Chapter

Combining Capability Indices and Control Charts in the Process and Analytical Method Control Strategy

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Abstract

Different control charts in combination with the process capability indices, C_p, C_{pm} and C_{pk}, as part of the control strategy, were evaluated, since both are key elements in determining whether the method or process is reliable for its purpose. All these aspects were analyzed using real data from unitary processes and analytical methods. The traditional x-chart and moving range chart confirmed both analytical method and process are in control and stable and therefore, the process capability indices can be computed. We applied different criteria to establish the specification limits (i.e., analyst/customer requirements) for fixed method or process performance (i.e., process or method requirements). The unitary process does not satisfy the minimum capability requirements for C_p and C_{pk} indices when the specification limit and control limits are equal in breath. Therefore, the process needs to be revised; especially, a greater control in the process variation is necessary. For the analytical method, the C_{pm} and C_{pk} indices were computed. The obtained results were similar in both cases. For example, if the specification limits are set at ±3% of the target value, the method is considered "satisfactory" ($1.22 < C_{pm} < 1.50$) and no further stringent precision control is required.

Keywords: control chart, average run length, capability indices, critical values, lower confidence bound

1. Introduction

At first, it is impossible to determine the quality of a product. However, it is necessary that the manufacturing processes are in control and stable as well as all the involved unitary processes in order to reduce the process variability. When an analytical procedure is performed on a sample, this is itself a process just as the manufacturing operation is a procedure. By analogy, we can apply the same rules and principles.

Control charts, as online statistical process control procedure, represent the first option for achieving this objective. Statistical process control allows to analyze the process stability and to estimate the process capability, knowing the level of

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variability. The Shewhart control chart is the most used technique to detect statistical changes in process quality. Walter A. Shewhart of the Bell Telephone Laboratories developed it in 1924. The control chart can be used as an estimating device, for example, process parameters such as the mean, standard deviation, fraction nonconforming, and so on may be estimated from a control chart. In addition, these estimates may be used to determine the capability of the process to produce acceptable results [1]. Shewhart control charts are effective when the in-control process data are stationary (i.e., the process data vary around a fixed mean in a stable manner) and uncorrelated. Under these conditions, their performance is predictable, allowing out-of-control situations to be reliably detected. In this type of control chart, the first step is as follows: a set of process data are collected and analyzed all at once in a retrospective analysis, constructing different control limits (such as warning and action control limits) in order to verify if the process is in control over the time during the collection of data. Second is to check if these limits can help to monitor future productions or samples. Alternatively, chart based on standard values allows specifying standard values for the process mean and standard deviation without analysis of the past data. A limitation of Shewhart control charts is that it uses only the information about the process contained in the last analyzed sample, ignoring any information provided by the set of collected data. This fact makes the Shewhart control chart relatively insensitive to small process shifts, about 1.5 standard deviations or less. The exponentially weighted moving average (EWMA) and the cumulative sum (Cusum) control charts are two good options in those situations where it is important to control small process shifts. Roberts [2] and later Crowder [3] and Lucas and Saccucci [4] introduced the EWMA control chart which analyzed different aspects of interest in detecting small changes in the process. Other authors, such as Lucas [5], Hawkins and Olwell [6], indicate that the Cusum control is more effective than the traditional Shewhart control chart in this type of situations.

In industrial activities or in the laboratory, it is necessary to obtain information about the performance of the process or analytical method when it is operating under statistical control. For this, the process or analytical method is in control and stable. Process capability indices (PCIs) give an indication of the capability of a process or analytical method [7]. They are designed to quantify the relation between the desired specifications and the actual performance of the process or analytical method. In addition, the capability indices are calculated, to evaluate whether the process under study is able to provide sufficient conforming units. The capability indices could be used to evaluate whether the analytical method is only able to provide enough conforming results to check if a method is fitted for its intended purpose [8]. Various examples of the usefulness of capability indices in the framework of analytical method validation can be found in the literature [9–11]. At first, the methodology described earlier can be applied to any process or analytical method in statistical control.

