Case Report

Statistical Control of the Production of Blood Components: Use of Process Capability Indexes

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Abstract

Controlling the production of blood components is required by regulations such as the European and North American. All production processes have a predictable error under stable conditions. This error is recognized as an expected error. When special causes influence this error, it can be significant. Capability indexes allow measuring production performance by ranking it. When special causes are involved, these indexes suggest production instability. In this situation, taking action is required to return the process conditions to stability. The article introduces a series of capability indices. It discusses, in some depth, their mathematical models as well as their classification levels. A statistical technique for the control of blood component production is suggested.

INTRODUCTION

Control of the production of blood components is required in the European Union [1] in the United States for blood banks and transfusion services [2]. The "Guide to the Preparation, Use and Quality Assurance of Blood Components" [3] include in Annex 4 a statistical process control (SPC) methodology. It suggests some practices, such as schemes for statistical sampling, control sampling frequency, and a set of cases. It is suggested to use graphs, statistical scanning methods, and statistical process control for dichotomous results.

All production processes have an expected error caused by common / natural / expected error sources. When it is significant, it is assumed that there are special causes of error [4].

Monitoring and improvement should not focus solely on the expected causes of uncertainty. They should also include tools that allow detecting minor problems but with an enormous impact on manufacturing. These failures affect not only product or service compliance but budget as well. Production is "acceptable" based on criteria, as in other industrial fields.

Two statistical measures of central tendency are proposed: random error (2.19 of [5]) and systematic error (2.17 of [5]). Whenever a normal distribution is not available, for example, with a number of samples less than or equal to 30, data transformation or an attribute approach as an alternative to a variable method is suggested.

Specification limits are selected according to requirements, e.g., legal applicable to blood components.

Often a sampling control is used. If you control lots without statistical sampling, the control is only valid for tested samples. In this case, the control is only on the tested samples and not on the production. Each sample should have an equal chance of being selected to be representative with a certain margin of confidence [6-7].

Statistical Process Control (SPC) uses charts to monitor product or batch data performance through sampling techniques. Control charts include limits so that you can identify whether the process is operating within or outside the limits. Out-of-bounds events have a significant probability of being associated with special causes of error.

The evidence-based SPC. It allows improving the performance of production batches, which allows the systematic delivery of a compliant production. An in-depth discussion of variable and attribute maps is published in [7-8].

Capability indexes measure the level of production performance. Allow to classify it and the possible taking of actions. A process under control may not meet specifications or vice versa. Note that individual sample results are checked against specifications, legal or internal, and not control limits. For example, specifications published by EDQM suggest the acceptance / rejection of whole blood or its derivatives.

Different statistical models for determining the capability

indexes are briefly discussed. A statistical technique for manufacturing blood components is suggested.

MATERIAL AND METHODS

Process capability index

$\hat{C}_p$ **Index:**

a) Mathematical model: Process capability indexes rank the ability of a process under control to meet goals. They should only be applied to stable / controlled processes. The indexes tell you how often the process meets specifications. It is determined original using $\hat{C}_p$ what is determined by the model:

$$\hat{C}_p = \frac{USL - LSL}{6\hat{\sigma}} \tag{1}$$

where USL is the specified upper limit, LSL is the specified lower limit and is the estimated process variability (within standard deviation limits). As the standard deviation is skewed, $\hat{\sigma}$ is more accurate to determine if it is the result of dividing $\bar{R}$ for each rational subgroup by d_2, which is the statistical correlation coefficient selected according to the rational subgroups in the table of control charts constants for sigma estimation [9]. If an average and standard deviation chart is used, the division is similar, where $\bar{R}$ it is replaced by s and d_2 by C_4 (see table of control charts constants for sigma estimation).

b) Interpretation of levels: If $\hat{C}_p$ = 1, it indicates that the process variation only meets the specifications, that is, the production process of a specific blood component is minimally capable;

If $\hat{C}_p$ < 1, it indicates that the process variation is outside the specification range, that is, the process is not capable of producing a particular blood component within the specification and needs to be improved, and;

If $\hat{C}_p$ > 1, it indicates that the process variation is more restricted than the specifications and exceeds the minimum capability, i.e., the process is capable and current practices should be maintained.

