Six Sigma Metrics and Quality Control in Clinical Laboratory

Shah S1, Saini R2, Singh SB3, Aggarwal O4, Goel AK5

1Dr Seema Shah, VMMC & Safdarjung Hospital, New Delhi, 2Dr Reetika Saini, Biochemistry, Vardhman Mahaveer Medical College & Safdarjung Hospital, New Delhi, 3Dr Sangeeta B. Singh, , Biochemistry, SHKM GMC, Nalhar, 4Dr Onam Aggarwal, Biochemistry, Maulana Azad Medical College, New Delhi, 5Dr Anil Kumar Goel, Paediatrics, SHKM GMC Nalhar, India

Address for correspondence: Dr Seema Shah, Email: sshah.goel@gmail.com

Abstract

Quality control in healthcare system is still less understood because of the relative complexity in choosing an appropriate Westgard rule. Six Sigma methodology is a manufacturing strategy first pioneered by Motorola Company in 1980s, with the goal of decreasing the defect rates in production. It has improved the production efficiency of different industries. To achieve the similar high quality and near zero defect rates in healthcare system, six sigma metrics is being used in many clinical laboratories and diagnostic industry. Six sigma metrics is used in combination with total allowable error (CLIA ’88 proficiency testing criteria), method imprecision and bias. The goal is to attain the highest possible sigma scale within the acceptable limits of total allowable error. This article reviews the different Westgard control rules and their implications in pointing towards a particular error, as well as basic principles of Six Sigma methodology & their practical utility in the clinical laboratory.

Keywords: Clinical laboratories; Quality control; Sigma Metrics; Six Sigma; Westgard rules

“Total quality management is a journey, not a destination.” Thomas Berry [1]

Introduction

The concept of quality management in healthcare system remains an evergreen discussion. A study by the Institute of Medicine reports annual preventable death of 44,000-98,000 in USA alone [2]. Among healthcare services, clinical laboratory services remain important as around 70% of the patient related decision are based on the clinical laboratory results[3]. The total testing procedure is divided into preanalytical, analytical and postanalytical phase. Estimated error rate in the three phases are 30-75% for preanalytical, 43-30% for analytical, and 9-55% for postanalytical phase [4]. Hence stringent quality control in clinical laboratory will improve patient care.

Principle and concept of quality management

“The main objective of internal quality control is to ensure day to day consistency.” (WHO 1981)

Quality is defined as conformance to the requirements of the end users [5]. It is assessed in terms of accuracy (closeness to the true value), precision (reproducibility of a test result), sensitivity and specificity. The three purposes of quality control are monitoring the accuracy and precision of the analytical processes and detection of immediate error. In simpler terms it is attainment of the intended quality of results. Implementing quality control is a continuous dynamic procedure so that patients test results produced by the laboratory are reliable and contribute to patient care.

The basic workflow in designing an quality control system involves five continuous steps of establishing goals (Quality Planning), planning of laboratory policies (Quality Process), implementation of the plan using specific procedures (Quality Control), assessing the effectiveness of the plan (Quality Assurance), and finally taking appropriate steps to achieve desired outcome (Quality Improvement) as suggested by Westgard et al as five steps of total quality management (TQM) [6].

What is Quality Control?

Quality control in medical laboratory is a statistical process to monitor and evaluate the analytical system. Its results are used to validate whether the system is working within the predefined conditions and to know whether the patients’ tests results are reliable or not. There are basically two types of schemes – internal quality control (IQC) and external quality control (EQC). IQC ensures a continuous monitoring of the analytical system, so as to check whether the results are reliable enough to be released. Control charts like Levey Jennings chart and Westgard’s rules are applied on daily QC data.

External quality control involves analysing and reporting of control samples supplied by an external agency, at a predefined time interval of a fortnight or a month. The external supplier of the QC sample studies the results of all the participating laboratories and then provides feedback to all [7]. The participating laboratories are divided in groups according to the analytical method and instruments used. This is followed by calculation of mean and standard deviation for a particular group and is
referred to as consensus mean and standard deviation. Individual laboratory’s performance is judged by comparing the mean, standard deviation and CV (coefficient of variation) with consensus mean, standard deviation and CV.

