Practical Clinical Biochemistry

Methods & Interpretations

As per the Competency-based Medical Education Curriculum (NMC)

Ranjna Chawla

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54 CHAPTER Lean Six Sigma (6σ) Approach for Clinical Laboratories

BC14.21
Describe Quality control.

INTRODUCTION

Quality in laboratory medicine needs to be maintained to give correct results for better diagnosis and disease management. Around 70% of the diagnosis of diseases is based on laboratory results. The goal of laboratory medicine is to give correct results to the right patient at the right time. This is to prevent any possibility of error and possible serious or fatal consequences in the proper treatment. So, in the health-care industry, the need to improve the quality of laboratory test results to a very high level has become the need of the hour.

The constant improvement of laboratory performance is very critical in maintaining accurate laboratory results. The automated results produced are closely monitored to make sure that no unreliable reports are dispatched. This is done by running internal control programs and by taking part in external quality assurance schemes.

For management of quality in business and industry, Six Sigma techniques are widely used. Since past decade, these techniques have also been successfully applied in the health-care sector. Lean and Six Sigma in health-care settings have helped in eliminating nonvalue adding steps (which help in enhancing laboratory efficiencies), in choosing an ideal Westgard rule (which helps in improving the quality to a Six Sigma level) and in drawing charts and monograms (which help in visualizing quality beyond calculations). This chapter covers the practical utility of lean Six Sigma method in improving the processes and quality in a clinical laboratory.

AIM OF LEAN

Anything that does not add value is considered a waste. The aim of lean is to cut time by eliminating nonvalue adding steps. So lean is a philosophy that helps in enhancing productivity by eliminating waste. In the laboratory setting, waste is often associated with waste of consumables, reagents, blood products, and technician's time.

This lean management theory was developed during 1990s by **Toyota Production System (TPS)**. Guiding principles of the lean manufacturing approach were formulated in 2001. Lean was designed to carry out more with fewer available resources, which helped in adding values and attitudes needed to sustain continuous improvement in the long run.

Lean applied to industries: There are seven types of waste that lean attempts to mitigate, i.e., overproduction, inventory, waiting, unnecessary transport, unnecessary processing, unnecessary human motions, and defects.

Lean applied to clinical laboratories: In clinical laboratories, the following five principles can help meet the goal:

1. ***To see what customer values*:** This requires a precise understanding of the specific needs of the customer. For clinical laboratories, the customer's perception of value is receiving accurate results in a timely way.
2. ***To understand the value stream*:** Value stream are those activities that, when done correctly and in the right order, give service that the customer values. For a laboratory, the value stream includes the set of activities needed to collect, transport, and process specimens in such a way that correct test results can be determined and provided back to the clinician.

3. ***To improve the workflow*:** In a lean organization work should flow steadily, without interruption from one value-adding activity to the next. Value-adding activities include those actions needed to get a result. Conversely, nonvalue adding includes those actions that serve no purpose in achieving a result. Such activities include the rework necessary to address problems of incorrectly ordered tests, instrument downtimes, and lost specimens.
4. ***To pull the work through the system*:** The system should react to the customer's demand. In other words, customers pull the work through the system. In nonlean organizations work is pushed through the system at the convenience of the operators, and so produces outputs which are not required. One should pull and not push through the value stream. The use of Kanban cards (visual cards as a signaling system), at the various benches within the laboratories, can help pull value through the stream. For example, specimens can be provided as the need exists, and not being pushed, potentially causing a backlog.
5. ***Perfection in work*:** A perfect process delivers just the right result to the patient. In this, every step is value-adding, producing a good result and desired output every time. In such actions, there is continuous flow and flexibility that does not cause any delay. As the first four principles are implemented, one gets to understand the system even better, and from this understanding, creates ideas for more improvement. A lean system thus becomes leaner and faster, and it becomes easier to find and eliminate waste.

TRADITIONAL VERSUS LEAN LABORATORY

In a traditional laboratory, every section is separate having its own staff and space. Daily workload is usually not evenly distributed since it is based on the workload of a particular section. Cross-training, i.e., learning how to do more than one specific job, is also a key to achieving a lean laboratory operation. It is also required to keep in view the shortage of laboratory professionals.

In a lean laboratory workplace, automated analyzers (for routine chemistry, immunoassay, coagulation profile, etc.,) are placed together in a U-shape. These automated analyzers are placed as close to the central processing area as possible to decrease excess motion. Manual testing can be in an area that is further away from specimen processing.

A lean laboratory workplace provides several advantages:

- Less staff is required
- Less wasted motion
- Enhanced teamwork.