$\hat{C}_{pk}$ **Index:**

a) Mathematical model: $\hat{C}_{pk}$ is another model for determining the capability index. It represents how centralized the data is between specification limits. To determine $\hat{C}_{pk}$ when a single-limit specification range is used, the upper specification limit or lower specification limit is determined $\hat{C}_{pk,upper}$ using the templates:

$$\hat{C}_{pk,upper} = \frac{USL - \hat{\mu}}{3\hat{\sigma}} \tag{2}$$

$$\hat{C}_{pk,lower} = \frac{\hat{\mu} - LSL}{3\hat{\sigma}} \tag{3}$$

where $\hat{\mu}$ is the mean of the production process and $\hat{\sigma}$ is the estimated variability of the process (within the standard deviation). $\hat{C}_{pk}$ is equal to the lower index. To determine $\hat{C}_{pk}$ when a specification range with double limits is used, the $\hat{C}_{pk,\,upper}$ and $\hat{C}_{pk,\,lower}$ is first determined. Then, the minimum index is selected:

$$\hat{C}_{pk} = \min\left[\hat{C}_{pk,\,upper}, \hat{C}_{pk,\,lower}\right] \tag{4}$$

b) Interpretation of levels

If $\hat{C}_{pk}$ < 1, indicates that the process is inadequate, i.e., the process is not capable of producing reliable blood components;

If $1 \le \hat{C}_{pk}$ < 1.33, indicates that the process is capable, rigorous quality control is required, i.e., the process produces a specific blood component that is minimally capable;

If $1.33 \le \hat{C}_{pk}$ < 1.5, indicates that the process is someone, indicating that no severe quality control is required;

If $1.5 \le \hat{C}_{pk}$ < 2, indicates that the process is excellent, no stringent quality control is required;

If $\hat{C}_{pk} \ge 2$, indicates that the process is super, minimal quality control is required.

Sigma metrics:

a) Mathematical model:

$$\sigma = 3 * \min\left[\hat{C}_{pk,\,upper}, \hat{C}_{pk,\,lower}\right] \tag{5}$$

b) Interpretation of levels

6-sigma ($\hat{C}_{pk}$ = 2) is classified as "world-class quality";

5-sigma ($\hat{C}_{pk}$ = 1.66) as the goal related to quality improvement;

4-sigma ($\hat{C}_{pk}$ = 1.33) as the typical sigma level in the industry, and;

3-sigma ($\hat{C}_{pk}$ = 1) as the minimum acceptable quality level.

Process performance index

$\hat{P}_p$ **Index:** Process performance indexes, $\hat{P}_p$ and $\hat{P}_{pk}$, rank how well the data fits within the specification boundaries, and rank how centralized the data is within the specification boundaries. They should be used when total production is known, and the laboratory is testing the performance of a production method. Mathematical models differ in using standard deviation rather than an $\bar{R} / d_2$ or s / C_4 ratio.

$\hat{P}_p$ is calculated using a model similar to $\hat{C}_p$:

$$\hat{P}_p = \frac{USL - LSL}{6s} \tag{6}$$

where USL is the specified upper limit, LSL is the specified lower limit, and s is the standard deviation of the overall results (general standard deviation).