The main objective of this work was to evaluate the use of control charts in combination with the process capability indices as key elements in determining whether the process or analytical method is fitted for its purpose. The process capability indices, C_p, C_{pk}, and C_{pm}, were computed. The level of variability (i.e., method or process performance) was evaluated through the control chart, whereas the method or process specifications (i.e., analyst/customer requirements) were analyzed under different criteria based on the specification limit range. Finally, to determine whether the process or method meets the present capability requirement and runs under the desired quality conditions, the Pearn and Shu [24] method

was used. All these aspects were analyzed using two examples: (1) the upper punch compaction force data obtained in a tablet manufacture process and (2) the RP-HPLC method data used for insulin quantitation in pharmaceutical preparations [12].

2. Control chart in unitary process

2.1 X-bar and MR-control chart

The stability of a process is an important property, since if it is stable in the current time frame, it is also likely to be so in the future, assuming that no major changes occur [13]. This means that the process variation is due only to random causes and all assignable or special causes have been removed. If this is fulfilled, one can draw conclusions about the process capability and use the result for predicting it in future or other conditions. Usually, the process mean is monitored using location charts such as the x-chart, and the process dispersion is monitored using dispersion charts such as the R- or S-chart [1]. These control charts are based on samples (or subgroups) of n observations taken at regular sampling intervals. There are, however, many applications in which the control charts are based on individual observations ($n = 1$) rather than samples of $n > 1$. In such cases the R-chart cannot be used, as it is impossible to calculate the within-sample variation when the sample size equals 1.

The control charts discussed above are designed under the assumption that a process being monitored will produce measurements that are independent and identically distributed over time, when only the inherent sources of variability are present in the process. For this, it is necessary to check the normality of the data, which is assessed through Q-Q plots and using statistical tests (e.g., Anderson-Darling, Shapiro-Wilk, or chi-square). **Figure 1** shows the Q-Q plots for tablet manufacturing process. Shapiro-Wilk test confirmed that data follow a normal distribution at 5% significance level.

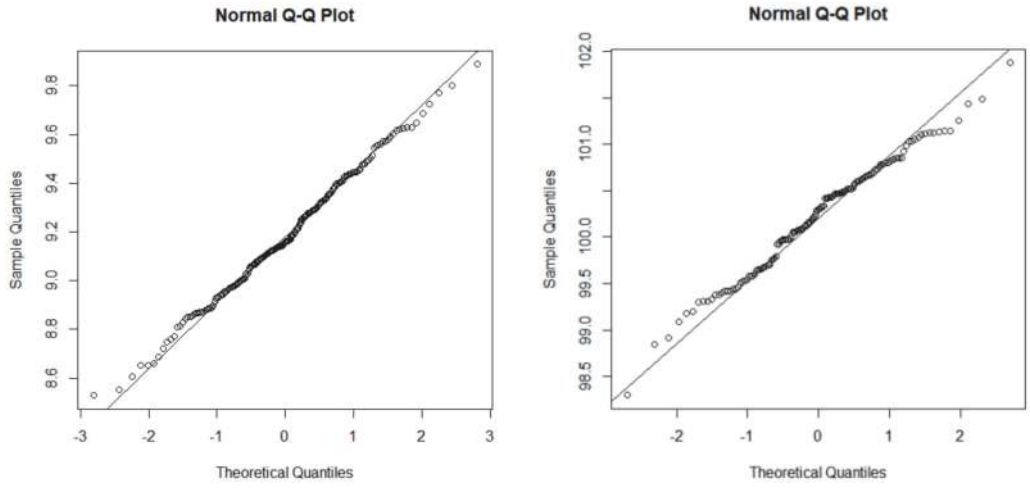

Figure 1.
Normal Q-Q probability plot for compaction process data (left) and HPLC analytical method data used for the insulin quantification (right).

Figure 2 shows the two control charts, one for monitoring the process center (x-bar chart) and the other for monitoring the process variation (MR-chart), when a separate observation is made at each sampling point [1].