AIM OF SIX SIGMA (6σ)

Six Sigma Principles in Industrial Sector

Six Sigma methodologies, a manufacturing strategy, were developed in 1986 by Motorola. It was developed with the goal of decreasing the defect rates in production. It has significantly improved production efficiency in various industries. The goal of Six Sigma (6σ) is to bring defects at a rate of 3.4 defects per million opportunities (DPMO), i.e., 3.4 defects in 1,000,000 opportunities.

Six Sigma Principles in Healthcare Sector

One of the first healthcare organizations to start Six Sigma was Commonwealth Health Corporation in 1998 in US. This was to help meet the high quality and near zero defect rates. Six Sigma improves assay quality by identifying biased and imprecise assays so that quality monitoring strategies can be worked out. It enables the laboratory to objectively and quantitatively assess the performance of the assays and instruments. Six Sigma offers ways to make fewer mistakes in all their activities (ranging from filling in a requisition form to the most complicated analytical process and report delivery) by eliminating

errors before they appear. The starting point of 6-sigma is to define what is considered as an error, to develop processes to quantify errors, and to use corrective procedures. Attainment of Six Sigma is envisaged as the gold standard for defining a world class measure of quality in the clinical laboratory. It can help cut costs associated with reagents, supplies, control material, labor, and quality control failure investigations.

WHY THE NAME SIX SIGMA

Sigma (σ) is the Greek mathematical symbol for standard deviation (SD). The sigma for a process refers to the number of SDs from the mean, before it is outside the acceptable limits. In Six Sigma, variation up to 6-sigmas, i.e., 6 standard deviations should fit within the tolerance limits for the process: hence, the name Six Sigma. Any process can be evaluated by determining how many sigmas fit within the tolerance limits, e.g., if sodium has Six Sigma performance, then the mean could shift by six SDs, and still meet the laboratory requirements.

PHASES OF LABORATORY TESTING WHERE DEFECTS (DELAYS) CAN OCCUR

Three phases where defects can occur are preanalytical, analytical, and postanalytical phases.

Preanalytical Phase

Counting defects by measuring preanalytical errors out of the total number of samples received, e.g., hemolyzed, clotted, lipemic, icteric, QNS (quantity not sufficient), wrong collection, etc.

Analytical Phase

Predicting process performance by measuring variation in all analytical processes.

To understand the analytical method performance on the sigma metrics scale, we do not have an easy comparative value against which we judge the test result. So instead, we control the data we are already collecting imprecision (expressed as coefficient of variation, CV) and trueness (expressed as bias).

Postanalytical Phases

Stat turnaround-times (TAT), i.e., time from order to completion of emergency department, is an indicator tracked by most laboratories. It is quite simple to know whether a test result is beyond the acceptable TAT. Laboratories have the desired TAT and real TAT and have to simply count the number of times the real TATs exceed that desired TAT. A defect would be any result not reported within the specified turnaround time.

CALCULATION OF SIX SIGMA

Six Sigma is both a metric and a methodology. Six Sigma as a metric requires defects to be clearly defined and is used as a scale for quality. Six Sigma as a methodology requires measuring variation and is used as a scale for measure.

Calculation of Sigma by Measuring Defects

This sigma approach is useful for pre- and postanalytical processes. Following steps are carried out:

Inspecting Outcome and Counting Defects

Calculating defects per million opportunities (DPMO)

DPMO = Number of defects × 1,000,000/ number of opportunities.

Converting DPM to sigma metric—Conversion of DPMO to sigma metric is done by using standard Six Sigma tables available.

If one knows what percent of test results fail the desired target, such as preanalytical errors **(Table 54.1)**, one can convert that into a DPM, which in turn becomes a sigma metric. If Six Sigma is carried out properly, it ensures that internal processes are running at best efficiency.

TABLE 54.1: A hypothetical calculation of sigma for preanalytical errors by measuring total opportunities and defects.

Preanalytical errors	*No. of total samples/ opportunities*	*No. of defects out of total samples*	*% Error*	*DPMO*	*Process sigma from Six Sigma tables/process sigma calculator*
Hemolyzed	1,000	20	2%	20,000	3.55
High PCV	1,000	10	1%	10,000	3.83
Wrong collection	1,000	7	0.7%	7,000	3.96
Lipemic	1,000	1	0.1%	1,000	4.6

TABLE 54.2: Error rate, DPM, and corresponding sigma.

Error rate	*DPM*	*Sigma*
Acceptable		
5%	50,000 DPM	3.15
1%	10,000 DPM	3.83
Goal		
0.1%	1,000 DPM	4.6
0.01%	100 DPM	5.2
Excellent		
0.001%	10 DPM	5.8

The goal should be an error rate of 0.1% or 1,000 DPM (4.6-sigma) to 0.01% or 100 DPM (5.2-sigma), and ultimately 0.001% or 10 DPM (5.8-sigma). A defect rate from 1% or 10,000 DPM to 5% or 50,000 DPM are often considered acceptable **(Table 54.2)**.