$\hat{P}_{pk}$ **Index**

The calculation of $\hat{P}_{pk}$ is identical to $\hat{C}_{pk}$, also differing in the use of s. It is determined using the models:

$$\hat{P}_{pk,\,upper} = \frac{USL - \bar{x}}{3s} \tag{7}$$

$$\hat{P}_{pk,\,lower} = \frac{\bar{x} - LSL}{3s} \tag{8}$$

where $\bar{x}$ is the average of the production process. $\hat{P}_{pk}$ is equal to the lower index. To determine $\hat{P}_{pk}$ when a specification range with

double limits is used, the $\hat{P}_{pk,\,\text{upper}}$ and $\hat{P}_{pk,\,\text{lower}}$ is first determined. Then the minimum index, $\hat{P}_{pk} = \min\left[\hat{P}_{pk,\,\text{upper}}, \hat{P}_{pk,\,\text{lower}}\right]$, is selected.

RESULTS

Figure 1 illustrates a process capability histogram with lower and upper specifications and a boxplot for hematocrit (ratio) in a sampling of 30 *red cells, leucocyte depleted in additive solution* components.

DISCUSSION

The $\hat{C}_p$ model is adapted from the C_p model as the sigma σ process is practically immeasurable and is replaced by a standard deviation estimate.

C_p classifies how the distribution of results fits within the specification limits. This index represents the relationship between the range of specification limits and the process range. There is no information if the process is within specifications. The value is always positive.

This can be interpreted as the index with the mean closest to the specification limit. The C_{pk} index is the ratio of the difference between the specification limit range (or vice versa) and the process mean for the process range. If the value is less than one, there are values out of specification. If the value is exactly zero, half of the values are out of specification.

Regularly, $\hat{C}_{pk}$ it is chosen $\hat{C}_p$ because it has a recognized limitation, assuming that the variability of the process is centered on the extent of the specification, which is not true in all cases. $\hat{C}_{pk}$ is statistically reliable in this condition. When a process is centered, $\hat{C}_p$ is equal to $\hat{C}_{pk}$. Both indexes should never be estimated from a small number of samples, as the results are unrealistic due to the sampling not being statistically representative of the production. If the C_p index is greater than C_{pk}, the process is decentralized.

Like the $\hat{C}_p$, $\hat{P}_p$ is not useful to identify in the process out of specification. The results for P_p and C_p differ because the standard deviation within the rational subgroup is less than $\overline{R}/d_2$. Both have the same limitation on centralization, which no one considers. They can be uniquely determined when USL and LSL limits exist, so they cannot be applied to some of the parameters used to control the production of blood components.

The process performance index estimates the process capability of a manufacturing process during its initial setup before being placed into a state of statistical control. However, it can also be used with capability indexes, given the small samples taken in transfusion medicine services, but never as an alternative to these. In the examples $\hat{P}_p$ and $\hat{P}_{pk}$, the indexes are not significantly different from $\hat{C}_p$ and $\hat{C}_{pk}$. Larger values of P_{pk} can be interpreted to indicate that a process is more capable of producing an output within the specification limits, although this interpretation is not consensual. Statistically, P_{pk} is meaningless if the process under study is not in control because one cannot reliably estimate the underlying probability distribution process.

Figure 2 shows a set of examples where P_{pk} analysis is

valuable to understand process capability better. **Figures 2-a** to **d** show a set of cases where the mean is around the centerline. **Figure 2-a** illustrates a case where the process is super with C_{pk} and P_{pk} indexes greater than two. **Figure 2-b** shows an example of the process with C_{pk} and P_{pk} indexes between one and 1.33. **Figure 2-c** demonstrates the case of a process not capable due to the two lower indexes. **Figure 2-d** shows an example where according to C_{pk} the process is classified as super, but according to P_{pk}, the process is not capable. The difference is due to the standard deviation and general standard deviation computation models. The process should be carefully monitored through control charts and decision rules. **Figure 2-e** illustrates a case of centerline deviation with data with low variance (similar to the results of **Figure 2-a** standard deviation) with an insignificant difference between the estimates. Finally, **Figure 2-f** illustrates the case where the internal and overall standard deviations are close (identical to the estimates in **Figure 2-b** and less than one. Capability is influenced in this example by a shift in the centerline.