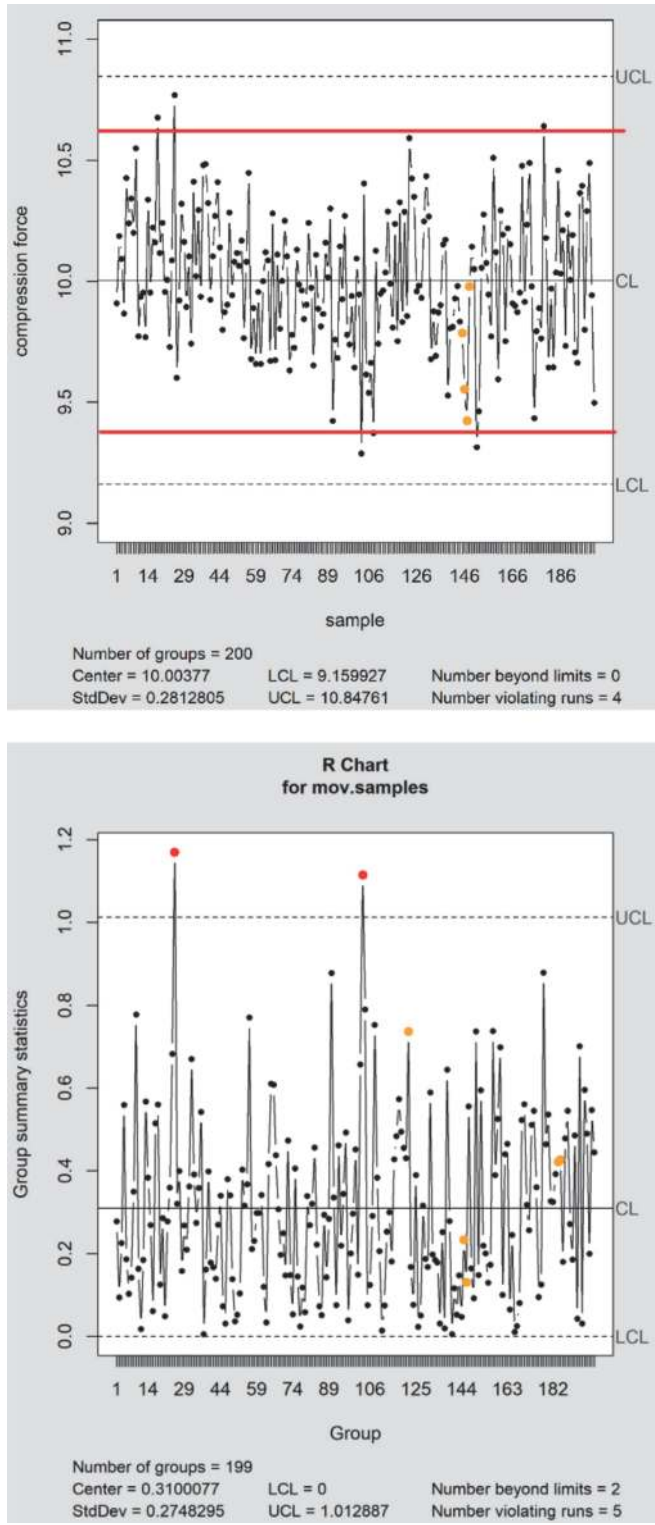

Figure 2.
Control charts for compaction process: (upper) x-bar control chart and (lower) MR-chart (UCL = upper control limit; LCL = lower control limit; CL = mean or average range for the MR-chart). The red line corresponds to the warning limits using a RSD of 6%.

For the x-bar control chart based on individual observations, the central lines (CL) and control limits (UCL and LCL) are:

$$UCL = \overline{X} + 3\frac{\overline{MR}_2}{d_2}; CL = \overline{X}; \text{L}CL = \overline{X} - 3\frac{\overline{MR}_2}{d_2} \tag{1}$$

where x-bar is the sample mean and MR2 is the mean moving range of length two.

In this case, the traditional choice is to use the moving range chart (MR-chart), which is the range of successive individual observations, to detect changes in the process variation [1].

$$MR_i = |x_i - x_{i-1}| \tag{2}$$

For the moving range charts, the following equations with n = 2 are used to establish the CL and control limits, respectively:

$$LCL = \overline{MR}_2 \cdot D_4; CL = \overline{MR}_2; UCL = \overline{MR}_2 \cdot D_4 \tag{3}$$

In formulating the control limits of x-bar and MR-control charts, several factors, d_2, D_3, and D_4, are constant, dependent on n, and assuming normal data distribution [14]. These values are tabulated and can be found in the bibliography [1]. In our case, d_2 = 1.128 and D_4 = 3.268, respectively.

In this first example, we used the upper punch compaction force as variable. The data used in this example were generated using a compress machine (model Korsch AG XP-1) for 10 min with a sample frequency of 20 samples/min. The collected data corresponds to the acetaminophen tablet batch to laboratory scale (data not published).