A Six Sigma is defined as 3.4 defects per million opportunities (DPMO) **(Table 54.3)**. A three-sigma process has about 66,807 defects per million tests.

TABLE 54.3: Table showing sigma metric, DPMO, percent defects, and percent yield.

Sigma metrics	*DPMO*	*Percent defects*	*Percentage yield*
1	691,462	69%	31%
2	308,538	31%	69%
3 Minimum	66,807	6.7%	93.3%
4	6,210	0.62%	99.38%
5	233	0.023%	99.977%
6 World class	3.4	0.00034%	99.99966%
7	0.019	0.0000019%	99.9999991%

Calculation of Sigma by Measuring Variation and Predicting Process Performance

This sigma approach is useful for analytical processes and is carried out in the following way:

To Calculate CV, Bias, and Total Allowable Errors (TEa) for an Analyte

Quality control includes management of internal and external quality. The two components which define the quality specifications of the patient results are: bias and CV. Internal quality helps in maintaining precision and accuracy which helps to calculate CV, whereas external quality control helps in maintaining accuracy which helps to calculate bias.

TEa is calculated by the specification given by CLIA/RCAP/RiliBÄK or other standard regulations as selected by the user.

Coefficient of variation (CV)

Closeness of values to each other, i.e., imprecision, is used to describe the variation of a test. The CV expresses the variation as a percentage of the mean. CV is calculated from the calculated laboratory mean and calculated standard deviation procured from the internal quality control data over preceding months.

CV% = (Standard deviation/Laboratory mean) × 100%

A test with high standard deviation means poor precision, greater instability, and high random error in the laboratory.

Generally, for all parameters, CVs of 5% or less generally denote a good method performance, whereas CVs of 10% and higher imply unsatisfactory performance.

So, CV provides a general perception about the performance of a method. The CVs and standard deviations (SDs) can be calculated using the Graph Pad Prism version 5.0.

Bias

Bias is deviation from the true value (accuracy). It indicates systematic difference between the result obtained by the laboratory's test method and the one obtained from an accepted reference. The true value with some traceability can be one of the following:

- From proficiency testing (PT)/external QC program
- From mean of peer group, e. g., participation in unity report (interlaboratory program available to clinical diagnostic laboratories for day-to-day performance comparison with peer group with at least 12 participants).
- From a comparative method (new vs old).
- From observed laboratory mean vs target mean.
- Bias from reference material or reference method/manufacturer value.

Bias emphasizes lack of agreement among methods being compared. Systematic error is detected as positive or negative bias for a given analytical method.

$$\text{Bias} = \frac{\text{Designated mean (Dm)} - \text{Laboratory mean (LM)}}{\text{Designated mean (Dm)}} \times 100$$

Designated mean (Dm) is the means of all laboratories using same instrument and method and is also provided by the reagent manufacturer.

Total allowable error (TEa)

Refers to allowable difference from the true value, i.e., the degree of change that needs to be detected in an analyte for a clinically important decision to be made.

TEa is a model that combines both CV (imprecision) and bias (trueness) of a method to calculate the impact on a test result. The sigma metrics were calculated using PT/EQA groups, CLIA, RCPA**,** biological variation database—minimum/optimum/desirable**,** RICOS Goals, RiliBÄK, etc. Following have been different models of TEa:

- ***2SD model TEa*:** Early definition of TEa used a 2SD model (meaning that 95% of the measured results were expected to be within the TEa).
- ***3SD model for TEa*:** Present day model (CLIA, CAP, New York state regulatory guidelines) uses a 3SD model (99.7% of your data will be within TEa)
  TEa (%) = Bias (%) + 1.65 × CV (%)
  (1.65 implies that 95% of the results fall within the TEa limit given a Gaussian distribution).

Selecting the optimum TEa

If TEa is too large ability to correctly interpret results is compromised.

If TEa is too small: The costs for keeping the process in control become excess.

The just right TEa allows correct interpretation of clinical issues and reasonable control of process costs. There is no consensus on the perfect TEa, but it is an important statistical quality control (SQC) tool. However, selecting the optimum TEa is the prerogative of a laboratory.

