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RESEARCH ARTICLE

Comparison of the sigma metrics using the total error allowable algorithm with variation of bias source

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Abstract

Sigma Metrics, as a quality indicator, have been widely applied in clinical laboratories to assess the performance of analytical methods. Described in the document Clinical and Laboratory Standards Institute (CLSI) EP15-A3, the use of target values can be sourced from certified reference standards, survey materials from the Proficiency Testing (PT)/External Quality Assessment (EQA), materials used in inter-laboratory quality control programs and internal quality control materials with predetermined targets. This research aims to determine whether there is a difference in the sigma metrics between the bias derived from the manufacturer's target value and those from the peer group source in the External Quality Assurance Services (EQAS) program. The research methodology employed is descriptive comparative analysis, utilizing the results of material inspection data for 15 internal quality control parameters of Clinical Chemistry over a span of 2 years at the Pramita Laboratory in Bandung. The calculation of the sigma metrics commences with computing the coefficient of variation (CV), and the appropriate Total Error aalowable (Tea) sources for each parameter are determined beforehand using the TEa algorithm. The research findings indicate a difference between the sigma metrics derived from the manufacturer's target value and those from the EQAS-peer group target value, accounting for 33% or 10 parameters out of the total parameters with 2 levels of inspection are calculated on the sigma scale. However, in 67% or 20 parameters out of the total parameters, no such difference is observed. Bias associated with the target value from the manufacturer and the EQAS peer group shows no significant difference, suggesting that the laboratory can utilize pre-existing target values confidently.

1. INTRODUCTION

Quality control has evolved as an integral component of overall quality management system. The language of quality is currently defined by the International Organization for Standardization (ISO) in an effort to standardize terminology and implement quality management practices globaly (1). Among healthcare services, clinical laboratory services hold paramount importance, as approximately 70% of clinical decisions regarding patients rely on laboratory results (2).

It has been reported that laboratories contribute up to 12 % of the total errors associated with the healthcare system (3). Different studies of the error distribution in medical laboratories can be conducted across various stages. Laboratory activities are typically categorized into 5 phases, starting from pre-pre-examination, pre-examination, examination, post-examination, and post-post-examination (4).

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Study have shown that the largest percentage of errors occurs in the pre-analytical phase, followed by the post-analytical and analytical. Each phase exhibits a range of possible errors percentages: 76.3% in the pre-analytical process, 2.1% in the analytical process, and 21.6% in the post-analytical process (5).

Quality indicators widely applied in clinical laboratories include sigma metrics, which aims to assess the performance of analytical methods. Sigma metrics are commonly employed to gauge the reliability and error rate of clinical use test (6). This model offers an objective approach to evaluate method performance as defect rate permillion opportunities (7).

Sigma metrics combine bias, precision, and total allowable error (TEa), with TEa representing the analytical objective or specification, while bias and coefficient of variation (CV) serve as indicators of systematic and random errors (8). Consequently, the focus of Sigmametrics lies in data collection and analysis for quality assurance (QA) purposes (9). Implementation of sigma metrics in laboratories can lead to error reduction by maintaining a ±6 Standar Deviation (SD) between the mean value and the range (10).

Several sources provide TEa values, such as Biological Variation (BV), RCPA (Royal College of Pathologists of Australasia), RiliBÄK (guidelines of the German medical association for the quality assurance of laboratory medical examinations), and CLIA (Clinical Laboratory Improvement Amendments). However, laboratory management must discern the most suitable TEa value for their specific conditions. Consequently, selecting appropriate quality standards for quality planning can pose challenges for laboratories (3).

Previous research conducted in 2014 by Hens Koen and colleagues (11) compared Six Sigma values using three different TEa sources. The study revelaed that while it's feasible to use TEa values from the same sources for different analytes, certain TEa values may offer quality estimates that inadequately represent the actual scenario (11). Some TEa values tend to be overlay lenient, providing overlay optimistic quality estimates, while other, particularly those derived from biotransformation sources, areo verly stringent, yielding overly pessimistic quality estimates. Hence, the selection of TEa is crucial as it significantly impacts the Six Sigma value (12).