The data analysis was performed using the R-program (version 3.6.1) and plotted using the "qcc" package [15].

Given the approximate normality of the data, we can use the x-chart to estimate the process mean, obtaining a value of 10.0 kN, whereas the MR-chart provides the process standard deviation, obtaining a value of 0.31 kN.

Figure 2 shows the x-bar control chart for the compression force variable. All plotted values fall within the control limits (9.16, 10.85), and therefore, the process is in statistical control. In addition, there is no evidence of cyclical or periodic behavior. However, there is a located zone between samples 148 and 152 indicating the nonrandom patterns present. This situation is related with the presence of "eight consecutive points plot on one side of the center line" [1] according to the application of decision rules for detecting this type of variation.

In the compaction process, it is usually to fix the warning limits at ±6% of the mean value (RSD = 6%). In such situation, there are six points beyond these limits, indicating the existence of a problem during the process. The MR-control charts exhibit two points above the upper control limits (UCL = 1.013), and therefore the process should be considered out of control (**Figure 2**). However, a point above the upper control limit followed immediately by a point below control limit would not signal an out-of-control alarm. A similar situation was observed when the warning limits were fixed at ±6% of the mean value. In addition, the control charts show other forms of nonrandom variation; all of them are due to the presence of "eight consecutive values on one side of the centerline." It is true that, when a point is plotted outside of the action limits, a search for an assignable cause is made and corrective action is taken if necessary. We have no explanation for this. The causes could be various: particle size and shape distribution, flow properties of the bulk

material, mix process, tablet weight, etc. In this last case, we weighted some tablet during the manufacture process, the mean value being 700 ± 5 mg (n = 40), but this tablet batch does not satisfy the proposed fragility test by the USP [16]. Therefore, the process may not be operating properly. In this case, the sensitivity of the control chart should improve, changing the sampling frequency and/or the sample size in order to obtain more information about the process.

This strategy may increase the risk of false alarms and be confusing to the operating personnel. In such situation, the average rung length (ARL) of the control chart is a good alternative. The ARL is the average number of points that must be plotted before a point indicates an out-of-control condition. If the process observations are uncorrelated, then in any Shewhart control chart, the ARL can be calculated as:

$$ARL = \frac{1}{p} \tag{4}$$

where p is the probability that any point exceeds the control limits. For the control at three sigma limits, p = 0.0027, and therefore, an out-of-control signal will be generated every 370 samples, on the average, even if the process remains in control. Some analysts like to report percentiles of the run length distribution instead of just the ARL [1]. The 10th and 50th percentiles are used more. In our example, around 10% of the time, the in-control run length will be less than 38 samples, and 50% of the time, it will be less than 256 samples.

For the MR-control chart, the probability that any point exceeds the upper control limit (1.013) is 0.0052, and therefore, ARL is 190; this supposes that an out-of-control sample will be generated every 190 samples on the average. The second point outsider of control limits (sample #98) is too far from this value (see **Figure 2**).

2.2 Cusum and EWMA control chart

Cumulative sum and exponentially weighted moving average control charts efficiently complement the x-bar and MR-control charts when there is interest in detecting small changes in the process, around ±1.5 SD, and the sample consists of an individual unit. However, many researchers have discussed which of them is better in accordance with the level of variability that must be detected [17]. In practice, the EWMA control chart worked well with the parameters λ = 0.4 (smoothing constant) and L = 3.054 (control limit width fixed at three standard deviations), a value recommended by Montgomery [1]. Under this scenario, the sample number 112 was out of the control limits (see **Figure 3**), whereas the sample number 153 is very close to this limit. Using a value of λ = 0.2, the change was clearer, since the samples closest were also affected (data not shown). The values of λ = 0.2 and 0.05 with the respective width of control limits L = 2.814 and 2.614 are the best option to detect the average changes at order of one standard deviation.

