Statistical Quality Control in Clinical Laboratories

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14.1 Quality Perceptions

In a biomedical laboratory, *normal range* is the most important "quality perception" for controlling quality. It has been an essential protocol to give "normal range" for each of the constituents of various body fluids. The normal range is also referred as "reference range" by which we mean that the concentration of a constituent of a biological fluid or sample must be within this range for the individuals considered to be in good health. In other words, we would assume that the values outside these limits warrant an alarm for thorough health checkup. There are set procedure for establishing such ranges. Modern medicine warrants the thorough investigations of biological material derived from the body of a patient to ascertain the cause and effect of disease before the commencement of medical or surgical treatment. Quality management in medical laboratories is a must for accreditation [24].

14.1.1 Normal Distribution Curve

Let us deliberate on an example from industry to understand the concept of "normal distribution" and "normal distribution curve." Suppose a "mineral water bottling plant" is packing water with a standard label of 200 ml per unit and states that there can be 5% natural variation in volume. In this case "normal range" would be 190–210 ml. If we collect a large sample of more than 30 bottles from various batches of mineral water, measure the volume of water in each bottle of the sample, and plot a scatter graph; that graph would be a "normal curve" if the distribution was normal. Such a curve is defined by "mean" ($\bar{x}$) and the "standard deviation" (s) and has been depicted in Fig. 14.1. Mean ($\bar{x}$), the arithmetic average, is determined by dividing the sum of determinations with number of determinations:

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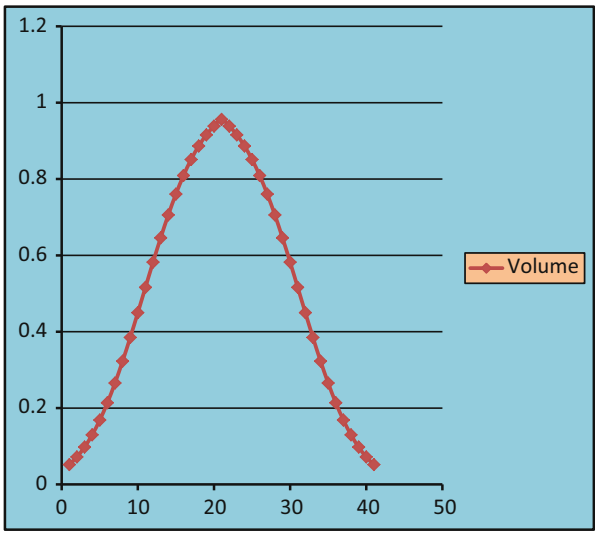

Fig. 14.1 Normal distribution curve for volume of mineral water

$$\bar{X} = \frac{\Sigma x}{n}$$

Standard deviation (sd, s, or σ) is computed by the following formula:

$$s = \sqrt{\frac{\Sigma(x - \bar{x})^2}{n}}$$

where:

n = number of determinations
$\bar{x}$ = Mean
x = each determination or observation

Note Abbreviation used for "standard deviation" could be SD, sd, or s when we use it for "standard deviation" of a sample from population and $\boldsymbol{\sigma}$ for "standard deviation" of population.

We have already learnt in Chapter 10 that for such a curve, 68.3% of values fall within $\bar{x} \pm 1$sd, 95.4% values within $\bar{x} \pm 2$sd, and 99.7% values fall within $\bar{x} \pm 3$sd. It is a universal practice to consider the "normal range" as $\bar{x} \pm 2$sd. With the "normal range" fixed as $\bar{x} \pm 2$sd, it would be obvious that values from 5% of the normal persons would lie outside the range. With a normal range set as $\bar{x} \pm 3$sd, only 0.3% values would lie outside the range; that means only 3 in 1000 persons would fall outside the range.

