*Research Article / Araştırma Makalesi*

# Evaluation of Biochemistry Tests with Six Sigma

## Altı Sigma ile Biyokimya Testlerinin Değerlendirilmesi

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Abstract

Background: Six sigma is a quality indicator used in biochemistry laboratories to evaluate analytical performance. We aimed to evaluate our analytical performance by calculating the six sigma values of some tests in our own laboratory.
Materials and Methods: In this study, we used the five-month internal quality control values of 49 biochemistry and immunoassay tests analyzed on Beckman Coulter AU 5800 and DXI 800 analyzers. We calculated six sigma data using 2 different allowed total error values (% TEa)[(Clinical Laboratory Improvement Amendments (CLIA) and Ricos biyological variation]. We accepted three and above six sigma values as an indicator of good performance.
Results: When we evaluated according to CLIA criteria, the analytical performance of ALP, CK and amylase was 6 and above, while according to Ricos, only the analytical performance of the prolactin test was 6 and above at both control levels.
Conclusions: Six sigma is important in quality control evaluation. When performing the sigma calculation, it should be kept in mind that the permissible total error values used may cause different performance data.

Key Words: Six sigma; Sigma metrics; Total quality management

Öz.

Amaç: Altı sigma, biyokimya laboratuvarlarında analitik performansın değerlendirmesi için kullanılan bir kalite indikatörüdür. Biz de kendi laboratuvarımızda bazı testlerin altı sigma değerlerini hesaplayarak analitik performansımızı değerlendirmeyi amaçladık.
Materyal ve Metod: Bu çalışmada, Beckman Coulter AU 5800 ve DXI 800 analizörlerinde çalıştığımız 49 biyokimya ve immunassay testinin beş aylık internal kalite kontrol değerlerini kullandık. 2 farklı izin verilen toplam hata değerleri (%TEa) [(Clinical Laboratory Improvement Amendments (CLIA), Ricos biyolojik varyasyon] ile altı sigma verilerini hesapladık. Üç ve üzeri altı sigma değerlerini iyi performans göstergesi olarak kabul ettik.
Bulgular: CLIA kriterlerine göre değerlendirme yaptığımız zaman ALP, CK ve amilazın analitik performansı 6 ve üzeri iken, Ricos'a göre sadece prolaktin testinin her iki kontrol düzeyinde analitik performansı 6 ve üzeri idi.
Sonuç: Altı sigma, kalite kontrol değerlendirmede önemlidir. Sigma hesabı yapılırken kullanılan izin verilen total hata değerlerinin farklı performans verilerine neden olabileceği akılda tutulmalıdır.

Anahtar kelimeler: Altı Sigma, Sigma ölçümleri, Toplam kalite yönetimi

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## Introduction

Six Sigma Methodology; is a quality management tool based on statistical calculations, focused on process variables and providing information about process performance (1). In our country, six sigma applications are very common in the industry, while applications in medical laboratories are not so much. In the study conducted by Aslan et al., process sigma levels in the analytical phase were determined and the patient was evaluated together with the test results; however, their relationship with preanalytic and postanalytic process variables could not be investigated (2).

In the six sigma methodology, variables are considered to be the main source of inaccuracies. In the six sigma methodology, process performance is evaluated according to the poor quality costs determined from the process sigma levels and the improvement is aimed at reducing the poor quality costs (1,2).

The degree of deviation from the targeted values in any process can be measured with the six sigma methodology. The sigma value indicates the frequency of occurrence of the error. While there are fewer errors in high sigma values, there are more errors in low sigma values.

The sigma value of a test is a well-defined and quantitative measurement of the quality of this test. Six sigma is a quality management procedure with the aim to improve assay quality. A sigma level <3 is an indicator of a poor performance procedure. A good performance is indicated by a sigma level >3. The above six sigma level is a world-class performance (3). Allowable total error (TEa) is the analytical quality specification that determines the acceptable limits for a single test result. In this study, we aimed to evaluate our laboratory analytical performance with Clinical Laboratory Improvement Amendments (CLIA) criteria and Ricos according to six sigma metrics.