Cusum control charts directly incorporate all the information into the sequence of sample values by plotting the cumulative sums of their deviations from a value objective [18]. Moreover, when a tendency up or down appears, it indicates the process average changes, which requires a search to determine the causes. Oliva and Llabrés described a similar situation [19]. The Cusum control chart showed a similar situation to those observed in the EWMA control chart for the sample number 112; it was out of the limits. When we fixed the shift detection at ±1 SD, the situation is totally different; 17 points were beyond boundaries, approximately 8.4%, especially located at the beginning and at the end of the process (data not shown); for a shift detection equal to ±1.5 SD, a unique value was out of this limit. However, the data

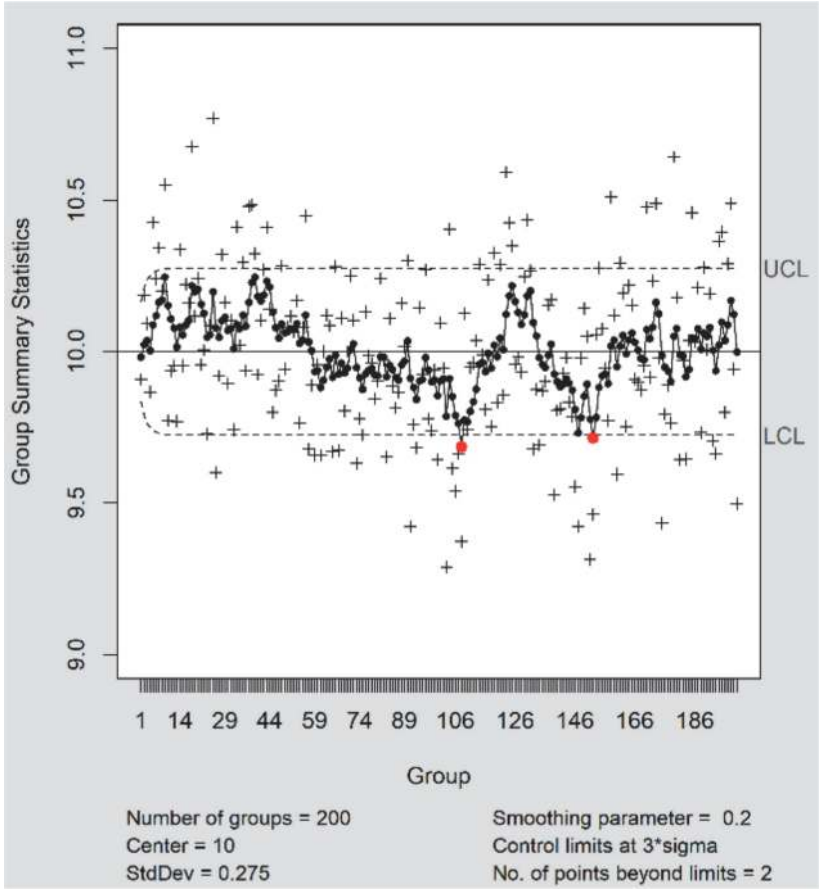

Figure 3.
EWMA control chart for the compaction process with the parameters λ = 0.2 and L = 3.054. Under these conditions, two points were beyond limits (#110 and #153, in red), whereas the number of points beyond limits was zero for λ = 0.4.

seems to describe a random way with an average of zero. There is no zone with an upward (C+) or downward (C−) tendency, perfectly defined, typical behavior of the Cusum control charts when the average process changes.

At first, the Cusum control chart performed better for detecting shifts lower than 1.5 SD. However, EWMA provided the forecast of where the average will be in the next period, which makes it easier to apply in the process control (**Figure 4**).

2.3 Computing the process capability indices and the specification limits

Details about PCIs and their statistical properties can be found in the literature [20, 21]. A capability index is generally a function of the process parameters, such as the mean μ, standard deviation σ, target value T, lower specification limit (LSL), and upper specification limit (USL) of x variable.

The C_{pm} index is the best option to drive the process (or method) to the target value since this is intended to account for variability from the process (or method) mean and deviation from the target value T [7]. For a normally distributed process that is demonstrably stable (under statistical control), Boyles [22] considered the maximum likelihood estimator of C_{pm} as:

$$C_{pm} = \frac{USL - LSL}{6\sqrt{\sigma^2 + (\mu - T)^2}} \tag{5}$$

where USL and LSL are the upper and lower specification limits, respectively. Their difference provides a measure of allowable process (or method) spread (i.e., customer/analyst requirements), whereas σ^2 and $(\mu - T)^2$ are a measure of precision and accuracy, respectively (i.e., process or method performance requirements). The mean of the process (or method) μ is estimated through the sample mean x-bar, whereas the following estimator for the standard deviation σ can be used:

$$\hat{\sigma} = \sqrt{\frac{\sum s_i^2}{m}} \tag{6}$$

where s_j is the standard deviation of each subgroup and m is the number of subgroups. If the process is monitored using the MR-control chart, the following estimator can be used:

$$\hat{\sigma} = \frac{\overline{R}}{d_2} \tag{7}$$

where $\overline{R}$ and d_2 are the average range (in our case, MR2) and tabulated constant that only depend on the sample size n, respectively [1].