Currently, many laboratories do not assess test quality based on sigma metrics. One of the barriers is the difficulty in determining the source of misleading value due to limited access and laboratories' non-participation in external quality assurance programs (7).

Ideally, CLSI EP15-A3 should explained that target values can be sourced from various sources, including certified reference standards, survey documentation from PT/EQA programs, materials utilized in interlaboratory quality control programs, and materials with predetermined target values (13). As described in CLSI EP15-A3, the utilization of target values can now extend to control materials previously employed, thereby offering numerous avenues fo laboratories to gauge examinations quality up to sigma metrics measurements.

It offers convenience for laboratories aiming to assess the quality of their examinations using a sigma metrics, utilizing bias source derived from existing manufacturer target values. Information is provided concerning the comparison of bias sources derived from the manufacturer's target value against sigma scale differences when employing target values from the peer group source of the EQAS program. This involves mapping the appropriate TEa using the TEa algorithm. The suitability of regulations for bias in sigma metrics is also assessed.

2. MATERIALS AND METHODS

2.1. Study Design

The data collection involved inspectiong internal quality control materials for a period of 2 years, spanning from 2021 to 2022, at Pramita Laboratory in Bandung City, West Java, Indonesia. The parameters evaluated were clinical chemical parameters specific to the Pramita Bandung Laboratory. Sigma metrics calculation was performed on a monthly basis, incorporating the calculation of the CV value and the determining the corresponding TEa source for each parameter using the TEa algorithm. In addition, sigma metrics were calculated based on the determined Tea, considering two different bias sources. The clinical chemistry parameters parameters assessed included Albumin, Alkaline Phosphatase, Serum Glutamic Oxaloacetic Transaminase (SGOT), Serum Glutamic Pyruvic Transaminase (SGPT), Total Bilirubin, Direk Bilirubin, Triglycerides, Cholesterol, HDL (high-density lipoprotein)-Cholesterol, LDL (low-density lipoprotein)-Cholesterol, Creatinine, Glucose, Uric Acid, Ureum, and Total Protein.

2.2. Precision and Bias

The determination of the TEa source began with bias, which was selected as the primary performance indicators. Bias was assessed using the results obtained form the BIO-RAD External Clinical Chemistry (EQAS) peer group program. Bias was estimated as the root mean square of the measured error and expressed as a percentage of the total allowable error [Bias (TEa%)]. Sigma metrics calculation was conducted monthly, commenincg with the computation of the Coefficient of Variation (%CV) value by the average value and then multiplying the result by 100.

2.3. Sigma Metrics Calculation

The sigma metric serves as the second performance indicator nad is computed based on the results acquired from the internal quality control participation scheme within the laboratory. The calculation follows the formula 1.

Sigma metric= [TEa (%) – bias (%)]/CV (%) ..... (1)

In this formula, the TEa expressed as a percentage, bias expressed as a percentage, and C expressed as a percentage are utilized.

2.4. Total Error Allowable Algorithm

A graphical tool and TEa algorithm were employed, incorporating four distinct TEa sources selected from Biological Variation (BV), Royal College of Pathologists of Australasia (RCPA), RiliBÄK (guidelines of the German Medical Association for the quality assurance of laboratory medical examinations), and Clinical Laboratory Improvement Amendments (CLIA). This graphical tool facilitated the integration of performance evaluations from external and internal quality assessment programs. Through the graphical tool, sigma metrics were plotted against bias (TEa%) values, resulting in the identification of four distinct areas corresponding to the different TEa sources. This visual representation, depicted in Figure 1, allowed for clear delineation and comparison of performance metrics derived from various TEa sources.