## Materials and Methods

Ethics approval was granted by the Ankara Numune Training and Research Hospital Ethics Committee with Protocol Number: E 17-1480. This study was carried out for six months in Ankara Numune Training and Research Hospital at Biochemistry Laboratory by using internal quality control (IQC) and external quality assessment (EQA) data applied as a requirement of routine laboratory procedures and health quality standards. The 49 clinical biochemistry parameters included in this study were: Albumin, Alanine Aminotransferase (ALT), Alkaline phosphatase (ALP), Aspartate Aminotransferase (AST), Amylase, Iron, Direct Bilirubin, Phosphorus (P), Chloride (Cl), Cholesterol, Creatinine, Creatine Kinase (CK), Glucose, Gamma-Glutamyl Transferase (GGT), High-Density Lipoprotein Cholesterol (HDL), Lactate Dehydrogenase (LDH), Low-Density Lipoprotein Cholesterol (LDL), Magnesium (Mg), Potassium (K), Total protein, Total bilirubin, Sodium (Na), Triglycerides, Urea, Uric acid, C-Reactive Protein (CRP), Rheumatoid Factor (RF), Cortisol, Free Thyroxine (FT4), Free Triiodothyronine (FT3), Insulin, Vitamin B12, Free Prostate Specific Antigen (FPSA), Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH), Estradiol (E2), Testosterone, Prolactin, Progesterone, Carbohydrate antigen 19-9 (CA 19-9), Cancer Antigen 125 (CA 125), Cancer Antigen 15-3 (CA 15-3), Alpha Feto-Protein (AFP), Carcinoembryonic Antigen (CEA), Ferritin, Folate, Thyroid Stimulating Hormone (TSH), Total Prostate Specific Antigen (Total PSA), Parathyroid Hormone (PTH). Six Sigma Value was calculated as follows, using the Total Allowable Error (TEa) obtained from literature, Coefficient of Variation (CV) obtained from internal quality control and the bias obtained from the external quality control data; Sigma value = (TEa% - Bias%) / CV%. The coefficient of variation is calculated as follows: CV (%) = (SD / $\overline{x}$) × 100. IQC data of 49 test parameters analyzed on Beckman Coulter AU 5800 and DXI 800 analyzer.

Bias is the difference between the value obtained from the analysis of a test and the reference value. In this study, the mean value calculated by EQA program for each test using the participant laboratory results was used as the reference value. Our laboratory was a member of the Randox International Quality Assessment Scheme (RIQAS) program at the time of this study. Between 01 May 2015 and 30 September 2015, bias % of each test was calculated separately for each month. The bias % as determined by the following formula: % Bias = [(Test Result - EQA Peer group Average value of the Test) ÷ Average EQA Average value peer group of the Test] × 100. The bias % values of each test were averaged for six months to be used in the formula. Total Allowable Error (TEa) is determined by the literature (4,5,6). Table 1 shows the TEa values of each reference.

Even tests performed on the same analyzer and the same control sample can perform differently according to the six sigma concept. It is thought that a separate internal quality control application can be defined for each test according to the Sigma value, on the one hand, performance improvement and on the other hand, false internal quality control rejection can be prevented.

## Results

In our laboratory; ALP, total bilirubin, LDH, GGT, amylase, cholesterol, CA 19-9, CA 125, CA 15-3, AFP, CEA, ferritin, folate, TSH, total PSA, LH, PTH tests show good performance at normal and abnormal levels. When sigma values were calculated with TEa ratios based on CLIA, sigma values of ALP, CK and amylase tests were found to be greater than 6 for both normal and pathological level control. In addition, cholesterol for pathological level control only and sigma value of total bilirubin test for normal control only

were calculated to be greater than 6 (Table 1, 2). When sigma values were calculated with TEa ratios based on the biological variation of Ricos, the sigma values of PRL tests for both normal and pathological level control were found to be greater than 6. Furthermore, for pathological level control only, the sigma value of the LH test was calculated greater than 6 (Table 3,4).

Table1. The TEa values of each reference.