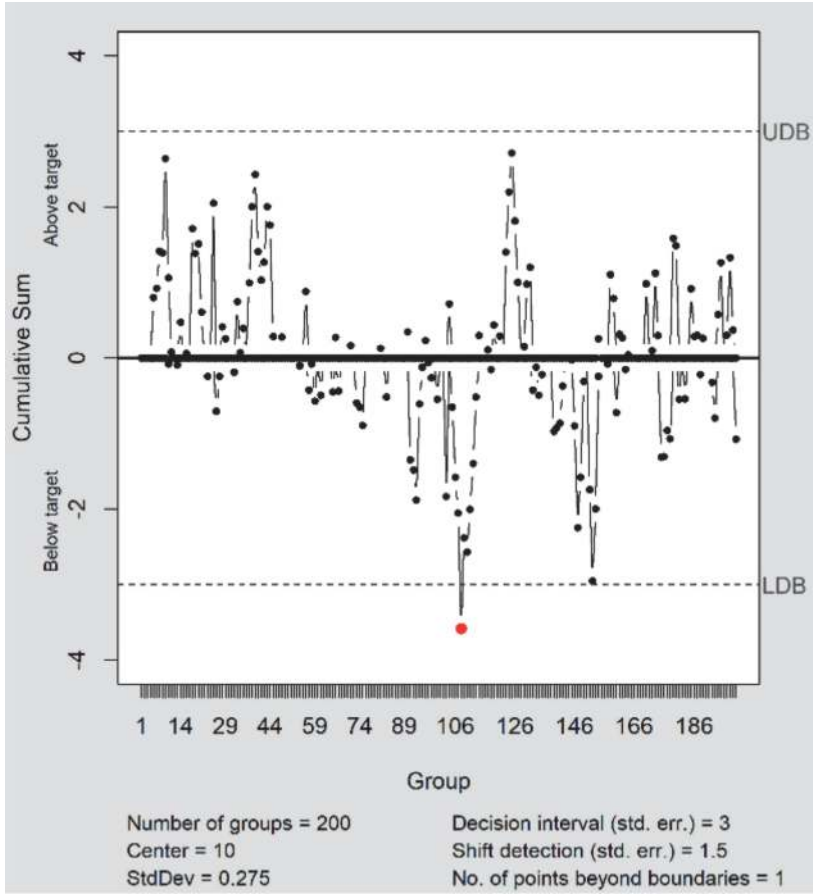

Figure 4.
Cusum control chart for the compaction process. The number of points beyond boundaries was one (#110, in red) for shift detection fixed at ±1.5 SD, whereas the number of points was 8.4% for detection fixed at ±1 SD.

The C_{pk} index is defined as the ratio of the minimal distance of the specification limits to the method average to three times the standard deviation of the method (if the average is in between the specification limits) [23].

$$C_{pk} = \min\left\{\frac{USL-\mu}{3\sigma}, \frac{\mu-LSL}{3\sigma}\right\} \tag{8}$$

C_{pk} is more commonly used because it is not dependent on the process or method being centered. However, C_{pm} is more sensitive to departure from the method target than C_{pk} is [24]. For example, when μ is within the interval of the specification limits, C_{pk} depends inversely on the method standard deviation σ (i.e., systematic error, σ^2) and becomes large as σ gets closer to zero. C_{pk} also depends on the distance of the mean from the specification limits (i.e., method centering).

If the method precision is improved, the C_{pm} will increase. If the method drifts from its target value (i.e., if μ moves away from T), then C_{pm} decreases. When both the method precision and the mean are modified, the C_{pm} index reflects these changes as well. This is also true for the C_{pk} index.