- Example when TEa for sodium is too big = ±9 (reference interval for sodium is 136–144 mmol/L)
  If target value of QC 140 ±3 mmol/L (1SD) ±3 SD becomes 131–149. This TEa completely covers the reference interval so that any discrimination between health and disease is impossible. So, TEa should never be wider than the reference interval.
- When TEa for sodium is too small = ±0.3
  If target value of QC 140 ±0.1 mmol (1SD) ±3 SD becomes 139.7–140.3. This TEa fails, because cost to maintain process control

is expensive. TEa should never be smaller than the last reportable digit. Typical SD is 1 mmol/L, which makes TEa of ±3 having range 137–143, which is well within reference interval range.

According to CLIA, TEa is ±4 mmol/L. This prevents setting unrealistic expectations at the low end and avoids unachievable 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. **Table 54.4** enlists TEa for some common biochemical parameters as given by Clinical Laboratories Improvement Act (CLIA) guidelines 1988, RCPA-QAP, RiliBÄK, and Ricos Goal desirable TEa.

TABLE 54.4: TEa for some of the common biochemical as per CLIA recommendation, RCPA-QAP, RiliBÄK and Ricos Goal desirable TEa.

	CLIA	***RCPA-QAP***	***RiliBÄK***	***Ricos Goal desirable TEa***
Glucose	Target value ±10% or 6 mg/dL (greater)	±8%	±15%	7%
Urea	Target value ±9% or 2 mg% (greater)	±12%	±20%	15.6%
Creatinine	Target value ±15% or ±0.3 mg/dL (greater)	±8%	±20%	8.9%
T. Bil	Target value ±20% or 0.04 mg/dL (greater)	±12%	±22%	27%
T. Protein	±10%	±5%	±10%	4%
Albumin	±10%	±6%	±20%	4%
Uric acid	±17%	±8%	±13%	12%
Cholesterol	±10%	±6%	±13%	9%
TG	±25%	±12%	±16%	26%
HDL-c	±30%	±12%	–	12%
Na	Target value ±4 mmol/L	±2%	±5%	0.7%
K	Target value ±0.5 mmol/L	±5%	±8%	6%
Cl	5%	3 mmol/L <100 mmol/L, 3% >100 mmol/L	8%	1.5%
Ca	0.25 mmol/L	0.1 mmol/L <2.5 mmol/L, 4% >2.5 mmol/L	10%	2.6%
AST	±20%	±12%	±21%	16.7%
ALT	±20%	±12%	±12%	27.5%
ALP	±30%	±12%	±18%	12%
Amylase	±30%	±10%	–	15%
CPK	±30%	±12%	±20%	30%
Iron	±20%	±12%	–	30.7%
Mg	25%	±8%	±15%	5%
Cortisol	25%	±15%	±30%	23%
fT4	Target value ±3SD	±12%	±20%	7%
TSH	Target value ±3SD	±20%	±24%	23%

CLIA—Clinical Laboratories Improvement Act.
RCPA-QAP: The Royal College of Pathology of Australia—Quality Assurance Performance.
RiliBÄK: Guidelines of German Medical Associates for the Quality Assurance of Laboratory Medical Examination.
Ricos Goals: Biological variation database.

To Calculate Sigma Using Standard Analytical Sigma Metric Equation

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 is calculated as follows:

$$\sigma \frac{\text{TEa} - \text{Bias}}{\text{CV}}$$

All variables are in their actual units, but the percentage version of the equation is most popular.

FUNCTIONING AT DIFFERENT SIGMA LEVELS

Starting from the goal is to cut the number of defects in half, is a more realistic goal than trying to meet 6-sigma for every process.

- Achieving a sigma level equal to or more than 6 must be encouraged in all laboratories. Six Sigma concentrates on regulating a process to 6 SDs. Performance above Six Sigma levels is a world class performance. When the method sigma is greater than or equal to 6, stringent internal QC rules need not to be adopted. In such cases, false rejections can be minimized by relaxing control limits up to 3SD.
- Achieving at sigma metric from 6.0 to 3.0 represents the range from best case to worst case.
- Functioning at the 3-sigma level is regarded as the least acceptable level of quality. A good performance is indicated by a sigma level more than 3 but a sigma level less than 3 is a sign of a poor performance procedure. Methods with sigma performance less than 3 are not considered acceptable for production and calls for the adoption of a newer and better method as quality of the test cannot be assured even after repeated QC runs.

***Changes in performance in laboratory to meet high sigma*:**

- To meet 3-sigma—usually only obvious changes and corrections are required.
- To meet the 4-sigma—processes must also be improved.
- To meet 5-sigma—the design of processes must be improved.
- To meet 6-sigma—requires rigorous tools and a design for perfection.

