5.64
ALP (IU/L)	10.68	15.55
ALT (IU/L)	10.83	13.61
AST (IU/L)	7.70	6.64
Urea (mg/dL)	3.73	5.97
CK (IU/L)	18.79	19.85
CK-MB (U/L)	14.08	36.21
Iron (ug/dL)	19.06	9.66
UIBC (ug/dL)	7.51	5.64
Phosphorus (mg/dL)	9.14	11.78
GGT (U/L)	6.68	22.45
Glucose (mg/dL)	6.00	7.71
Calcium (mg/dL)	8.38	11.40
Chloride (mmol/L)	4.46	3.73
Total Cholesterol (mg/dL)	4.64	11.87
HDL (mg/dL)	5.55	21.23
LDL (mg/dL)	3.56	23.88
Creatinine (mg/dL)	3.65	5.46
LDH (U/L)	16.60	17.46
Magnesium (mg/dL)	6.57	13.12
Potassium (mmol/L)	6.97	5.35
Sodium (mmol/L)	4.19	4.96
Total Protein (g/dL)	10.00	7.56
Triglyceride (mg/dL)	12.65	9.13
Uric acid (mg/dL)	8.64	11.40
Amylase (U/L)	27.18	56.17
Lipase (U/L)	9.35	12.34
Direct Bilirubin (mg/dL)	8.75	5.23
Total Bilirubin (mg/dL)	6.66	7.56
CRP (mg/dL)	11.40	40.65

IQC: internal quality control.

Table 5. Distribution of analytes grouped according to calculated sigma values

Sigma metrics	IQC 1	IQC 2
Group 1 (<3 sigma)	-	-
Group 2 (3–6 sigma)	Albumin Creatinine LDL Cholesterol Urea Chloride Total Cholesterol HDL Cholesterol Sodium	Albumin Urea UIBC Chloride Creatine Potassium Sodium Direct Bilirubin
Group 3 (>6 sigma)	ALP ALT AST CK CKMB Iron UIBC Phosphorus GGT Glucose Calcium LDH Magnesium Potassium Total Protein Triglyceride Uric Acid Amylase Lipase Direct Bilirubin Total Bilirubin CRP	ALP ALT AST CK CKMB Iron Phosphorus GGT Glucose Calcium Total Cholesterol HDL Cholesterol LDL Cholesterol LDH Magnesium Total Protein Triglyceride Uric Acid Amylase Lipase Total Bilirubin CRP

IQC: internal quality control.

DISCUSSION

Control of the laboratory's work processes is crucial to the quality of the laboratory's test results. Measuring and monitoring performances provide opportunities to improve processes in laboratories. (25). Six sigma method is an effective tool to monitor processes and prove their performances (18, 6). It also provides a quantitative comparison of various methods, automated analysers and laboratories around the world (15).

There are many analytical performance evaluation studies using six sigma method. Mao et al. found that sigma values of urea and sodium tests were below 3 in their performance evaluation study using six sigma method (26). Afrifa J et al. conducted an analytical performance evaluation study at the University of Cape Cost Hospital Clinical Chemistry Laboratory and reported the sigma value of HDL cholesterol, urea, creatinine, and potassium tests >1 sigma for both control levels. The sigma levels of chloride and sodium tests were found to be >1 sigma for the IQC 1 and <1 sigma for the IQC 2. In contrast, sigma levels of total cholesterol, total protein and AST tests were reported as <1 sigma for IQC 1 and >1 sigma for IQC 2. The sigma values of glucose and ALP were reported as >1 sigma and TG sigma values were reported as >2 sigma for both control levels. Accordingly, the authors reported that the unsatisfactory sigma levels (<3 sigma) obtained in the study showed that instability and low consistency of results (27). In the study of Aslan et al., analytical process sigma levels were determined and the results were evaluated together with the patient test results. According to the obtained data, sigma levels of total protein, urea, LDH, sodium and albumin tests were found to be low (<3 sigma) (19). In the study of Singh et al., sigma levels of AST, CK, amylase and triglyceride tests were higher than 6 sigma; sigma levels of urea, total cholesterol, HDL cholesterol, sodium and potassium tests were found to be less than 3 (28). In a similar study by Nanda et al., sigma levels of AST, ALT, ALP, total bilirubin and uric acid calculated as >6 sigma. In the same study, sigma levels of glucose, creatinine, triglyceride tests were between 3–6 sigma and sigma levels of urea, albumin, total protein, total cholesterol and chloride tests were reported as <3 sigma (29).

The sigma values can be influenced by the selected TEa target value. In the study of Hens et al. (17), sigma levels were evaluated according to TEa. The results of the study showed that sigma levels change according to the TEa value used (17). In our study, the analytical process was evaluated and TEa values were determined according to CLIA'88 (17). In the tests we evaluated, all of the calculated process sigma levels were >3 sigma. The sigma levels of IQC1 calculated for albumin, creatinine, LDL, urea, chloride, total cholesterol, HDL cholesterol and sodium; IQC2 sigma levels for albumin, urea, UIBC, chloride, creatinine, potassium, sodium and direct bilirubin tests were between 3–6 sigma. The sigma levels of IQC1 calculated for ALP, ALT, AST, CK, CKMB, iron, UIBC, phosphorus, GGT, glucose, calcium, LDH, magnesium, potassium, total protein, triglyceride, uric acid, amylase, lipase, direct bilirubin, total bilirubin and CRP; sigma levels of IQC2 calculated for ALP, ALT, AST, CK, CK-MB, iron, phosphorus, GGT, glucose, calcium, total cholesterol, HDL, LDL, LDH, magnesium, total protein, triglyceride, uric acid, amylase, lipase, total bilirubin and CRP tests were ≥6 sigma (Table 4, Table 5).

The Six Sigma Methodology is an important method for the evaluation of the analytical phase, which is an important part of the total testing process, the reliability, reproducibility of laboratory tests, and the rearrangement of quality control rules according to sigma values. It enables the identification and measurement of the most common errors that pose risk to patients and cause cost loss. This approach serves as a guide to the quality control strategy. The sigma levels of the tests we evaluated in our study were calculated to be above 3. This result indicates that our laboratory's analytical processing performance was good or first-class in the period we evaluated.

Six sigma method is a process evaluation method which has been used more frequently in clinical laboratory recently because it provides a different approach to problems. Clinical laboratories play an important role in the patient-related process. Today, 60–70% of important decisions such as patient admission, discharge and treatment are affected by laboratory results. Therefore, the process sigma level in the health sector should always be targeted as the best (if possible zero error). The best or world class processes is at 6 sigma level (2). In our study, we found that sigma levels of albumin, chloride and sodium tests were between 3 and 6 sigma

for IQC 1 and IQC 2 levels. In addition, the sigma levels of the LDL cholesterol, urea, total cholesterol, HDL cholesterol, sodium, UIBC, potassium, direct bilirubin were between 3 and 6 sigma for IQC 1 or IQC 2 levels. We think these results may be due to the frequency of routine calibration. Our result indicates that there is a probability of error between 3.4 and 66807 for 1 million tests in these tests in the analytical process. In the Six Sigma methodology, a problem solving model consisting of "Define, Measure, Analyze, Improve, Control" methods is used to perform many activities from problem definition to problem solving (7). In our study, "Define, Measure" steps were used and error probabilities were evaluated. According to the results of our study, we planned to identify the root causes of the problems and to find solutions by using "Analyze, Improve, and Control" steps for these tests and to evaluate our progress by repeating our process performance studies.

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