Pearn and Shu [24] proposed the lower confidence bounds "C" on C_{pm} to measure the minimum capability of the process, based on the sample data. In this case, the critical values (Co) are used for making decisions in method capability testing with a designated type-I error, α, which is the risk of misjudging an incapable method (Ho: $C_{pm} \leq C$) as a capable one (H1: $C_{pm} > C$), where C is the required process capability. This supposes that the decision-making procedure ensures that the risk of making a wrong decision will be no greater than the preset type-I error α. The algorithm proposed by Pearn and Shu [24] was used to compute the lower confidence bounds C. For this, the sample of size n, the confidence level γ (0.95), the estimated value C_{pm}, and the parameter ξ must be provided. In practice, the parameter $\xi = (\mu - T)/\sigma$ is unknown, but it can be calculated from the sample data as $\xi = \left(\overline{X} - T\right)/S_n$, S_n being the process standard deviation.

Pearn and Chen [25] and Pearn et al. [26] have developed a procedure to obtain the lower confidence bounds and critical values of C_p and C_{pk} to determine whether a process or method meets the capability requirement or not.

To calculate the PCIs, it is necessary to know the inherent variability in a process (using the control chart) and the customer requirements in terms of specification limits [27]. Control limits are set by the process and formulas; they are the voice of the process. The specification limits (LSL, USL) may be flexible, not rigorous, based on different criteria, since they represent the voice of the customer [7, 28]. The focus is to set some specification limits and compare them with the control limits of the process since they are the voice of the performance of the process (**Figure 5**).

Bouabidi et al. [8] proposed fixing the specification limits at ±5% around the true or nominal value, although Oliva and Llabrés [29] have proposed a lower variation level. The true value can be calculated using different procedures depending on variable characteristics. Other criteria could be to fix the specification limits equal to the control limits, which are just $\mu \pm 3\sigma$ if a normal distribution is assumed.

Since the method is in control, capability indices can be computed, in this case, the indices C_p and C_{pk} (**Table 1**). To calculate the C_{pm}, the method mean and variability must be estimated relative to the method target and specification limits [25]. In this case, the T value is unknown given the process characteristic; no independent approach is available to calculate it since this response depends on working conditions. If the fixed T value is equal to the process mean, this implies that C_{pm} is equal to the C_p index.

$$C_p = \frac{USL - LSL}{6\sigma} \tag{9}$$

With respect to specification limits, we cannot apply Bouabidi et al.'s [8] proposed criteria, based on variations around the target value T. Other criteria could be to fix the specification limits equal to the control limits. In this case, the C_{pk} index was 1.03. To determine if the process meets the capability requirement, we must calculate the critical value Co for C_{pk} based on α risk, sample size, and C value (i.e., the required process capability) [25]. We find the critical value Co =1.095, based on C = 1.0, α = 0.05, and sample size n = 200, demonstrating that the process fails to meet the capability requirements (**Table 1**).