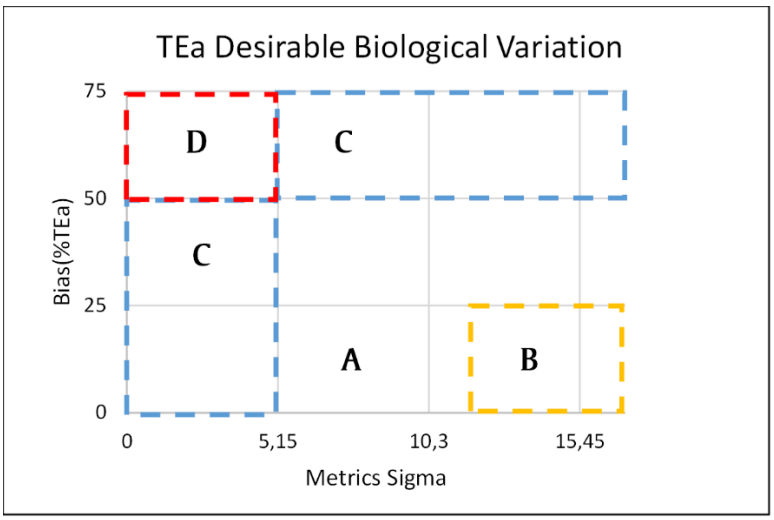

Figure 1. Graphic tool for integrating external and internal quality assurance program performance

The graph is divided into 4 areas (Area A-D) representing the results of the laboratory's internal and external performance (Figure 1). Area A indicates that both the internal and external performance results are deemed acceptable according to the TEa used. Area B shows that the performance results are very good, although there is a possibility that the TEa used is too loose. Area C indicates inconsistent performance results. Area D suggests poor performance, with a possibility that the TEa used is too strict.

However, prior to determining the sigma metric, the TEa value is initially mapped to each parameter using graphical tools (refer Figure 1), followed by a decision-making process based on the TEa selection algorithm. Initially, all examination parameters were tested using TEa derived from Desirable Biological Variation. If the examination results fall within area A on the graph, Desirable Biological Variation can be utilized as of Tea source. However, for examinations falling within area B on the graph, a reevalution using TEa derived from Optimal Biological Variation is necessaty, as it is conceivable that the initial TEa used may be too lenient, thus requiring a tighter TEa. Meanwhile, examination parameters positioned within areas C and D on the graph must undergo retesting Tea derived from Minimum Biological Variation. The decision to select the TEa fot testing is made based on the examination results are on the graph. If the examination falls within Area B, a stricter Tea is employed. For examinations in areas C and D, a looser TEa is applied.

Before mapping, according to Sten Westgard, decision-making for the selection of sigma matrices at two different control material levels involves selecting the sigma value at the control material level closest to the value of the medical decision levels (14). However, if the sigma metrics at the other level are lower than the selected sigma level, quality improvement must still be carried out on the inspection performance. After determining the most optimal TEa source, proceed with the calculation of the sigma metrics according to the determined Tea. This involves utilizing two sources of bias, the manufacturer's target value and the target value of the EQAS program peer group results.

2.5. Categorization of Sigma Metrics

Sigma metrics are categorized based on the Westgard Sigma Rules, which are employed to assess the performance of analytical processes in clinical laboratories. The categories are outlined in Table 1 (15).

Table 1. Categorization based on Westgard Sigma Rules

Category	Sigma	Evaluation
1	<3	These tests are considered unreliable and should not be used for routine test purposes. They are likely to cost a laboratory a lot of time, effort, and money to maintain the quality of test results.
2	≥3 and <4	These tests are considered acceptable for routine use, but they may have some issues that need to be addressed.
3	≥4 and <5	These tests are considered good, with fewer defects per million outcomes than a three Sigma process.
4	≥5 and <6	These tests are considered excellent, with fewer defects per million outcomes than a six Sigma process.
5	≥6	These tests are considered world-class, with the fewest defects per million outcomes

The categorization of Sigma metrics serve as atool to evaluate the performance of analytical processes and identify areas that require improvement. It aids laboratories in planning their quality control frequency and in maintaining the reliability and profitability of their processes (16).