***Should sigma value more than 6 be achieved*:** Sigma value of 14, 20, and 30 are essentially no different from each other. If sigma is increased from 6-sigma to 7-sigma, defects reduce from 340 to 2 defects per 100 million **(Table 54.5)**. Although, real improvement from achieving 5-sigma to 6-sigma is very less from achieving 6-sigma to 7-sigma, but practically improvement from 5-sigma to 6-sigma is more effective. The increase in cost incurred in achieving 6-sigma to 7-sigma may not justify the advantages of increase in sigma metrics from 6 to 7.

Extremely high sigma metrics may show that you have chosen a tighter quality need.

Graphic Presentation of Six Sigma using Total Allowable Error (TEa) for Given Analyte, Systematic Error (Bias %) and Imprecision (CV %)

If we measure some analyte in the patient's sample, then the true value that represents the patient's real clinical status is in the center **(Fig. 54.1)**. As we run tests on this patient again, we never get all the results to

TABLE 54.5: Quantification of sigma beyond six.

Sigma	*DPMO*	*Defects in whole no*
6s	3.400 DPMO	3.4 defects per MO
7s	0.020 DPMO	2 defects per 100 MO
7.5s	0.001 DPMO	1 defect per 1,000 MO
7.86s	0.0001 DPMO	1 defect per 10,000 MO
8.53s	0.000001 DPMO	1 defect per 1,000,000 MO

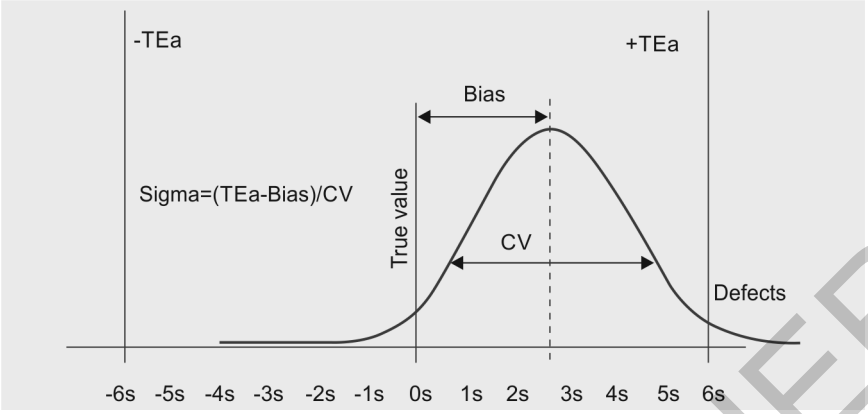


Fig. 54.1: Graphic presentation of Six Sigma metrics.

be exactly the same, and the values take on the form of a normalized distribution around that value instead. The TEa is the tolerance limits on either side. If we can squeeze six standard deviations of our analytical method distribution within that TEa, in the absence of any bias, we will meet that Six Sigma goal and expect to generate fewer than four clinical defective results. When bias exists, it shifts our distribution away from the patient's true value. On the other hand, when we have a larger and larger imprecision, it spreads our distribution wider and wider. The combined impact of imprecision and bias may cause the thicker parts of the tails of our distribution to exceed the TEa, which means generating more defective test results.

To implement suitable Westgard QC rules for each analyte: Quality control in healthcare system is still less understood because of the relative complexity in choosing an appropriate Westgard rule. The aim of Six Sigma is to simplify the process of choosing Westgard rule and thus to improve the reliability of the results of diagnostic tests. Selecting an appropriate Westgard rule is done using the Six Sigma principle, along with total allowable error, method imprecision, and bias for that particular analyte. The goal is to meet the highest possible sigma scale within the acceptable limits of total allowable error. Selection of several QC materials and repetitions (measurements) needed is also done as per sigma values achieved as per the following Westgard rules:

≥6σ – 2 levels of QC per day with a $1_{3.5s}$ greater rule

5σ – 2 or 3 levels of QC per day with a $1_{2.5s}$ or 1_{3s} rule

4σ – 3 or 4 levels of QC per day with a $1_{3s}/2_{2s}/R_{4s}/4_{1s}$ rule

3.5σ – 6 QC per day with a $1_{3s}/2_{2s}/R_{4s}/4_{1s}$ rule

Less than 3.5σ—most affordable levels of QC per day with a $1_{3s}/2_{2s}/R_{4s}/4_{1s}$ rule as the sigma value decreases, the chance of missing an error increases. Therefore, the best Westgard rule is the one with a sigma value closest to, but smaller than, the sigma value of the test. For low sigma values (<3.5-sigma) reducing analytical bias and imprecision is a key to improve the quality. For lower sigma values, more QC samples and following more Westgard rules are recommended. Example:

a. For total protein:
   TEa = 10%
   If bias of a laboratory for it is 3% and CV% at 2% for Protein Sigma = (TEa–Bias)/CV% = (10% – 3%)/2% = 3.5 S
   So, Westgard rule corresponding to sigma of 3.4 is chosen to check the performance of cholesterol assay, i.e., a multirule of 13s/2 22s/R 4s/41s is applied with two levels of control.
b. For TG: TEa = 25%
   If bias of a laboratory is 13% and CV% at 2% for TG

Sigma = (TEa – Bias)/CV%
= (25% – 13%)/2% = 6S

So, a Westgard rule of 13.5s two levels of control is enough to check its performance.

