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Statistical control of the production of blood components by control charts of attribute to improve quality characteristics and to comply with current specifications

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ABSTRACT

Statistical process control (SPC) is closely related to good quality control practices in the manufacturing process. One of the primary goals is to detect unnatural patterns, allowing the production service to control the conformity of the blood components produced. Despite being recommended by national and international standards, its exercise is not uniform, and sometimes the methodology used is misinterpreted as SPC. When the input data has a Gaussian distribution, control charts for variables are proposed. However, when the data distribution is not normal, control charts for attributes are suggested. This article presents and discusses four statistical procedures for the control of attributes using *p*-, *np*-, *u*-, and *c*-charts. An empirical demonstration shows these models are reliable for in routine use in the Blood Establishment quality control, as also suggests the use when the control charts for variables are inapplicable.

1. Introduction

This manuscript follows our previous What's Happening article, where the general principles of statistical process control (SPC) in the production of blood components and control charts for variables are discussed. For a more in-depth understanding of the basic concepts related to the SPC principles and its implementation in a Blood Establishment, the causes of variation, data reliability, and the importance of the normal distribution on the quality control, see [1]. It must be emphasized that the control of the production of blood components is mandatory by The European Directive 2002/98/EC [2] and The European Committee (Partial Agreement) on Blood Transfusion (CD-P-TS) TS111 "Good Practices Guideline" [3]. The TS111 stipulations are included on the 19th edition of The European Directorate for the Quality of Medicines & HealthCare (EDQM) of the Council of Europe guideline (Appendix 4 of [4]). Such requisite is also part of the American Association of Blood Banks (AABB) standards [5].

SPC could be understood as an influential group of problem-solving tools valuable in attaining process stability and improving capability through the decrease of the variability. If a blood component is to meet or exceed specifications, it should be manufactured by a stable or repeatable process. Consequently, the production process must be capable of operating with little variability around the target or nominal dimensions of the quality characteristics of the blood components.

It is noteworthy to mention that the common/natural/expected causes of error are predictable roots of failure mutual to any manufacturing process. In this condition, the special error is higher than what is probable. Therefore, special causes of failure are supposed to happen. The variance and out-of-specification results are considered predominantly in a short-term strategy. The common and special causes are observed in a long-term. The long-standing method is also intended to the constant satisfaction of high-quality specifications, preventing measures and significantly decreasing the products' price. The short-term is associated primarily with the corrective actions, and long-term with opportunities for improvement.

Moreover, specification limits are designated agreeing to the requirements for blood components. The uses of control charts are intended to identify nonconforming lots or individual components and to detect trends. Capability indexes are used to measure and classify the level of production ability to meet the specifications. Hence it should be clear that blood component samples are verified according to requirements, not according to control limits. A manufacturing process is

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classified as “world class quality” since the attribute results are “on target” with “minimum variance.”

The primary choice of charts in SPC is the control charts for variables. However, since subgroups data is not normally distributed, two alternative strategies are applicable: (a) control charts for variables using normal transformed data or (b) control charts for attributes. In the situation that a characteristic/parameter to be checked cannot be suitably represented numerically, each result is inspected and classified as conforming/nondefective or nonconforming/defective to a specification. This type of characteristics is referred as attributes. For instance, the case of the parameter to be checked in *platelets*, *apheresis*, *leucocyte-depletedin additive solution* is the residual leucocyte count. This measurand distribution is close to a negative binomial distribution (NBD) [6]. On this scenario, the attribute is a characteristic of the number of leucocytes according to a specification: $< 1 \times 10^6$ or $\geq 1 \times 10^6$ per unit, respectively, conforming or not conforming to the EDQM guideline (Component monographs Part C. Platelet components of [4]). Control charts for attributes are recognized as necessary on an SPC strategy as an alternative to the charts for variables. They help to classify areas of production by priorities of improvement, they are essential to administrative processes due to its focus on defects and defective products, and because they distinguish common causes from special causes. Control charts for attributes are applied to determine if the defective product rate is stable and distinguish a deviation from stability in a production process. Several types of control charts are available according to the attributes type and sampling methods. The four main models are considered: *p*-, *np*-, *u*-, and *c*-charts.

Sampling practices suggest testing a representative lot of the manufacturing in controlled conditions consistent with good practices. The proportion is related to full produced blood components for a specified period. Therefore, an appropriate sampling method is needed. The use of inadequate sampling methods could origin biased results followed by biased decisions. It could be applied simple random, systematic, and stratified sampling models [7]. For a more in-depth discussion on sampling models of produced blood components, see [8]. See [9] for further details on SPC applied to the production of blood components.