2.6. Statistical Analysis

After determining the most optimal TEa source, the calculation of the sigma metrics is carried out according to the determined Tea, utilizing with two sources of bias: the manufacturer's target value and the target value of the EQAS program in which the laboratory participated. The bias used to determine the sigma metrics is calculated using two different sources of bias, derived from the manufacturer's target value and the target value of the BIORAD External Quality Assurance Services (EQAS) program.

The results of the sigma metrics calculation with bias variation sourced from the manufacturer's target value and the EQAS program, area then analyzed using the Statistical Product and Service Solution (SPSS) program. If the data distribution is normal, difference in the sigma scale with bias variation are analyzed using the Paired Sample T-Test. If the data distribution is not normal, the non-parametric statistical test, Wilcoxon test, is performed. Data is processed to identify differences in sigma scale with different sources of bias variation.

3. RESULTS AND DISCUSSION

TEa determination of the TEa is the initial step, and the results of the TEa algorithm are presented in Table 2. Following the identification of the most appropriate TEa source, the calculation of sigma value commenced with two distinct bias sources, derived from the manufacturer's target value and the target value of the EQAS results.

Table 2. The distribution of test sites in the chart by TEa source expressed in percentage

TEa source	Area A	Area B	Area C	Area D
BV	33%	4%	40%	23%
RCPA	20%	0%	80%	0%
RiliBÄK	30%	0%	70%	0%
CLIA	60%	0%	40%	0%

This study utilized two levels of control material for each inspection parameter, and the sigma matrix was calculated at both levels. The results revealed thay out of the total parameters tested, 20 parameters, or 67%, showed no difference in the sigma matrix when considering bias variations originating from the manufacturer's target value compared to the target value of the EQAS peer group results. However, the sigma matrix obtained with bias derived from the manufacturer's target value and the EQAS target value exhibited varying results, with the average sigma matrix using bias from the manufacturer's target value slightly higher, albeit with a very slight difference.

Of the 10 parameters, representing 33% of the total parameters tested, showing differences, all sigma matrix results varied. These variations stemmed from bias originating from the manufacturer's target value and the EQAS peer group results. On average, the average sigma matrix with a bias from the manufacturer's target value also exhibited a higher sigma matrix. However, exception included Alkaline Phosphatase level 2, LDL-Cholesterol level 2, and Ureum level 1 parameters, where the difference obtained wereat a 2-sigma level. This deviation is is possible as daily control results tend to be higher than the manufacturer's target value, even though the overall sigma matrix is quite good on average. >3. Further exploration revealed significant difference disparities between the manufacturer's target value and the EQAS peer group target value in observed months. Notably, the disparity approached almost 5% in the LDL-Cholesterol level 2 and Alkali Phophatase level 2 parameters. Moreover, the EQAS peer group target values exhibited a notable bias, contributing to a lower sigma matrix compared to the sigma matrix against the manufacturer's target value. Nonetheless, the overall sigma matrix remains quite satisfactory, averaging over 3. Precision tests were carried out to evaluate random errors, expressed in CV%. This finding indicated that 98% of the CV% values for both level 1 and level 2 control materials across for all parameters were acceptable.

The results indicate that the TEa source aligning best with laboratory performance is Biological Variation, as evidenced by evenly distributed value across all four areas. However, there is a notable concentration up to 40% is in area C, where the performance results display inconsistency or excessively tight TEa values. Interestingly, apart from TEa derived from BV, no other TEa source falls within area B, where performance resultsare considered overly loose.

TEa sources categorized as overly stringet are RCPA and RiliBÄK, with 70% and 80% of tested parameters respectively falling within area C on the graph. This suggests significantly difficulty for several parameters to reach a sigma value >5.15 when utilizing these Tea standards. The following results are presented in the form of a table.

The sigma metrics calculation results, considering two variations of bias sources, were analyzed using the Statistical Product and Service Solution (SPSS) program. The data underwant processing to identify differences in the sigma scale with varying bias variation sources.