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.

VISUALIZING WORLD CLASS QUALITY BEYOND CALCULATIONS

a. Method Decision Chart

Calculation of sigma metrics is, although taxing, but at the same time it can be accomplished. But, with so much sample load, laboratories want simplicity and not so many calculations to be added to their files. Method decision chart often also called a sigma bull's-eye graph **(Fig. 54.2)** is a visual tool that takes all the information from the equation and turns it into a graphic format.

This chart arranges the imprecision along the x-axis and bias along the y-axis, thus the performance data from an analytical method transforms into graph coordinates. The scale of Y-axis is 0 to TEa and scale of X-axis is 0 to TEa/2. Sigma metrics lines are drawn as per **Table 54.6**.

TABLE 54.6: Calculation of X-axis and Y-axis points for drawing Sigma metrics lines.

Criterion	*Y-axis*	*X-axis*	*Sigma*
Bias +2S	TEa	TEa/2	2
Bias +3S	TEa	TEa/3	3
Bias +4S	TEa	TEa/4	4
Bias +5S	TEa	TEa/5	5
Bias +6S	TEa	TEa/6	6

Sigma metrics zones superimposed on the graph **(Fig. 54.2)** are the following:

- The zone closest to the graph's origin is with world class quality, i.e., Six Sigma.
- Followed by Six Sigma is five sigma zone which is excellent.
- Then is four sigma zone considered as good.
- After four sigma is three sigma zone, i.e., marginal and then is two sigma zone, i.e., poor.

The rest of the graph, for sigma metrics performance below two sigma, is labeled as unacceptable. As methods get closer to the bull's eye, it means the sigma metrics are higher and fewer defects are being generated.

A normalized method decision chart means multiple analytes with different TEa's can be adjusted to be displayed on a single chart. So, on this visual tool we can know sigma as

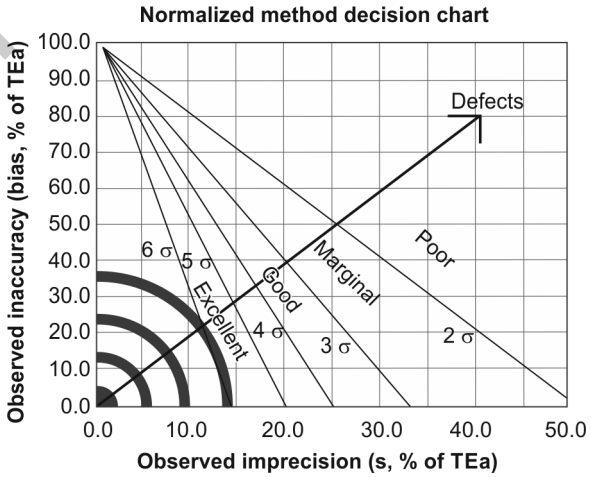


Fig. 54.2: Normalized sigma metrics bull's-eye chart.

per the intersect point that we get from the graphic format (CV is plotted on X-axis and Bias on Y-axis), which we had calculated in the preceding chapter from standard analytical sigma metric equation.

$$\sigma \frac{\text{TEa} - \text{Bias}}{\text{CV}}$$

b. Operational Process Specifications (OPSpecs) Charts

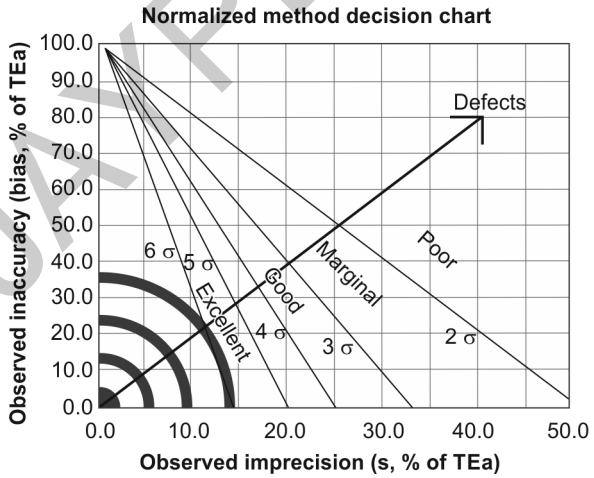
An OPSpecs chart plots the allowable bias versus the allowable imprecision, and provides the information needed to select appropriate quality control rules, and number of runs required to assure a defined quality need. It can be used for the following:

- Using the TEa, precision and accuracy of an analyte, ideal Westgard rule can be selected using OPSpecs charts.
- Is a tool that details how many rules and controls are needed to give the necessary error detection (with a minimum of false rejection) for the method.
- Consider how improving a test's precision and accuracy will change the operating point of the method, and therefore, result in simpler and less expensive quality control.
- Estimate the largest allowable imprecision for a test from the X-intercepts of the operating lines for the QC rule being implemented.