**QUALITY CONTROL PLANNING:** Choosing a specific QC procedure is done with the aim of minimizing the false rejection and maximizing the error detection. CLSI (formerly NCCLS, National Committee for Clinical Laboratory Standards) has recommended following essential steps for setting up a QC system [8].

1. Defining quality requirement of the test
2. Evaluating tests’ performance as method precision and bias
3. Identifying the possible QC procedures with regard to rules to apply, candidate control material, levels and numbers of control samples, time of run for the control sample and frequency of QC running
4. Prediction of performance of QC procedure
5. Setting up goals based on required quality
6. Selecting an appropriate QC procedure

**Defining the quality requirements** involves establishing analytical goals as per the total allowable error (error within acceptable limits), which is done by a hierarchy of approaches published as list of models for quality specifications in the Scandinavian Journal of Clinical and Laboratory Investigation [9]. When feasible and appropriate, models higher in the list are preferred over those lower in the list [9].

**Table/Fig. 1:** Shows TEa for some of the common biochemical and other investigations as per CLIA recommendation

| Analyte or test                          | CLIA criteria for Acceptable performance |
|------------------------------------------|-----------------------------------------|
| Blood Glucose                           | Target value ±10% or 6mg/dl (greater)   |
| Bilirubin, Total                         | Target value ±20% or 0.04mg/dl (greater)|
| ALT                                      | ±20%                                    |
| AST                                      | ±20%                                    |
| ALP                                      | ±30%                                    |
| Total Protein Serum                     | ±10%                                    |
| Albumin                                  | ±10%                                    |
| Cholesterol Total                       | ±10%                                    |
| Triglyceride                             | ±25%                                    |
| Cholesterol, HDL                         | ±30%                                    |
| Calcium Total                            | Target value ±1.0mg/dl                  |
| Sodium                                   | Target value ±4 mmol/l                 |
| Potassium                                | Target value ±0.5 mmol/l                |
| LDH                                      | ±20%                                    |
| Amylase                                  | ±30%                                    |
| Creatine Kinase                          | ±30%                                    |
| Creatine Kinase , MB                     | Target value ±3SD or presence/absence  |
| Blood urea                               | Target value ±9 % or 2 mg% (greater)   |
| Creatinine                               | Target value ±15% or ± 0.3 mg/dl(greater)|
| Uric acid                                | ±17%                                    |
| TSH                                      | Target value ±3 SD                     |
| Thyroxine Total                          | Target value ±20% or ± 0.10mcg/dL(greater)|
| Triiodothyronine Total                   | Target value ±3 SD                     |
| Alcohol,carbamazepine,gentamycine,Phenytoin, valproate, theophylline,Quinidine, tobramycin | Target value ±25 |
| Alpha-1 antitrypsin                      | Target value ±3 SD                     |
| Alpha-fetoprotein                        | Target value ±3 SD                     |
| Anti-Human Immunodeficiency virus, Hepatitis (HBsAg, anti-HBc, HBeAg) | Reaction or nonreactive |
| Complement C3                            | Target value ±3 SD                     |
| Complement C4                            | Target value ±3 SD                     |
| IgA                                      | Target value ±3 SD                     |
| IgE                                      | Target value ±3 SD                     |
However generally the criteria lay down by CLIA (Clinical Laboratories Improvement Act) ‘88 proficiency limits [10] or biological variation values as published in Scandinavian Journal [11] are used to set up the maximum acceptable error for individual tests. For example as per CLIA recommendation a TEa (total allowable error) of ±10% or ±6 mg/dl (greater of the two) is accepted for the blood glucose determination whereas for blood pH it is ±0.04 only. Table / Fig. 1 Enlists TEa for some common biochemical parameters [10]. Table / fig. 2 Shows Biological Variation Values for common biochemical investigations [11]. This table provides desirable analytical quality specifications for imprecision, bias and total error based upon biological variation