The initial test involved comparing the Sigma metrics for identical parameters. The results revealed differences in the sigma metrics when utilizing bias derived from the manufacturer's target value versus the target value of the EQAS-peer group results. Specifically, out of the total parameters, 33% or 10 parameters exhibited differences in the calculated sigma scale (Table 3), while 67% or 20 parameters showed no variance (Table 4).

Furthermore, the statistical test was conducted by comparing the sigma metrics fow all parameter against the manufacturer's target value and the target value of the EQAS peer group. The results are presented in Table 5.

Table 3. Statistical test results indicating a difference in the average sigma metrics with two variations bias source

Parameters	Sig (2-tailed)	Statistical Test
SGPT_Manufacturer1 - SGPT_EQAS1	0.015	Wilcoxon
SGPT_Manufacturer2 - SGPT_EQAS2	0.000	Paired Sample T - Test
LDL_Manufacturer1 - LDL_EQAS1	0.015	Wilcoxon
LDL_Manufacturer2 - LDL_EQAS2	0.000	Paired Sample T - Test
TP_Manufacturer1 - TP_EQAS1	0.003	Wilcoxon
TP_Manufacturer2 - TP_EQAS2	0.001	Paired Sample T - Test
SGOT_Manufacturer1 - SGOT_EQAS1	0.031	Paired Sample T - Test
GLUS_Manufacturer1 - GLUS_EQAS1	0.030	Paired Sample T - Test
Ureum_Manufacturer1 - Ureum_EQAS1	0.022	Paired Sample T - Test
ALP_Manufacturer2 - ALP_EQAS2	0.000	Paired Sample T - Test

Table 4. Statistical test results indicating s no difference in the average sigma metrics with two variations of bias sources

Parameters	Sig (2-tailed)	Statistical Test
Albumin_Manufacturer1 - Albumin_EQAS1	0.302	Paired Sample T - Test
Albumin_Manufacturer2 - Albumin_EQAS2	0.159	Paired Sample T - Test
BILT_Manufacturer1 - BILT_EQAS1	0.790	Wilcoxon
BILT_Manufacturer2 - BILT_EQAS2	0.472	Paired Sample T - Test
BILD_Manufacturer1 - BILD_EQAS1	0.655	Paired Sample T - Test
BILD_Manufacturer2 - BILD_EQAS2	0.097	Paired Sample T - Test
CHOLES_Manufacturer1 - CHOLES_EQAS1	0.204	Paired Sample T - Test
CHOLES_Manufacturer2 - CHOLES_EQAS2	0.419	Paired Sample T - Test
TG_Manufacturer1 - TG_EQAS1	0.128	Paired Sample T - Test
TG_Manufacturer2 - TG_EQAS2	0.638	Wilcoxon
HDL_Manufacturer1 - HDL_EQAS1	0.105	Paired Sample T - Test
HDL_Manufacturer2 - HDL_EQAS2	0.576	Paired Sample T - Test
CREA_Manufacturer1 - CREA_EQAS1	0.241	Paired Sample T - Test
CREA_Manufacturer2 - CREA_EQAS2	0.098	Paired Sample T - Test
AU_Manufacturer1 - AU_EQAS1	0.576	Paired Sample T - Test
AU_Manufacturer2 - AU_EQAS2	0.089	Paired Sample T - Test
ALP_Manufacturer1 - ALP_EQAS1	0.224	Wilcoxon
SGOT_Manufacturer2 - SGOT_EQAS2	0.773	Paired Sample T - Test
GLUS_Manufacturer2 - GLUS_EQAS2	0.978	Paired Sample T - Test
Ureum_Manufacturer2 - Ureum_EQAS2	0.457	Paired Sample T - Test

Table 5. Statistical test results of the average sigma metrics with two variations of bias sources for all parameters

Paired Samples Test								
	Paired Differences					t	df	Sig. (2-tailed)
	Mean	SD	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
Manufacturer-Eqas	0.10861	1.96584	0.10361	-0.09515	0.31237	1.048	359	0.295

The statistical analysis revealed a significant value (>0.05), indicating no difference between the Sigma metrics when using the manufacturer's target value and the EQAS peer group as a whole.