| | CLIA | | TEa (%) | Ricos | | TEa (%) |
|---|---|---|---|---|---|---|
| | Normal | Pathologic | | Normal | Pathologic | |
| ALP (U/L) | 6,075 | 6,01 | 30 | 2,335 | 1,55 | 12,04 |
| AST (U/L) | 3,52 | 2,29 | 20 | 2,932 | 1,68 | 16,69 |
| TBIL (mg/dL) | 9,386 | 2,39 | 20 | 12,636 | 3,23 | 26,94 |
| CRE (mg/dL) | 2,059 | 1,889 | 15 | 1,211 | 1,093 | 8,87 |
| TRIG (g/dL) | 2,754 | 2,603 | 25 | 2,987 | 2,817 | 25,99 |
| K (mEq/L) | 0,10 | 0,145 | 5 | 1,588 | 2,193 | 5,61 |
| AMYLASE (U/L) | 11,404 | 13,110 | 30 | 5,165 | 4,919 | 14,6 |
| ALT (U/L) | 2,789 | 2,237 | 20 | 3,869 | 3,464 | 24,48 |
| DBIL (mg/dL) | | | | 19,804 | 27,265 | 44,5 |
| GLU (mg/dL) | 2,471 | 2,303 | 10 | 1,54 | 1,206 | 6,96 |
| UREA (mg/dL) | 1,500 | 2,672 | 9 | 2,764 | 4,306 | 15,55 |
| Mg (mg/dL) | 4,090 | 4,229 | 25 | 0,752 | 0,765 | 4,8 |
| CL (mEq/L) | 1,699 | 2,511 | 5 | -0,203 | 0,418 | 1,5 |
| CK (U/L) | 11,825 | 16,749 | 30 | 11,943 | 16,887 | 30,3 |
| LDH (U/L) | 1,752 | 0,957 | 20 | 0,136 | -1,699 | 11,4 |
| Ca (mg/dL) | 1,24 | 0,38 | 1 | 0,693 | 0,999 | 2,55 |
| P (mg/dL) | | | | 1,828 | 2,207 | 10,11 |
| U URIC ACIDE (mg/dL) | 3,452 | 3,710 | 17 | 2,478 | 2,600 | 11,97 |
| GGT (mg/dL) | | | | 8,437 | 14,714 | 22,11 |
| ALB (g/dL) | 2,378 | 2,476 | 10 | 0,966 | 0,992 | 4,07 |
| CHOL (mg/dL) | 2,905 | 6,828 | 10 | 2,656 | 6,526 | 9,01 |
| T.PROTEIN (g/dL) | 2,053 | 2,147 | 10 | 0,743 | 0,775 | 3,63 |
| Fe (ug/L) | 5,647 | 2,281 | 20 | 9,036 | 3,721 | 30,7 |
| Na (mEq/L) | 0,73 | 0,51 | 4 | -1,010 | -1,416 | 0,73 |
| HDL (mg/dL) | 3,449 | 3,093 | 30 | 1,398 | 1,243 | 11,63 |
| LDL (mg/dL) | | | | 1,752 | -7,841 | 11,9 |
| CRP (g/L) | | | | 10,953 | 17,111 | 56,6 |
| RF (U/mL) | | | | 2,665 | 2,349 | 13,5 |

*ALB: Albumin, ALT: Alanine Aminotransferase, ALP: Alkaline phosphatase, AST: Aspartate Aminotransferase, Ca: Calcium, CL: Chloride, CHOL: Cholesterol, CRE: Creatinine, CK: Creatine kinase, CRP: C-Reactive Protein, DBIL: Direct bilirubin, GGT: Gamma Glutamyl Transferase, GLU: Glucose, HDL: HDL Cholesterol, Fe: Iron, LDH: Lactate Dehydrogenase, LDL: LDL Cholesterol, Mg: Magnesium, Na: Sodium, P: Phosphorus, K: Potassium, RF: Rheumatoid Factor, TBIL: Total bilirubin, T.PROTEIN: Total protein, TRIG: Triglyceride.*

Table 2. Groups by CLIA and Ricos

| Group | CLIA | | Ricos | |
|---|---|---|---|---|
| | Normal | Pathologic | Normal | Pathologic |
| 0- 2.99 | CRE | AST | ALP | ALP |
| | TRIG | TBIL | AST | AST |
| | ALT | CRE | CRE | CRE |
| | GLU | TRIG | TRIG | TRIG |
| | UREA | ALT | K | K |
| | CL | GLU | GLU | GLU |
| | LDH | UREA | UREA | Mg |
| | ALB | CL | Mg | CL |
| | CHOL | LDH | CL | LDH |
| | T.PROTEIN | ALB | LDH | Ca |
| | K | T.PROTEIN | Ca | P |
| | Ca | K | P | URIC ACIDE |
| | Na | Ca | URIC ACIDE | ALB |
| | | Na | ALB | T.PROTEIN |
| | | Fe | CHOL | Na |
| | | | T.PROTEIN | HDL |
| | | | Na | RF |
| | | | HDL | LDL |
| | | | LDL | Ca |
| | | | RF | |
| 3- 3.99 | AST | URIC ACIDE | ALT | TBIL |
| | URIC ACIDE | HDL | | ALT |
| | HDL | | | Fe |
| | Mg | | | |
| 4- 5.99 | Mg | Mg | AMYLASE | AMYLASE |
| | Fe | | | UREA |
| **≥ 6** | ALP | ALP | TBIL | DBIL |
| | TBIL | CHOL | DBIL | CK |
| | AMYLASE | AMYLASE | CK | GGT |
| | CK | CK | CRP | CRP |
| | | | Fe | CHOL |
| | | | GGT | LDL |