It is a graph very similar to the Six Sigma method decision chart, in that the imprecision CV forms the X-axis, and the bias forms the Y-axis **(Fig. 54.3)**. Where the OPSpecs chart differs from method decision chart is that the lines displayed on the chart are no longer sigma metrics zones, they represent the performance of different QC rule.

For drawing the chart define the analytical quality need for the test in the form of TEa. Calculate the SD or CV for the method. Calculate the bias. Calculate normalized operating point, which is observed imprecision and inaccuracy expressed as a percentage of the allowable total error. Plot normalized operating point by calculating CV% and bias as follows and selects the relevant QC rule. A normalized method decision chart/OPSpecs chart means multiple analytes with different TEa's can be adjusted to be displayed on a single chart. For example:

- For 10% TEa, a 2% observed CV would be 20%; a 4% observed bias would be 40%.
- For 20% TEa, a 2% observed CV would be 10%; a 4% observed bias would be 20%.
- For 30% TEa, a 2% observed CV would be 6.7%; a 1% observed bias would be 13.3%. The diagonal lines displayed in the chart



		Pr	N	R
2σ	12s	0.09	2	1
3σ	12.5s	0.03	2	1
4σ	13s/2 2s/R 4s	0.01	2	1
5σ	13s	0.00	2	1
6σ	13.5s	0.00	2	1

Fig. 54.3: OPSpecs chart.
(Pr: probability of false rejections; N: number of measurements; R: runs)

represent (in order from right to left) different quality control (QC) rules listed in the key at right (from top to bottom). As performance is closer to the bull's eye, the plotted point is within the ring of that QC rule, which means that a particular rule combination will give adequate error detection and proper analytical quality assurance.

c. Deciding QC Frequency and Run Length Using Nomogram

A sigma-metric SQC run size nomogram is for estimating the number of patient samples between QC events for bracketed operation of a continuous analytical testing process.

Up until about a decade ago, QC frequency was entirely determined by rule of thumb. Sometimes, it was planet-based QC frequency: once a day. At other times, it was labor-based QC frequency: once a shift. But it was surely not patient-based QC frequency, driven by the performance of the method and the quality required for the proper use and interpretation of the test results.

Until recently, the decision on QC frequency no longer has to be calculated and understood mathematically but could instead be simply interpreted graphically. Through a series of publications in 2017–18, Westgard extended these graphic simplifications to create more practical QC frequency nomograms. Now laboratories can simply observe a graph that compares their sigma metrics on the X-axis with the number of patient samples that can be run between controls on the Y-axis **(Fig. 54.4)**. The different lines in the graph represent the QC procedures that may be chosen by the laboratory. In order to decide QC frequency, a laboratory should do the following:

- Decide the sigma metric of a method
- Find the appropriate QC design
- Find the intersection of the sigma metric and QC procedure line on the nomogram.

If a laboratory has a Six Sigma method, then any QC procedure will do and at least 500 patients or possibly many more can be run in between QC events without the risk of reporting any wrong result.

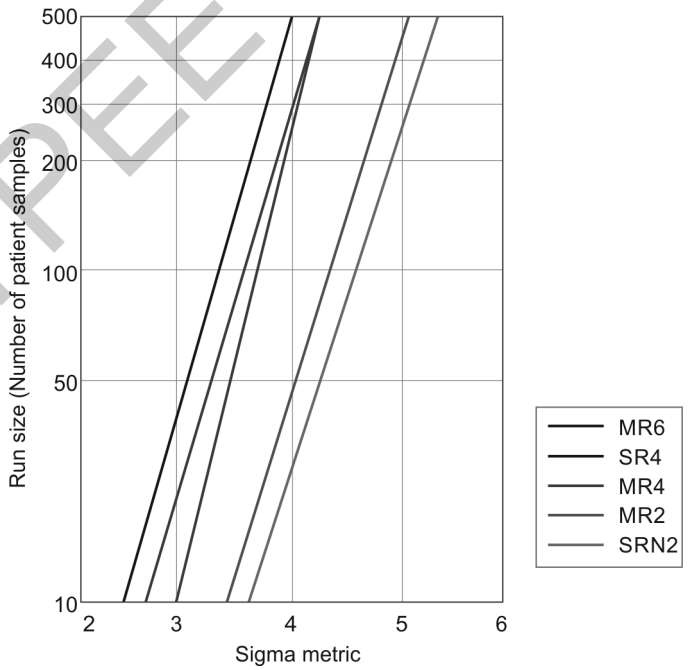


Fig. 54.4: Sigma metric run size nomogram.