The determination of TEa begins with utilization of graphs and TEa value mapping algorithms. The objective is to encourage laboratories to adopt examination performance specifications derived from Biological Variation (BV) as a means to evaluate examination performance and achieve optimal analytical performance specifications (17). From the results obtained, 11 out of 15 parameters are able to utilize TEa with sources derived from BV.

The graph and algorithm employed in mapping the TEa value offer several advantages. Firstly, the graph is designed by combining the performance of Internal Quality Assurance and External Quality Assurance, two crucial tools used for assessing the performance of laboratory examinations (3). In addition, the algorithm utilized in selecting TEa value sources serves to standardize and synchronize inspection performance specifications or objectives in accordance with the Hierarchy introduced in the 2014 Milan Consensus (18).

Examinations yielding sigma values below 5.15 sigma, as per Westgard's rule, require more frequent use of the control material and/or higher frequency runs to enhance the probability of error detection (19). Hence, it becomes necessary to assess inspection perfomarnce using additional TEa sources lower in hierarchy, with results falling within area A on the graph. This ensures that control rules remain simple, yet maintain a high probability of error detection and a low probability of false rejection (3).

The average value of the overall sigma metrics, obtained by comparing the greatest sigma value between the two sources, show that the calculation of the bias source using the manufacturer's target value yields a higher percentage than when using the target value derived from the EQAS peer group. In the testing methodology between the manufacturer and EQAS, differences arise, where the target value set by the manufacturer is based on internal validation and specific characteristics of the method (20), whereas EQAS covers a wide range of testing methods and platforms used by various laboratories (21). Some weaknesses to be considered include how the laboratory obtains results, such as the technical expertise of the lpersonnel conducting the test, sampling errors, improper testing processes or incorrect interpretation (22). Manufacturers provide grades based on the data and knowledge the possess about their products. They have access to the specifications and characteristics of the product being designed, as well as in-depth knowledge of its expected performance (23).

However, manufacturers also have a weakness where their business interest in promoting and selling their products can introduce bias in setting target values. Manufacturers may tend to set higher target values to impress users or consumers without fully considering the limitations or constraints that may arise in their use (24).

In another study, Çevlik et al. (25) evaluated six sigma using bias calculated from internal and external quality control. They concluded that when calculating sigma values, both IQC and EQA data are highly useful in evaluating the analysis stage, and they observed minimal differences between sigma calculations based on both data. They further concluded that % bias can be calculated from IQC data when external quality assurance data is not available (25).

The results obtained from the sigma metrics indicate no difference between the manufacturer's target value and the target value of the EQAS peer group. However, it may be necessary to consider the difference in the target value of the national and international External Quality Assurance provider results. The criteria recommended by ISO 15189 for reliable EQAS maintenance include compliance with ISO 17043 standards (26). While these standard outlines requirements, it does not specify the criteria and procedures that providers should follow. Consequently, some national and international providers design their schemes based on different options, resulting in varying information in each Proficiency Testing report (13).

3. CONCLUSIONS

Based on the results of the research conducted, it can be concluded that the statistical test calculations using the paired sample t-test and Wilcoxon test demonstrate a difference between the sigma metric derived from the manufacturer's target value and the target value of the EQAS-peer group results. Specifically, out of the total parameters with 2 levels of inspection calculated on the sigma scale, there were difference observed in 10 parameters, which acoounts for 33% of the total parameters. Conversly, there were no difference detected in the results of 20 parameters, constituting 67% of the total parameters. Consequently, the determination of sigma metrics with 2 sources of bias remains feasible. Notably, the overall sigma metric calculation showed no difference when utilizing a bias source from the manufacturer's target value compared to the target value of the EQAS peer group results.

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