Table 2: Shows Biological Variation Values for common biochemical investigations

| Analyte                  | Biological Variation | Desirable Specifications |
|-------------------------|----------------------|--------------------------|
| CVw | CVb | Imp (%) | Bias (%) | TEa (%) |
| Amylase | 8.7 | 28.3 | 4.4 | 7.4 | 14.6 |
| ALT | 19.40 | 41.6 | 9.7 | 11.48 | 27.48 |
| Albumin | 3.2 | 4.75 | 1.6 | 1.43 | 4.07 |
| ALP | 6.45 | 26.1 | 3.23 | 6.72 | 12.04 |
| AST | 12.3 | 23.1 | 6.15 | 6.54 | 16.69 |
| Bilirubin total | 21.8 | 28.4 | 10.90 | 8.95 | 26.94 |
| Bilirubin conjugated | 36.8 | 43.2 | 18.4 | 14.2 | 44.5 |
| Calcium | 2.1 | 2.5 | 1.05 | 0.82 | 2.55 |
| Cholesterol | 5.95 | 15.3 | 2.98 | 4.1 | 9.01 |
| Creatine kinase (CK) | 22.8 | 40.0 | 11.4 | 11.5 | 30.3 |
| CK MB, % | 6.9 | 48.2 | 3.5 | 10.8 | 16.5 |
| CK MB, activity | 19.7 | 24.3 | 9.9 | 7.8 | 24.1 |
| CK MB, mass | 18.4 | 61.2 | 9.2 | 14.88 | 30.06 |
| Urea | 12.1 | 18.7 | 6.05 | 5.57 | 15.55 |
| Creatinine | 5.95 | 14.7 | 2.98 | 3.96 | 8.87 |
| Urate | 8.6 | 17.5 | 4.3 | 4.87 | 11.97 |
| Glucose | 5.6 | 7.5 | 2.8 | 2.34 | 6.96 |
| HDL cholesterol | 7.3 | 21.2 | 3.65 | 5.61 | 11.63 |
| Lactate dehydrogenase (LDH) | 8.6 | 14.7 | 4.3 | 4.3 | 11.4 |
| LDL Cholesterol | 7.8 | 20.4 | 3.9 | 5.46 | 11.9 |
| pCO2 | 4.8 | 5.3 | 2.4 | 1.8 | 5.7 |
| pH [H+] | 3.5 | 2.0 | 1.8 | 1.0 | 3.9 |
| Phosphate | 8.15 | 10.8 | 4.08 | 3.38 | 10.11 |
| Potassium | 4.6 | 5.6 | 2.3 | 1.81 | 5.61 |
| Protein | 2.75 | 4.7 | 1.38 | 1.36 | 3.63 |
| Sodium | 0.6 | 0.7 | 0.3 | 0.23 | 0.73 |
| TSH | 19.3 | 24.6 | 9.7 | 7.8 | 23.7 |
| Thyroxine (T4) | 4.9 | 10.9 | 2.5 | 3.0 | 7.0 |
| Thyroxine, free (FT4) | 5.7 | 12.1 | 2.9 | 3.3 | 8.0 |
| Triglyceride | 19.9 | 32.7 | 9.95 | 9.57 | 25.99 |
| Triiodothyronine (T3) | 6.9 | 12.3 | 3.45 | 3.53 | 9.22 |
| Triiodothyronine, free (FT3) | 7.9 | 17.6 | 4.0 | 4.8 | 11.3 |
| Parathyroid hormone (PTH) | 25.9 | 23.8 | 13.0 | 8.8 | 30.2 |

Evaluating test performance in terms of method precision and bias are done as per the following equations:

Bias is calculated from the EQC data using the following formula:
Bias = \( \frac{\text{mean of all laboratories using same instrument and method} - \text{lab’s mean}}{\text{mean of all laboratories using same instrument and method}} \times 100\% \)

CV is calculated from the calculated laboratory mean and calculated standard deviation procured from the internal quality control data over preceding months.

\[ \text{CV\%} = \frac{\text{Standard deviation}}{\text{Laboratory mean}} \times 100\% \]

CV is used to compare precision, to check manufacturer’s claims, peer group QC report and as a part of internal quality control. A test with high standard deviation means poor precision, greater instability and high random error in the laboratory.

**Prediction of performance of QC procedure** is done using operational process specifications (OPSpecs) charts available in the Westgard website at [www.westgard.com](http://www.westgard.com). These charts describe operational limits for imprecision and inaccuracy for specific QC procedure. Using the TEa, precision and accuracy of an analyte, optimal Westgard rule can be selected using OPSpecs charts.

**The goals of internal QC** is to catch all significant error (probability of error detection) with minimum false rejection (probability of false rejection).