For Six Sigma methods, the QC frequency can be reduced to 1 control per 1,000, 2,000, or even higher numbers of patient samples, or they can use extended QC limits such as 4s or wider.

If a laboratory has a sigma of three or less, then QC frequency must be greatly increased, to something closer to one control per 100 or per 50 patient samples. Methods below 3 and 2-sigma would theoretically require almost constant running of controls, a frequency that may be impractical.

MR6 represents a full implementation of "Westgard **Rules**" using 6 control measurements (either 6 controls run at once or 3 controls run with 2 measurements being made on each control).

MR N4 represents the $1_{3s}/2_{2s}/R_{4s}/4_{1s}$ multirule procedure with N = 4 control measurements.

MR N2 represents the $1_{3s}/2_{2s}/R_{4s}$ control rules with N = 2 control measurements.

SRN2. Single-rule procedures using the 1_{3s} control rule and N = 2 control measurements.

SRN4 Single-rule procedures using the 1_{3s} control rule and N = 4 control measurements.

SIX SIGMA DMAIC METHODOLOGY

To eliminate defects and reduce variation Six Sigma uses DMAIC methodology. This is a stepwise approach for enhancing quality and producing the desired goals. DMAIC is the following five-stage Six Sigma system to find and solve problems.

Define—the problem or opportunity and the expected outcome of laboratory processes.

Measure—the current performance and ability. Establish and measure QC systems as per real need. Collect relevant data and document the same.

Analyze—to find the cause of the defect under investigation. Periodical analysis of data to investigate and find the deficiency.

Improve—by implementing potential solutions. Assess the effectiveness and relevant improvement. Do pilot runs to prove a new process ability.

Control—by standardizing solution and monitoring performance. As per assessment, implement and control the process to make sure that any deviations from target are corrected before they result in defects.

In this, the laboratory turnaround time for each test, total delay time in the sample reception area, and percentage of steps involving risks of medical errors and biological hazards in the overall process are measured.

DMADV Approach

Apart from the "DMAIC" methodology, which is essentially used for a pre-existing process that is defective, the "DMADV" (Define, Measure, Analyze, Design, and Verify) methodology is used when a new process is being developed or a pre-existing defective process has failed, even the "DMAIC" correction. The difference lies only in the last two steps, "Design"—detailed design of the process to meet the customer needs and "Verify"—the design performance and its ability in meeting the customer needs.

BENEFITS, LIMITATIONS, AND CHALLENGES OF SIX SIGMA

Six Sigma Benefits

Clinical laboratories remain in a constant effort to increase their workload, decrease error, improve the quality, and decrease the cost. To meet these goals, sigma metrics have become a useful tool for all parts of the quality control (QC) design process. Six Sigma not only allows benchmarking the performance of methods and instruments on a universal scale, it allows laboratories to easily visualize performance (using tools like method decision chart, OPSpecs chart, and QC frequency nomogram), optimize the QC rules, and numbers of control measurements they carry out, and now even schedule the frequency of running those controls. The most popular outcomes from Six Sigma are as follows:

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- For publishing research work, students can refer to the chapter on *Components Associated with Research Work and Its Publication.*
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- A useful book for bridging the gap between clinicians and clinical laboratories.

Ranjna Chawla PhD is a Senior Biochemist (Scientist IV), Department of Biochemistry, Govind Ballabh Pant Institute of Postgraduate Medical Education and Research (GIPMER), Government of NCT of New Delhi, India. She has around 40 years of experience in various capacities.

She completed her Doctorate from the Postgraduate Institute of Medical Education and Research (PGIMER) in Chandigarh. She has been associated with prestigious institutions such as PGIMER, Chandigarh; Lady Hardinge Medical College (LHMC), Delhi; Government Medical College (GMC), Chandigarh; Guru Nanak Eye Center (GNEC), Delhi, and Nehru Homoeopathic Medical College and Hospital (NHMC), Delhi. She has investigated various projects of UGC, ICMR, and AYUSH and has also published numerous research papers in national and international journals. Dr Chawla has utilized her teaching and research experience to understand the problems of students and incorporate the latest developments in the field of biochemistry.

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