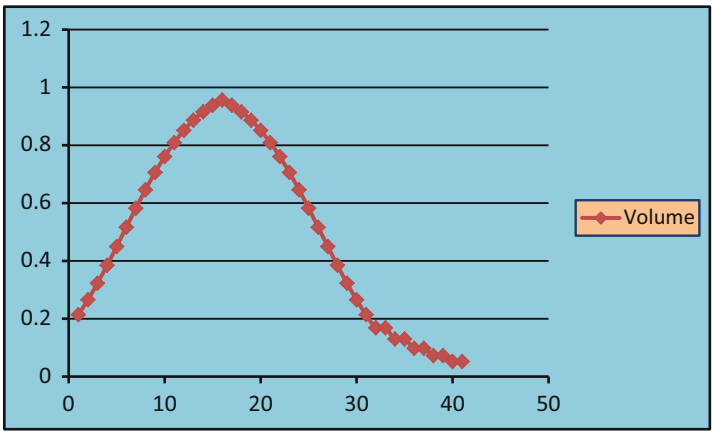

Fig. 14.2 Skewed distribution curve for volume of mineral water

It has been observed that sometimes majority of values at the lower end are close to zero. Under such conditions we get a skewed curve as shown in Fig. 14.2. It is necessary that the working "normal range" should include majority of normal values and very few abnormal values. The $\bar{x} \pm 2\text{sd}$ is the most satisfactory normal range/reference range as considered by the "International Organization for Standardization" (ISO).

The "International Organization for Standardization" (ISO) is an "International Authority" for setting up standard guidelines for various organizations and laboratories. The International Organization for Standardization is based in Geneva, Switzerland, and 163 countries are its members. The international standard for medical laboratories was first published in the year 2005. It was based on ISO 15189:2003(1st edition) and later revised as ISO 15189:2007 (2nd edition). Further revision was done in the year 2010, and the current version is ISO 15189:2012 (3rd edition). The ISO 15189:2012 provides standard guidelines for "requirements for quality and competence in medical laboratories." The main goal of ISO 15189:2012 is the "Global Harmonization of Medical Laboratories" in terms of quality of their services. The need of the hour is the "total quality management" (TQM) as per ISO 15189:2012. The "statistical quality control" (SQC) is of utmost importance for competence.

14.1.2 Errors

Standard operating procedures (SOPs) should be prepared by all the clinical laboratories and followed to avoid operational and technical errors. Errors may be divided into two groups:

1. Errors due to faulty methods used: These may be inherent due to methodology or due to incorrect composition of reagents used or due to faulty apparatus. Such defects would lead to incorrect determinations even by experienced staff. Faulty apparatus and reagents would affect the determinations of all the batches.
2. Errors due to faulty performance: An inaccurate result may be obtained for a single determination due to wrongly performed step of the procedure. In this case other determinations in the batch could be considered reliable.

14.1.3 Check over Errors

Errors can be kept under control by use of known "standard solutions" or blood samples of known concentration of constituents. A wide range of pooled sera and some urine samples are now available from numerous makers and suppliers for most of the constituents now measured. Various scientific groups/committees have been formed all over the world for accreditation and licensing of medical laboratories for quality services.

Internal and external audit of performance of such checks have been made mandatory for ISO Certifications and Accreditation. Checks are introduced at frequent intervals, and the persons performing the test are kept blind about the predetermined value of the constituent being determined. King and Woottan (1956) were the first to introduce such checks with a batch of each determination. We need to draw charts for each determination, and on these charts daily value of known standard is plotted in order to know the extent of variations from the standard value. When these determinations are outside the minimum permissible range, results are declared invalid, and alarm is raised for repeating the batches.

14.1.4 Permitted Variations

Permitted variations for the inorganic and organic constituents of the blood have been decided by quality control bodies/committees. For inorganic constituents such as sodium (Na^+), potassium (K^+), and chloride (Cl^-), permitted variations are $\pm 3\%$, whereas for organic constituents such as glucose, urea, uric acid, cholesterol, bilirubin, and albumin, permissible variations could range from $\pm 5\%$ to $\pm 10\%$.

When determinations are made in batches, we may omit control occasionally in case of nonavailability of control sera or standard. In batches we find many results within "normal range." All abnormal results in a batch would lead to suspicion of something wrong with the procedure or the equipment used. When some investigations are done rarely or in very small batches, we should include normal samples in duplicate along with standard control. When spectrophotometric or colorimetric methods are used, it is advisable to avoid delay in taking optical density measurements.

The indication of a possible change in operation of a technique can be obtained from daily "mean" of successive batches by plotting charts. At present we run large

batches on "autoanalyzers" for substances such as glucose, urea, uric acid, sodium, potassium, and chloride; the mean remains remarkably constant from day to day. For substances like calcium, alkaline phosphatase, and transaminases, determinations are done in small batches daily; weakly means could be taken.