Figure 1 shows a manufacturing process histogram with lower and upper limits. $\hat{C}_{pk}$ of 2.24 indicates that the process is super, so minimal quality control is required. The $\hat{C}_{pk}$ index is in agreement with $\hat{C}_p$, $\hat{P}_p$, and $\hat{P}_{pk}$ favoring a statistically stable process.

Sigma represents the standard deviation number of a given process. A 3-sigma process has 2600 parts per million (ppm) defective and is recognized as the minimum capability index in production. A 6-sigma process has an exclusively 3.4 ppm defect. Consequently, a 6-sigma process has a lower chance of manufacturing products out of specification when compared to a 3-sigma process. Sigma can be calculated simply by multiplying C_{pk} by three, being analogous to the C_{pk} performance in **Figure 2**.

Consequently, the performance typically required is around 4 sigma. As can be seen, the ratings approach C_{pk} levels. The production of blood components has some parameters with performance higher than 6-sigma, equivalent to "world-class quality". However, some never reach a high sigma level, mainly due to the biological variation of the tested parameters. For further details on the 6-sigma concept, see [10]. Typically, a
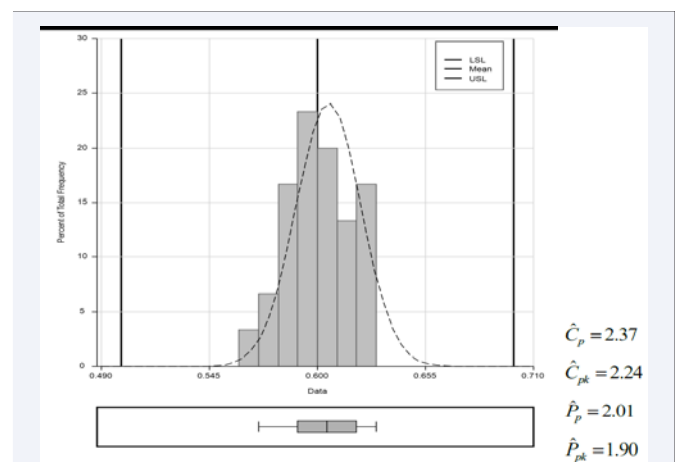

$\hat{C}_p = 2.37$

$\hat{C}_{pk} = 2.24$

$\hat{P}_p = 2.01$

$\hat{P}_{pk} = 1.90$

Figure 1 Process capability for hematocrit (ratio) in a sampling of 30 red cells, leucocyte depleted in additive solution components.