**Selecting an appropriate QC procedure** is done with sigma metrics. The appropriate IQC procedure is one having a 90% chance of detecting medically important errors (Ped ≥0.90) and a 5% chance of false rejection (Pfr ≤0.05), preferably 1% or less.

**Candidate control material:**

Ideal QC material should have same material matrix as the patients sample, long stability, ready to use with minimum operators handling. There should be little or zero vial to vial variation for a particular lot and it should cover the clinically important range for analyte concentration. It should be tested in the same manner as patient’s sample.

It may further be of dependent or independent type. Independent control or third party control provides an independent assessment of the testing method and also detects changes associated with lot variation of reagent or calibrator, which might be missed by a dependent control. A dependent control is manufactured by the same company supplying the analytical instruments or reagents. A control sample by the same manufacturer as that of calibrator, will shift in the same direction as calibrator and fails to detect any error and correct values are obtained for the control sample falsely which fails to detect error in the analytical system. Similarly package QC sample (supplied along with reagent vial) show reagent lot specific target values and hence reagent lot to lot variations will be missed. So independent or third party QCs with peer group comparison data should be used to see if other users are also experiencing the similar reagent lot related shift in QC values.

However if commercial third party control is not available, pooled patients sample may be used and result matched with previous result.

The number of levels of QC samples, frequency of running the QC and time of run varies from laboratory to laboratory, according to the sample load for a particular analyte, number of analytical run per day, shift change of the laboratory staff and of course as per the laid down criteria of different accreditation bodies (12).

As per NABL guidelines [13] frequency and number of QC samples to be run as per the sample load is as follows:

- < 25 per day - one level QC once a day.
- 25-75 per day - two level QCs once a day.
- >75 per day - two level QCs at least twice a day

**Identifying candidate IQC procedure:**

Several statistical process control rules as proposed by Dr. James O.Westgard in 1981 are used to assay quality control performance [14].

Rules are expressed as \( N^L \) where \( N \) represents the number of control observations to be evaluated and \( L \) represents the statistical limit for evaluating the control observations. Thus \( 1^3s \) represents a control rule which is violated when one control observation exceeds the \( \pm 3s \) control limits.

Six basic rules are used in various combinations as a multirule procedure, where some rules detect random error while others are sensitive to systematic error as presented in table /figure 4. These rules are used with Levey-Jennings (LJ) chart [15]. The LJ charts are prepared by calculating the mean and S.D of the control material by analyzing it for a minimum of 20 times over a 30 day time period. Concentration of the analyte is plotted on the Y axis and time as day on X axis. Horizontal lines are drawn at mean, mean ±1 SD, ±2SD and ±3 SD. Each day’s data is plotted on the charts [14].
However, there is no particular set of rules that is right for all the tests and methods as some methods have better precision than others and hence rules should be selected as per the quality required and the observed performance for the test.

**Table/Figure 4: Table showing different Westgard rules and their implications**

| Rules | What does it mean | Type of error | Alarm produced |
|-------|------------------|---------------|----------------|
| $1_{2s}$ | one level of control is beyond $\pm 2$ SD | Random or systematic | Warning rule |
| $1_{3s}$ | one level of control is beyond $\pm 3$ SD | Random or beginning of systematic error | Rejection rule |
| $2_{2s}$ | two levels of control are beyond $\pm 2$ SD on same side of the mean | Systematic error | Rejection rule |
| $4_{1s}$ | four consecutive data in one level of control more than $1$ SD on the same side of mean | Systematic error | Not a rejection rule. Indicates the need to perform instrument maintenance or reagent calibration |
| R$_{4S}$ | Two levels of control show a difference of $4$ SD. There is at least a $4$ SD difference of value between two control levels within a single run | Random error | Rejection rule |
| 10$_X$ | Rules are violated when there are $10$ control results on the same side of the mean regardless of the specific standard deviation that they are located in. | Systematic error | Rejection rule (this rule has a lower probability of false rejection than 7x, 8x, or 9x rule) (this rule can be applied within a control level or across control levels indicating systematic bias over a particular range or over broader analytical range respectively) Indicates the need to perform instrument maintenance or reagent calibration. |
| 7x, 8x, 9x, 12x | These rules are violated when there are 7 or 8 or 9 or 12 control results on the same side of the mean regardless of the specific standard deviation that they are located in. | Systematic error | Rejection rule (12x has a lower probability of false rejection than 7x, 8x, or 9x or 10x rule) (These rules can be applied within a control level or across control levels indicating systematic bias over a particular range or over broader analytical range respectively) |
| 7$_T$ | Seven consecutive readings of a single level of control show either a strict increasing or strict decreasing pattern | Systematic error | Rejection Rule (Strict increasing or decreasing pattern means each subsequent point shows incremental increase or decrease from the previous point) |
| 2 of $3_{2s}$ | Two of three levels of control are beyond $\pm 2$ SD on same side of the mean | Systematic error | Rejection rule (applied when testing three or more levels of control in one run) |
| $1_{2.5s}$, $1_{3.5s}$, $1_{4s}$, $1_{5s}$ | one level of control is beyond $\pm 2.5$, $3.5$, $4$ or $5$ SD respectively | Random sometimes systematic error | These rules are modified rules |
If 1\(2s\) rule is taken as rejection rule, it will result in varying percentage of false rejection as per the number of levels of control used [14]