14.1.5 Accuracy and Precision

We must understand the meaning of these two terms in a clinical laboratory. The term "accuracy" reflects how close is the "mean" ($\bar{x}$) of large number of determinations to the actual amount of the substance present in the test specimens or standards.

The "precision" refers to the extent to which the repeated determinations on an individual specimen or "standard control" by applying a certain technique are consistent. This reflects the range of error of the method used and may vary from technologist to technologist. We understand from the facts that a method with high degree of precision may not be very accurate. The precision refers to the "variable error," whereas the accuracy refers to the "constant error" inherent in a method. The degree of precision can be obtained by carrying out more than 30 determinations in duplicates and taking difference of each set and calculating "standard deviation" (s) by the following formula:

$$s = \sqrt{\frac{\Sigma d^2}{n}}$$

where d = difference between each pair of duplicates.

n = the number of duplicates.

The limits of precision are generally taken within 95% limits, as worked out by $\bar{x} \pm 2s$, where $\bar{x}$ is the mean of the set of determinations and s is the "standard deviation" as calculated above for at least 30 sets of duplicates. Alternatively, "standard deviation" can be calculated by multiplying the "mean" difference between pairs by 0.88.

$$s = \bar{d}(0.88)$$

14.2 Quality Control Measures

We can take the following measures for control of quality:

1. Use of quality control materials
2. Use of control charts for SQC

3. Participation in interlaboratory comparison programs
4. Analysis of quality control data

14.2.1 Use of Quality Control Materials

The laboratory should use quality control materials that react to the testing procedures in a manner as close as possible to patients' samples. These materials should be periodically depending on the stability of standard operating procedures (SOPs) to avoid risk to the patient from erroneous results.

As stated earlier, quality control standards are available commercially. However, if these are not available, pooled sera from one's own laboratory can be used as standard. Quality control manager should collect surplus sera, urine, and fluids daily and store in a deep freezer and keep on adding these until sufficient volume has accumulated. These should be thawed, Millipore filtered, and analyzed to determine the concentration of constituents, divided in aliquots, and stored in deep freezer for daily use as standards.

14.2.2 Control Charts

The "control charts" are the graphic tools developed for detecting unnatural pattern of variation in laboratory investigations or production process (in industry) and determining the permissible limits of variations. The permissible limits are called "upper control limit" (UCL) and "lower control limit" (LCL).

14.2.3 Advantages of Control Charts

There are three major advantages of control charts:

1. Control charts define the goals to be achieved.
2. These act as tools to attain the determined goals.
3. These enable us to take decision to accept or reject the batch of determinations or items.

14.2.4 The Mean Chart ($\bar{x}$ Chart)

The mean chart is used to express the quality average of given set of determinations or samples drawn from a given process. Make the following calculations:

1. Take mean of various samples (say mean of a batch of fasting blood sugar determinations): $\bar{x} = \dfrac{\Sigma x}{n}$.

2. Take "grand mean" ($\overline{\overline{x}}$), that is, mean of means all batches (samples) done in a week or a month: $\overline{\overline{x}} = \frac{\Sigma \bar{x}}{n}$.
3. Take "range" of various samples item wise: (range = largest item – smallest item)
4. Take mean of Range: $\bar{R} = \frac{\Sigma R}{\text{No. of Batches of Samples}}$
5. Set up control limits: $\overline{\overline{x}} \pm 2\sigma$
6. We can also set up limits as
   Upper Control Limit (UCL) $= \overline{\overline{x}} + A\bar{R}$
   Lower Control Limit (LCL) $= \overline{\overline{x}} - A\bar{R}$
7. The value of A is calculated as
   $A = \frac{3}{\sqrt{n}}$ (when $n > 25$)

Example 1 Data of the month of January for "blood urea" determinations carried out at emergency laboratory of a hospital has been given as daily mean for the batches as 28, 27, 25, 29, 27, 29, 30, 25, 26, 28, 29, 31, 27, 28, 29, 25, 29, 27, 29, 30, 25, 26, 28, 29, 31, 30, 25, 26, 28, and29 mg/dl. Prepare a "mean chart" for "blood urea" quality control, and discuss its utility.