A) $C_{pk} = 2.70; P_{pk} = 2.99$

B) $C_{pk} = 1.17; P_{pk} = 1.22$

C) $C_{pk} = 0.51; P_{pk} = 0.55$

D) $C_{pk} = 2.44; P_{pk} = 1.38$

E) $C_{pk} = 0.94; P_{pk} = 0.93$
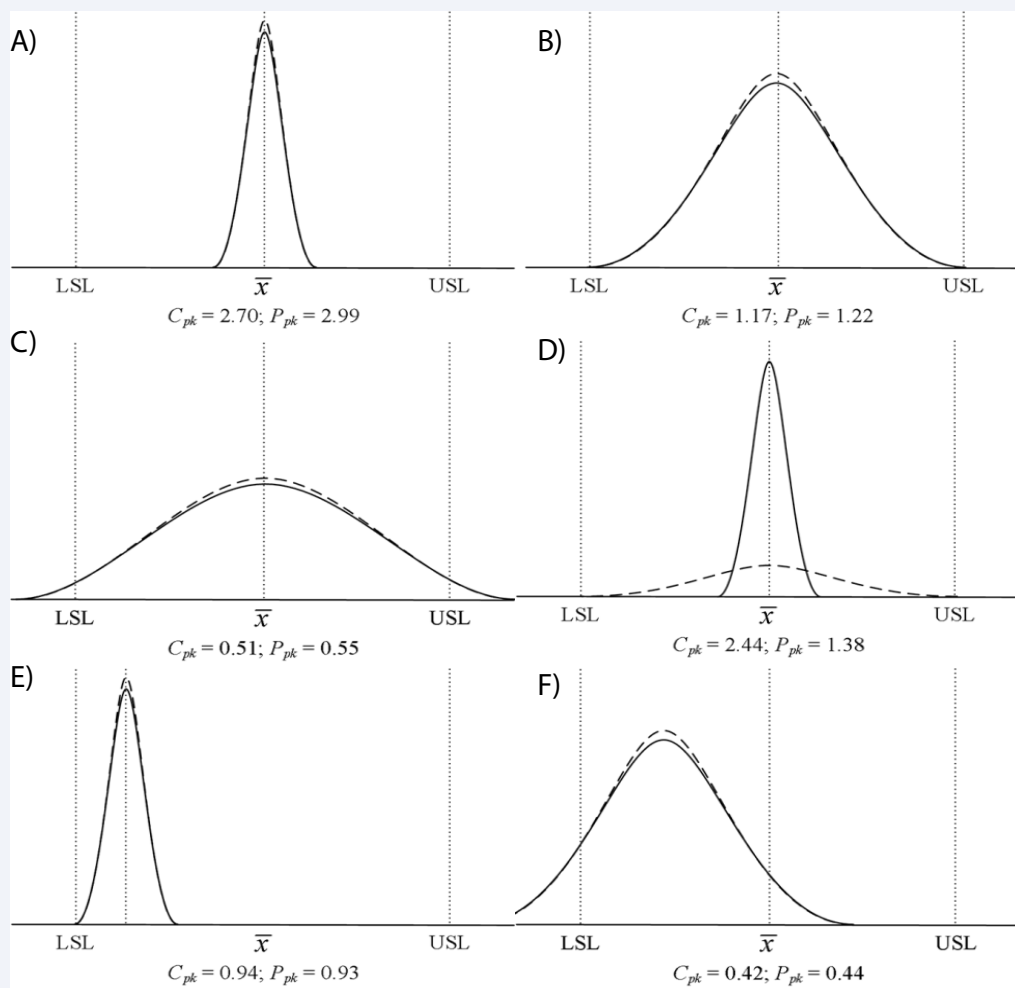
F) $C_{pk} = 0.42; P_{pk} = 0.44$

Figure 2 Four cases of process capability and performance indexes.

manufacturing process is classified as "world-class quality" when the average results are "on target" with "minimal variation". Working with "minimal variation" is only practicable when the process shows a reasonable degree of statistical control.

The difference between C_p and P_p and C_{pk} and P_{pk} is not significant if the distribution is normal and the process is under control since the difference between the internal standard deviation ($\bar{R}/d_2$) and the general standard deviation it's smaller. However, in cases with unnatural sources of variation, the C_{pk} index is greater than the P_{pk}. We suggest using it together with C_p and C_{pk}. The C_p and C_{pk} indexes should be close in the P_p and P_{pk} results. If C_p and C_{pk} are significantly higher than P_p or P_{pk} (minimum one-third higher), the process may not be stable enough to calculate capability ratings. In this case, the assessment of process stability is mainly done through graphs rather than process capability indexes, using a rigorous quality control strategy.

A strict corrective-action/preventive-action (CAPA) policy should be implemented, focusing on opportunities for improvement. These actions are critical for the continuous improvement of production processes.

In conclusion, the use of the C_{pk} or Sigma metric for production control is suggested. The use of the process performance index is only suggested as a complement to the C_{pk} or Sigma index. Furthermore, the approaches can be transposed to functions in spreadsheets, such as small transfusion medicine services. For more extensive services or those involving statistically complex techniques, it is suggested to use commercial software which can be found anywhere. Under certain conditions, the use of quality control/biostatistics consultancy can be recommended.

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