- 5\%\ of\ total\ analytical\ run\ with\ 1\ level\ of\ control\ used
- 9\%\ of\ total\ analytical\ run\ with\ 2\ levels\ of\ control\ used
- 14\%\ of\ total\ analytical\ run\ with\ 3\ levels\ of\ control\ used

This is because the data show a normal Gaussian distribution with following distribution pattern:

- 68.3\%\ of\ data\ are\ within\ ±\ 1\ SD\ (standard\ deviation)\ of\ the\ mean
- 95.5\%\ of\ data\ are\ within\ ±\ 2SD\ of\ the\ mean
- 99.7\%\ of\ data\ are\ within\ ±\ 3\ SD\ of\ the\ mean

As per NABL, the criteria to accept or reject run are as follows [13]:

With one level QC material reject QC if

- a. It is outside 3 SD (1\(3s\))
- b. Two consecutive values obtained are outside 2 SD on the same side but within 3 SD (2\(2s\))
- c. Ten consecutive values are above or below the mean, but within 2 SD (10x)

With 2 level QC materials reject QC if

- a. Either QC value is outside 3 SD (1\(3s\))
- b. Both QC values are outside 2 SD on the same side, but within 3 SD (2\(2s\))
- c. Difference between both QC values is >4 SD i.e. one level QC is >2 SD and other level QC is <2SD (R 4s).
- d. Ten consecutive values of the same level QC are >/< the mean, but within 2 SD (10x).
- e. Five consecutive values of one level QC and five consecutive values of other level QC are >/< the mean but within 2 SD (10x).

Time of run of QC samples can be decided by different strategies with run scheduled at either fixed time interval, random time interval or average interval of 8 hours between 2 consecutive QC run (16).

Number of Quality Control to choose:

Application of Six Sigma (\(\sigma\)) principles provides a scientific basis for designing an appropriate QC strategy for improving the quality control process. Evaluation of laboratory’s performance on six sigma scale was first studied by Nevalainen D et al and Westgard JO in the year 2000 and 2001 respectively [17,18].

The concept of six sigma metrics was pioneered by Motorola company in mid 1980s, with the aim of improving their manufacturing process so that virtually no defective product would be produced. Making a process six sigma compliant essentially implies decreasing the variation from the system so that the standard deviation becomes so small that six numbers of standard deviation fits within the tolerance limits. A process which is six sigma compliant will produce only 3.4 defects per million opportunities even with a 1.5 SD shift in mean value.

For calculating a sigma metric, one needs to find out numbers of defects produced per million opportunities. This can be converted to a sigma metric by comparing with normal Gaussian distribution. As per Gaussian distribution 0.682689 \%\ of\ the\ distribution\ falls\ within\ one\ standard\ deviation, implying 0.317310 \%\ of\ the\ data\ outside\ the\ one\ standard\ deviation\ range. Multiplying by 1,000,000(1million) gives a value of 317,310 defects per 1 million opportunities, which corresponds to tolerance limits of one standard deviation, or a 1 \(\sigma\) process [19]. Table 5 shows defects per million opportunity for a perfectly centred process (no deviation from mean value) different for sigma metrics 1 – 6. Assuming a 1.5 SD shift in mean will produce a defect of only 3.4 per million opportunities for six sigma compliant process as per table / figure 6 and table / figure7.