Solution
Arrange all the daily means as in Table 14.1, and calculate grand mean ($\overline{\overline{x}}$) and "standard deviation" to set the limits of mean chart for "blood urea" quality control.

$$s = \sqrt{\frac{\sum (x - \bar{x})^2}{n}} = \sqrt{\frac{99}{30}} = \sqrt{3.3}$$
$$= 1.82 = 2(\text{Rounded off to whole number})$$

$$\textbf{UCL} = \overline{\overline{x}} + 2\sigma = 28 + 2 \times 2 = 28 + 4 = 32$$
$$\textbf{LCL} = \overline{\overline{x}} - 2\sigma = 28 - 2 \times 2 = 28 - 4 = 24$$

From the above calculations, the "control limits" for "blood urea" determinations come out to be 24 to 32 mg/dl. The "mean chart" for the above data has been exhibited as Fig. 14.3.

Comments
All the daily means of 'blood urea determinations" provided (ranging from 25 to 31 mg/dl) are within "control limits." Hence, the quality is within "control," and there is no sign for alert.

14.2.5 The Cumulative Sum Chart (CUSUM Chart)

The "cumulative sum chart" was introduced by Woodward and Goldsmith in 1964. It is just a variant of "mean chart." A mean value as close as possible to the actual mean of the daily means ($\overline{\overline{x}}$) is chosen, and every day the difference of day's mean

Table 14.1 Daily means of blood urea determinations in a month

Day ID	Daily mean ($\bar{x}$)	$\bar{x} - \bar{\bar{x}}$	$\left(\bar{x} - \bar{\bar{x}}\right)^2$
1	28	0	0
2	27	−1	1
3	25	−3	9
4	29	1	1
5	27	−1	1
6	29	1	1
7	30	−2	4
8	25	−3	9
9	26	−2	4
10	28	0	0
11	29	1	1
12	31	3	9
13	27	−1	1
14	28	0	0
15	29	1	1
16	25	−3	9
17	29	1	1
18	27	−1	1
19	29	1	1
20	30	2	4
21	25	−3	9
22	26	−2	4
23	28	0	0
24	29	1	1
25	31	3	9
26	30	2	4
27	25	−3	9
28	26	−2	4
29	28	0	0
30	29	1	1
Description	$\bar{\bar{x}} = 28$		Sum = 99

from this is calculated and added to the sum of all previous differences. The result is plotted on a chart. The direction of this graph line depends on the mean chosen. The grid line of mean value chosen as grand mean ($\bar{\bar{x}}$) should pass through the graph as astride. Any upward or downward deflection of the graph of CUSUM would be a warning sign of nonconformance of quality. The "CUSUM chart" would be like "mean chart" if values are within the "control limits."

Suppose the mean value selected was grand mean ($\bar{\bar{x}}$) of previous month, that is, 28 mg/dl. The differences of daily means from this "proposed grand mean" were worked out, and CUSUM with reference to this was computed during the next month

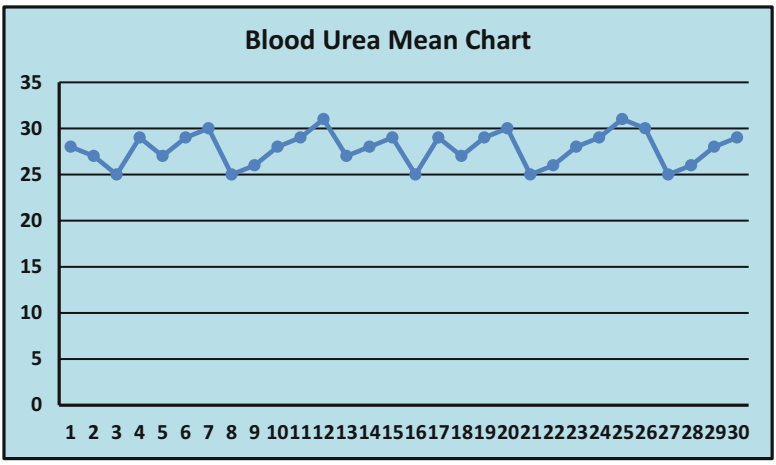

Fig. 14.3 The mean chart for blood urea batches within a month

for the batches of blood urea determinations as depicted in Table 14.2. The "CUSUM chart" for this data has been shown in Fig. 14.4.

$$\mathbf{UCL} = \text{Cusum Mean} + 2\sigma = 29 + 2 \times 2 = 29 + 4 = 33$$
$$\mathbf{LCL} = \text{Cusum Mean} - 2\sigma = 29 - 2 \times 2 = 29 - 4 = 25$$

Comments
Cumulative sum values of "blood urea determinations" for a month are around the grand mean of previous month and conform to the control limits (25–33 mg/dl). Hence, the quality is within "control," and there is no sign for an alert. In the case of nonconformity, corrective actions are taken after identification of the cause of variation.