*ALB: Albumin, ALT: Alanine Aminotransferase, ALP: Alkaline phosphatase, AST: Aspartate Aminotransferase, Ca: Calcium, CL: Chloride, CHOL: Cholesterol, CRE: Creatinine, CK: Creatine kinase, CRP: C-Reactive Protein, DBIL: Direct bilirubin, GGT: Gamma Glutamyl Transferase, GLU: Glucose, HDL: HDL Cholesterol, Fe: Iron, LDH: Lactate Dehydrogenase, LDL: LDL Cholesterol, Mg: Magnesium, Na: Sodium, P: Phosphorus, K: Potassium, RF: Rheumatoid Factor, TBIL: Total bilirubin, T.PROTEIN: Total protein, TRIG: Triglyceride.*

## Discussion

The use of sigma values as a quality indicator provides two main benefits. First, thanks to the six sigma concept the opportunity to determine the probability of unsafe results can be found in a system considered to be under control.

Another benefit of using sigma values is that it allows making adjustments in control applications.

Table 3. Hormone test results (normal/pathologic) according to Ricos

| | Ricos | | TEa(%) |
|---|---|---|---|
| | Normal | Pathologic | |
| CA 15-3 | 3,388 | 3,370 | 20,8 |
| CA 19-9 | 8,211 | 5,356 | 46,03 |
| CA 125 | 8,350 | 6,724 | 35,4 |
| AFP | 4,409 | 2,822 | 21,9 |
| CEA | 3,897 | 3,756 | 24,7 |
| E2 | 3,256 | 5,218 | 26,86 |
| FSH | 3,549 | 3,971 | 21,19 |
| LH | 6,553 | 5,248 | 27,92 |
| PROLACTIN | 8,684 | 8,604 | 29,4 |
| TESTOSTERONE | 2,955 | 2,836 | 13,61 |

*AFP: Alpha Feto Protein, Ca 19-9: Carbohydrate antigen 19-9, Ca 125: Cancer Antigen 125, Ca 15-3: Cancer Antigen 15-3, CEA: Carcinoembryonic Antigen, E2: Estradiol, FSH: Follicle Stimulating Hormone, LH: Luteinizing Hormone.*

Table 4. Hormone test results (normal/pathologic) according to Ricos

| Grup | Ricos | |
|---|---|---|
| | Normal | Pathologic |
| 0- 2.99 | TESTOSTERONE | TESTOSTERONE |
| | | AFP |
| 3- 3.99 | CA 15-3 | CA 15-3 |
| | FSH | FSH |
| | E2 | |
| | CEA | CEA |
| 4- 5.99 | AFP | E2 |
| | | LH |
| **≥ 6** | PROLACTIN | PROLACTIN |
| | LH | |

*AFP: Alpha Feto Protein, Ca 19-9: Carbohydrate antigen 19-9, Ca 125: Cancer Antigen 125, Ca 15-3: Cancer Antigen 15-3, CEA: Carcinoembryonic Antigen, E2: Estradiol, FSH: Follicle Stimulating Hormone, LH: Luteinizing Hormone.*

Nanda et al. (8) determined six sigma values were greater than 6 for some routine biochemistry tests (AST, ALT, ALP, total bilirubin and uric acide) on Cobas Integra analyzer. Sigma values less than 3 were calculated for total protein, albumin, total cholesterol and chloride tests in their study. When these data are compared with our study, it is seen that sigma value less than 3 is calculated for total cholesterol and chloride but it is greater than 3 in our study. Sigma value was found to be less than 3 for albumin in both studies (8).

Singh et al. (3) reported that sigma values for AST, CK, amylase and triglyceride were greater than 6; sigma values for urea, total cholesterol, HDL cholesterol, sodium and potassium less than 3 were obtained. When these data were compared with the data obtained in our study, the tests performing sigma values greater than 6 were consistent (9,10).

Chaudhary et al. (9) reported that sigma values for glucose, ALP, total protein, triglyceride, HDL-cholesterol, amylase and uric acid were determined for greater than 3 and sigma values for AST, ALT and total cholesterol were less than 3 (9).

In our study, the sigma values obtained for each test according to CLIA criteria were found different from other studies in the literature. Autoanalyzer, reagent, calibrator and control differences used are possible causes of this situation. In conclusion, it is seen that using sigma values as a quality indicator for the evaluation of the analytical phase is very useful in terms of integrating both IQC and EQA data.

*Ethical Approval: Ethics approval was granted by the Ankara Numune Training and Research Hospital Ethics Committee with Protocol Number and date: E 17-1480 / 03.01.2018.*

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