| Sigma metrics | Defects per million |
|---------------|---------------------|
| 1 \(\sigma\)    | 317,310             |
| 2 \(\sigma\)    | 45,500              |
| 3 \(\sigma\)    | 2699                |
| 4 \(\sigma\)    | 63                  |
| 5 \(\sigma\)    | 0.573               |
| 6 \(\sigma\)    | 0.002               |

Table / figure 5: Number of defects per million in a particular SD as per the normal Gaussian distribution with perfectly centred mean
Table /figure 6: Defects per million in different range of SD assuming a 1.5 SD shift in mean

| Sigma metrics | DPMO  | Percent defects | Percentage yield |
|---------------|-------|-----------------|------------------|
| 1             | 691,462 | 69%             | 31%              |
| 2             | 308,538 | 31%             | 69%              |
| 3             | 66,807  | 6.7%            | 93.3%            |
| 4             | 6,210   | 0.62%           | 99.38%           |
| 5             | 233     | 0.023%          | 99.977%          |
| 6             | 3.4     | 0.00034%        | 99.99966%        |

The advantage of adopting a performance goal of six sigma is that small shifts in mean (classically described as a shift of 1.5 SD from the mean) will still be acceptable within the tolerance limits, without increasing the defect rate.

Table / Figure 7: Diagrammatic presentation of six sigma assay quality with a 1.5 SD shift in the mean

Choosing a specific Westgard Rule:

The sigma value is a good indicator of the performance characteristic of the test in question, as it considers both bias and imprecision. Bias refers to the systematic error of the assay and imprecision is the analytical S.D of the method.

For analytical processes with known total allowable error and for which analytical performance can be estimated in the form of accuracy (bias) and precision (CV%), sigma value can be calculated from the following equation:

\[
\sigma = \frac{(T\varepsilon_a - \text{Bias})}{\text{CV}_a}
\]

TEa as per CLIA 1988

Bias : systematic error of the assay
CV : analytical SD or variation of the assay

Choosing suitable Westgard QC rules for each analyte is done in five steps:

1. Calculation of analytes \( CV, \) bias and \( T\varepsilon_a \)

\( CV_a (\%) \): Coefficient of variation is calculated by using standard deviation (SD) and mean of the test as per the equation:\n
\[
\text{CV}\% = \left( \frac{\text{S.D}}{\text{Mean}} \right) \times 100\%\n\]

This information can be derived from results of laboratory’s internal QC program.

Bias (\%): It indicates systematic difference between the result obtained by the laboratory’s test method and that obtained from an accepted reference. The reference can be another test method, a standard or a consensus reference like mean of a group using same method, instrument and reagent i.e peer group comparison. Bias is calculated from results of an external QC program.

\[
\text{Bias} = \frac{(\text{mean of all laboratories using same instrument and method} - \text{lab’s mean})}{\text{mean of all laboratories using same instrument and method}} \times 100\%\n\]

TEa (\%): It indicates allowable difference from the true value. If the difference between the true concentration of an analyte and the reported concentration in a patient’s sample exceeds TEa, the result is considered unreliable. A list of TEa is given by CLIA 1988 as in table 1.

2. Calculation of the Sigma value of the test using the formula:

\[
\sigma = \frac{(T\varepsilon_a - \text{bias})}{\text{CV}_a}\n\]

3. Selection of the optimal Westgard QC (multi)rule is done using the table showing the hypothetical sigma values for different Westgard rules.
If the calculated sigma of an assay is more than the sigma for a particular Westgard rule then that particular rule is suitable for monitoring the error of the test. The table shows Westgard rules and their corresponding hypothetical sigma values along with the number of QC materials and repetitions (measurements) needed.

As the Sigma value of the Westgard rules decreases, the chance of missing an error increases (p error detection decreases). Therefore, the best Westgard rule is the one with a Sigma value closest to, but smaller than, the Sigma value of the test.