14.2.6 Participation in Interlaboratory Comparison Programs

Clinical laboratories should participate in the interlaboratory comparison programs such as "external quality assessment" (EQAS) program or proficiency testing programs. Each laboratory should monitor the results of interlaboratory comparison program(s) and implement the corrective actions when the determined criteria are not fulfilled.

Every laboratory should draft documented procedure for participation in interlaboratory comparison. The document should include defined responsibilities and instructions for participation. The interlaboratory comparison program chosen by the laboratory should provide clinically relevant challenges that mimic the

Table 14.2 CUSUM of blood urea determinations in a month

Day ID	Daily mean ($\bar{x}$)	$\bar{x} - \bar{\bar{x}}$	CUSUM
1	28	0	28
2	27	−1	27
3	29	1	28
4	29	1	29
5	27	-1	28
6	27	-1	27
7	26	−2	25
8	31	3	28
9	26	−2	26
10	28	0	26
11	27	−1	25
12	31	3	28
13	29	1	29
14	30	2	31
15	27	−1	30
16	28	0	30
17	30	2	32
18	28	0	32
19	29	1	33
20	26	−2	31
21	29	1	32
22	26	−2	30
23	28	0	30
24	29	1	31
25	27	−1	30
26	30	2	32
27	27	−1	31
28	28	0	31
29	29	1	32
30	28	0	32
Description	$\bar{\bar{x}} = 28$		CUSUM mean = 29
			$\sigma = 2$

patients' samples and have the capacity of examining entire examination process, including preexamination procedures as well as post examination procedures.

14.2.7 Analysis of Quality Control Data

Quality control data should be analyzed and reviewed periodically by "quality control agencies" to detect trends in examination performance that may indicate

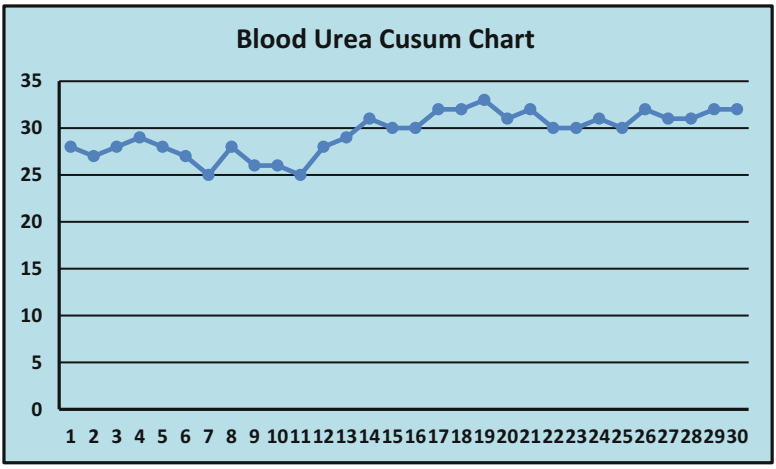

Fig. 14.4 CUSUM chart for blood urea

problems in the examination systems. Corrective actions should be taken in case of nonconformities.

Suppose 50 clinical laboratories participate in "external quality assessment program" for blood urea determination following same SOP. These laboratories would return the results of blood urea value of the external quality control sample to the "external quality control body or agency." The "external quality control body or agency" would find out the "group mean"(GM) and "standard deviation" (SD) of 50 results received and then compute Z distribution for the result of each laboratory (LR) by the formula:

$$Z = \frac{|\,\mathrm{LR} - \mathrm{GM}\,|}{\mathrm{SD}}$$

14.2.8 Decision

$$\begin{aligned} Z &\leq 2.0 \qquad (\mathrm{OK}) \\ Z &> 2.0 \quad \text{Alert is issued.} \end{aligned}$$

Suppose GM = 30 mg/dl with SD = 1.9 and the result of your clinical laboratory for the provided standard sample is 28 mg/dl.

$$Z = \frac{|\,28 - 30\,|}{1.9} = \frac{2}{1.9} = 1.05 \;\; \text{(Perfect)}$$

Hence, the "quality control" of your clinical laboratory would be adjudged within permissible limits for blood urea determination.