The focus of this article is the selection and implementation of suitable control charts for attributes as an SPC methodology in a Blood Establishment following current best practices. The cases are from the database of the Quality Control, Portuguese Institute of Blood and Transplantation, Portugal.

2. Material and methods

2.1. Control charts for attributes

The control charts for attributes require a count of a characteristic/attribute of a parameter to be checked (input) instead of an analytical measurement. For instance, the case of the residual leucocyte count checked in *platelets, apheresis, leucocyte-depleted in additive solution*. The classification of attribute results is according to the state of conformity, i.e., no/yes, non-conforming/conforming. Let contemplate *p*-, *np*-, *u*-, and *c*-charts. On a brief introduction, *p*-charts are used to control discrete attribute data. It is intended to control defective and non-defective components in a production process. This chart plots the proportion *p* of the data falling into the relevant category over time using sampling with dimension not fixed. *np*-charts is aversion of the *p*-chart used to control data from a fixed subgroup, i.e., a sample with the same size. The *np*-chart shows the number of occurrences in a category over time rather than the proportion in the category. The actual amount in a category is determined by multiplying the samplesize *n* by proportion *p*. *c*-charts is close to the *np*-chart since both require a fixed number of samples per data point. However, differently, fromthe *np*-charts that represent the proportion data in a specific category, *c*-charts plots count data, i.e., the number of defects/nonconformities. Finally, the *u*-charts, which is a more general version of the *c*-chart oriented to data points that do not come from an equal number of samples. Since the sample sizes are different, the control limits are mobile. Typically, the number of subgroups m is ≥ 25, and the number of samples n is usually from three to five.

2.1.1. Defective products (nonconform products)

2.1.1.1. p-chart with variable sample size. The center line is equal to the average of the number of process fraction nonconforming p. The mathematical model is as follows (entry 7.2 of [10]):

$$\overline{p} = \frac{\sum_{i=1}^{m} D_i}{mn} = \frac{\sum_{i=1}^{m} \hat{p}_i}{m} \tag{1}$$

where a number of nonconforming samples i, p_i is the ratio of nonconforming samples i, $i = 1, \ldots, m$, m is the number of preliminary samples, and n is the number of samples of the rational subgroup. m should be no less than 20.

The control limits, the upper control limit $UCL_{\overline{p}}$, and the lower control limit $LCL_{\overline{p}}$, are computed using the following models:

$$UCL_{\overline{p}} = \overline{p} + 3\sqrt{\frac{\overline{p}(1-\overline{p})}{n}} \tag{2}$$

where $\overline{p}$ is the average of the ratio of nonconforming samples, and n is the number of samples of the rational subgroup, and;

$$LCL_{\overline{p}} = \overline{p} - 3\sqrt{\frac{\overline{p}(1-\overline{p})}{n}} \tag{3}$$

2.1.1.2. np-chart with fixed sample size. The center line is equal to the average of the number of the defectives in sampling $\overline{p}$. The model derived from the Eq. (1), as follows (entry 7.2 of [10]):

$$n\overline{p} = \overline{p}(n) \tag{4}$$

where $\overline{p}$ is the average of the number of process fraction nonconforming, and n is the number of samples of the rational subgroup.

The control limits, the upper control limit $UCL_{n\overline{p}}$, and the lower control limit $LCL_{n\overline{p}}$, are calculated using the following models:

$$UCL_{n\overline{p}} = n\overline{p} + 3\sqrt{n\overline{p}(1-\overline{p})} \tag{5}$$

where $\overline{p}$ is the average of the ratio of nonconforming samples, and n is the number of samples of the rational subgroup, and;

$$LCL_{n\overline{p}} = n\overline{p} - 3\sqrt{n\overline{p}(1-\overline{p})} \tag{6}$$

2.1.2. Defects (nonconformities)

2.1.2.1. u-chart with variable sample size. The u rate mathematical model is as follows (entry 7.2 of [10]):

$$u = \frac{x}{n} \tag{7}$$

where x is the number of nonconformities in a sample, and n is the number of samples of the rational subgroup.

The center line $\overline{u}$ is equal to the average of the number of process fraction nonconforming u.

The control limits, the upper control limit $UCL_{\overline{u}}$, and the lower control limit $LCL_{\overline{u}}$, are computed using the following models:

$$UCL_{\overline{u}} = \overline{u} + 3\sqrt{\frac{\overline{u}}{n}} \tag{8}$$

Where $\overline{u}$ is the observed average number of nonconformities per unit in a initial set of data, and n is the number of samples of the rational subgroup, and;

$$LCL_{\overline{u}} = \overline{u} - 3\sqrt{\frac{\overline{u}}{n}} \tag{9}$$

2.1.2.2. c-chart with fixed sample size. The c is the number of