Example:

a) For Total Cholesterol:
    TEa= 10%
    If bias of a lab for it is 3% and CV% at 2 %
    Sigma = (TEa−Bias)/ CV%
    = (10%-3%)/2%= 3.5 S
    So Westgard rule corresponding to sigma of 3.4 is chosen to monitor the performance of cholesterol assay i.e, a multirule of 1\[3s]/2 2\[s]/ R 4\[s]/ 4 1s is applied with two levels of control.

b) For Creatinine: TEa = 15%
    If bias of a lab is 3% and CV% at 2% for creatinine
    Sigma = (TEa−Bias)/ CV%
    = (15%-3%)/2%= 6S
    So a Westgard rule of 1\[3.5s] two levels of control is sufficient to monitor its performance.

Table/ Figure 8: Hypothetical sigma values for different Westgard rules [20]

| Sigma | Westgard rules | Levels of control | Measurements | p error detection | P false rejection |
|-------|----------------|-------------------|--------------|------------------|------------------|
| 6.0   | 1\[3.5s]       | 2                 | 1            | 0.98             | 0.01             |
| 5.8   | 1\[3.5s]       | 2                 | 1            | 0.98             | 0.00             |
| 5.6   | 1\[3s]         | 2                 | 1            | 0.97             | 0.00             |
| 5.4   | 1\[3s]         | 2                 | 1            | 0.94             | 0.00             |
| 5.2   | 1\[3s]         | 2                 | 1            | 0.91             | 0.00             |
| 5.0   | 1\[2.5s]       | 2                 | 1            | 0.96             | 0.03             |
| 4.8   | 1\[2.5s]       | 2                 | 1            | 0.93             | 0.03             |
| 4.6   | 1\[3s]         | 2                 | 1            | 0.92             | 0.01             |
| 4.4   | 1\[2.5s]       | 2                 | 1            | 0.96             | 0.04             |
| 4.2   | 1\[2.5s]       | 2                 | 1            | 0.92             | 0.04             |
| 4.0   | 1\[3s]/2 2\[s]/ R 4\[s]/ 4\[1s] | 2 | 2 | 0.91 | 0.03 |
| 3.8   | 1\[3s]/2 2\[s]/ R 4\[s]/ 4\[1s] | 2 | 2 | 0.86 | 0.03 |
| 3.6   | 1\[3s]/2 2\[s]/ R 4\[s]/ 4\[1s] | 2 | 2 | 0.79 | 0.03 |
| 3.4   | 1\[3s]/2 2\[s]/ R 4\[s]/ 4\[1s] | 2 | 2 | 0.65 | 0.03 |
| 3.2   | 1\[3s]/2 2\[s]/ R 4\[s]/ 4\[1s] | 3 | 2 | 0.48 | 0.03 |
| 3.0   | 1\[3s]/2 2\[s]/ R 4\[s]/ 4\[1s] | 3 | 2 | 0.36 | 0.02 |

Source: Schoenmakers CHH,Naus AJM,Xvermeer HJ, Loon DV and Steen5 G, Practical application of Sigma Metrics QC procedures in clinical chemistry. Clin Chem Lab Med 2011;49(11):1837–1843

Table clearly shows that with increased numbers of levels of QC, a particular Westgard rule produces a lower sigma value. Multirule combinations though more powerful than single rule, does not have a very high sigma value.

Simple guidelines for choosing the Westgard rules and levels of QC as proposed by Westgard are as follows [21]:

- $\geq 6\sigma$: - 2 levels of QC per day with a 1\[3.5s] greater rule
- $5\sigma$: - 2 or 3 levels of QC per day with a 1\[2.5s] or 1\[3s] rule
- $4\sigma$: - 3 or 4 levels of QC per day with a 1\[3s]/2 2\[s]/ R 4\[s]/ 4 \[1s] rule
- $3.5\sigma$: - 6 of QC per day with a 1\[3s]/2 2\[s]/ R 4\[s]/ 4 \[1s] rule
- $<3.5\sigma$: - maximum affordable levels of QC per day with a 1\[3s]/2 2\[s]/ R 4\[s]/ 4 \[1s] rule
Another guideline as published by Cooper et al., suggests grouping of tests as per sigma performance and QC strategy as follows:[22]

- >6σ (excellent tests) – one QC per day (alternating levels between days) and a 1σ rule.
- 4σ–6σ (suited for purpose) – two levels of QC per day and the 1.5σ rule.
- 3σ–4σ (poor performers) – combination of rules with two levels of QC twice per day.
- <3σ (problems) – maximum QC, three levels, three times a day. Preferably testing specimens in duplicate.

To infer, for lower sigma values, more QC samples and more powerful QC rules are recommended. In general, for large sigma value processes (≥6σ) simple QC rules with low false rejection rates are adequate. For intermediate sigma value processes (sigma values between 3.5 and 6) quality goals are met with more elaborate QC strategies. For low sigma values (<3.5 sigma) reducing analytical bias and imprecision is a key to improve the quality.

Troubleshooting QC results:

Whenever QC results exceed defined Westgard rules, corrective actions taken and should be documented before reporting the patients results. It should be done in five steps as follows:

- Inspection of Levey Jennings chart or the rules violated to determine the type of error as different Westgard rules are sensitive to systematic or random error. Westgard rules 1σ, and R 4, are sensitive to random error and 2 2σ/4 1/10σ are sensitive to systematic error.
- Relating the type of error to possible causes
- Common factors if multiple tests affected
- Relating the error to any recent changes
- Taking the corrective steps and documenting the remedy

Relating the type of error to possible causes:

Systematic error affects all samples equally in a proportionate manner. Systematic error may result in shift of the mean of the control either in a gradual manner (Trend) or abruptly (Shift). Causes of systematic error include change in lot of reagent or calibrator, improper preparation of reagent, deterioration of reagent or calibrator, wrong calibrator values, improper volumes of reagent or sample because of pipettor misadjustment, problems in the temperature of the reaction chamber or incubation chamber and also deterioration of the light source. Most commonly improper calibration is the cause of systematic error, which produces error for all patients’ results.

Random error is a sudden unexpected deviation from the expected result. It may not cause a shift in the mean as error produced occur randomly. It may be caused by bubbles in the reagent or sample line, inadequately mixed reagents, fluctuating electricity supply, fluctuating incubation or reaction chamber temperature, a small clot in the pipettor and of course operator to operator variation in following different steps of reaction procedure (particularly in semiautoanalyzers settings).

Common factors if multiple tests affected: When multiple tests are affected, the common factors between all the affected tests are found like tests using same filter, same lamp, same reaction kinetics (end point vs. rate) or similar volume of sample.

Relating the error to any recent changes: If the rules violated indicate a systematic error producing a sudden shift in the mean then reagent, calibrator and maintenance records are studied to find out if the sudden shift has followed any reagent or calibrator replacement or any instruments maintenance.

If the error produced shows systematic trend, it indicates slowly deteriorating reagent or calibrator, deterioration of filter or lamp or slowly deteriorating temperature adjustments over a long time interval.

Random error occurs without a defined pattern or frequency. It can be identified by delta checks or precision checks by doing paired runs (duplicate runs). A delta check identifies a random error by comparing the current results with a previous result from the same patient and monitoring the difference (delta) between the two results. Delta limits take into account analyzer’s imprecision and systematic error as well as physiological variation of the analyte. Precision checks can be done by running patients’ sample in pairs or duplicates at fixed or random sample interval.

Finally the documentation of the corrective steps is done.

Conclusion

Clinical laboratories are in a constant search of methods to solve analytical problems and decrease errors to a negligible level. With the advent of consumer protection acts and legal suits citing medical errors, in the healthcare industry, the need of improving the quality of healthcare services to near zero level has become the need of the hour. Clinical labs remain in a constant effort to increase their work load, decrease error, improve the quality and decrease the cost. To achieve these goals more automated and computerized technology has come up for clinical chemistry, immunochemistry and hematology. The automated results produced, should closely be monitored so as to ensure that no unreliable reports are generated or despatched to a patient. This is done by running the
different levels of control materials, covering the clinical decisive range, for every analyte. Different Westgard rules are used to monitor the results of internal quality control datas and different Westgard rules have varied sensitivity to random or systematic error and thus violation of different rules points towards a particular error.

The performance of an analytical process is judged by its imprecision and bias as compared to a particular reference method or reference values. Selecting an appropriate Westgard rule is done using Six Sigma principle, along with total allowable error, method imprecision and bias for that particular analyte. Six Sigma methodology has greatly improved the process outcome in various production industries, with a goal of 3.4 DPMO. Recently its use in healthcare system, to improve the quality to a six sigma level has come up. It can be used to choose an optimal Westgard rule and thus can improve the reliability of the results of diagnostic tests.

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