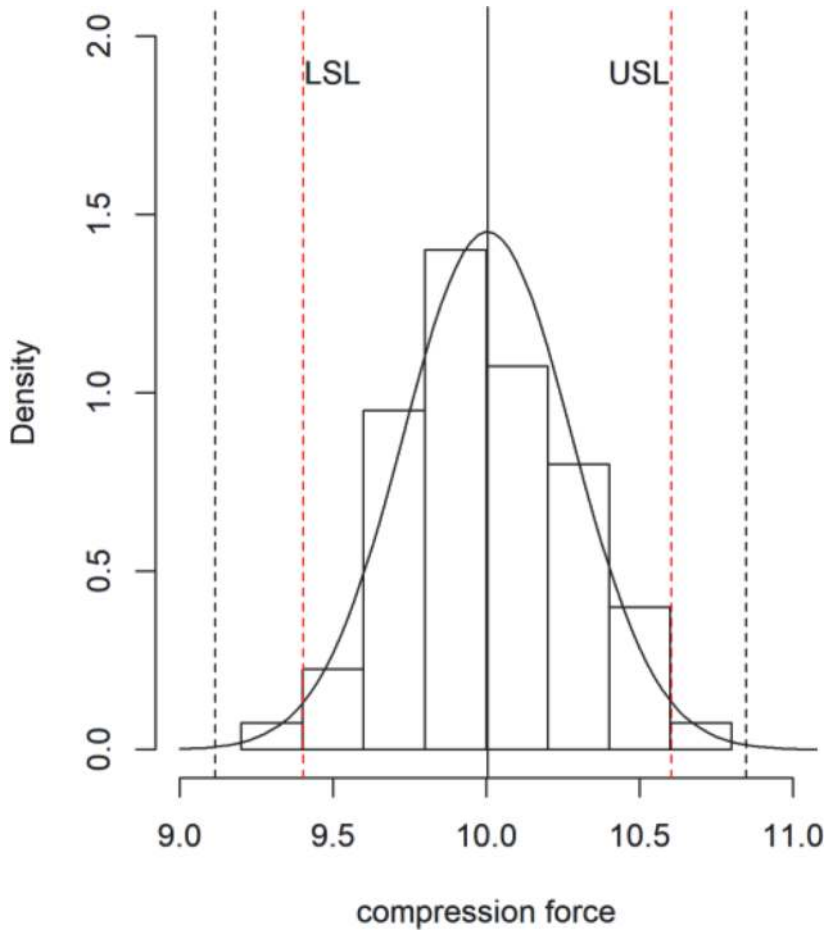

Figure 5.
The black-dashed line shows the specified limits (USL and LSL) established at ±10% of mean value, whereas the red-dashed line corresponds to limits at ±6% of the mean value. The black line is the process mean.

USL-LSL	C_p	Co	C_{pk}	Co	Process capability
±3SD	1.02	1.081	1.03	1.095	Inadequate
±6% of x-bar	0.73	1.081	0.73	1.095	Inadequate
±10% of x-bar	1.21	1.081	1.21	1.095	Capable

Table 1.
C_p and C_{pk} values as a function of the specification limit (USL-LSL). The process capability is based on the critical values (Co) according to Pearn et al. [26].

A similar result was obtained for the C_p index. A value of 1.02 was obtained, whereas the critical value Co with α risk of 0.05 was 1.081 [26], and therefore, the process does not satisfy the minimum process capability requirements.

An alternative way to increase the process capability is to improve the process performance (modifying the allowable process spread through specification limits) or reduce the process systematic error (i.e., process standard deviation). In this last case, the quality improvement effort should focus on reducing the process variation, for example, changing the sampling frequency could solve the problem.

The process performance may modify the function of the specification limit width. In the compaction process, it is usually to fix the warning limits at ±6% of the mean value (RSD = 6%). If the specification limits are fixed at this level, the estimated C_{pk} is lower than the critical value (0.73 < 1.095), and therefore, the process is not capable. If the specification limits are fixed at ±10% of the process mean value, the estimated C_{pk} value is 1.23 and exceeds the critical value of 1.095, indicating that the process is capable. This option does not suppose a real improvement in the process capability since the process conditions are maintained. The control limits are driven by the natural variability of the process, whereas the specification limits are determined externally by the manufacturing engineering, the customer, etc. We should know the process variability when setting specification limits. In our opinion, it is necessary to establish a compromise between the specification limit width and process variability.

3. Control chart in analytical method

3.1 X-bar and MR-control chart

The main objective of any validation process is to check the maintenance of validation conditions in the laboratory over a long time period. In this second example, we used the insulin peak area expressed as concentration (U/mL) as control parameters [12]. For this, a standard solution with a nominal concentration of 100 U/mL was analyzed each working day (n = 144). The predicted concentration for the standard solution was obtained from the method calibration. This value is not independent due to the measurement errors which depend on various factors related to the method and its validation but not on the analyst [29].

Histogram and normal probability plots show that the collected data follow the normal distribution (**Figure 1**). The Shapiro-Wilk test confirmed this assumption. Therefore, control charts can be used to obtain the method requirements.

The method mean was estimated to be 100.227 U/mL from the x-bar control chart (**Figure 6**), while the method standard deviation was estimated to be 0.60 U/mL from the MR-chart. The control limits were estimated using the "qcc" package from the R-program [15].

The x-bar control chart shows that all plotted values fall within the control limits (98.40, 102.06), and therefore, the method is in statistical control. In addition, there is no evidence of cyclical or periodic behavior. However, the sample (#74) was outside of the control limits, but the cause of this was attributable to introducing a new column, whereas the sample #86 was related with the presence of "eight consecutive points plot on one side of the center line" [1]. The application of decision rules for detecting nonrandom patterns on control charts indicates that, in this situation, the method is out of control. However, the use of these rules allows enhancing the sensitivity of control charts against only criterion of control limit violation.

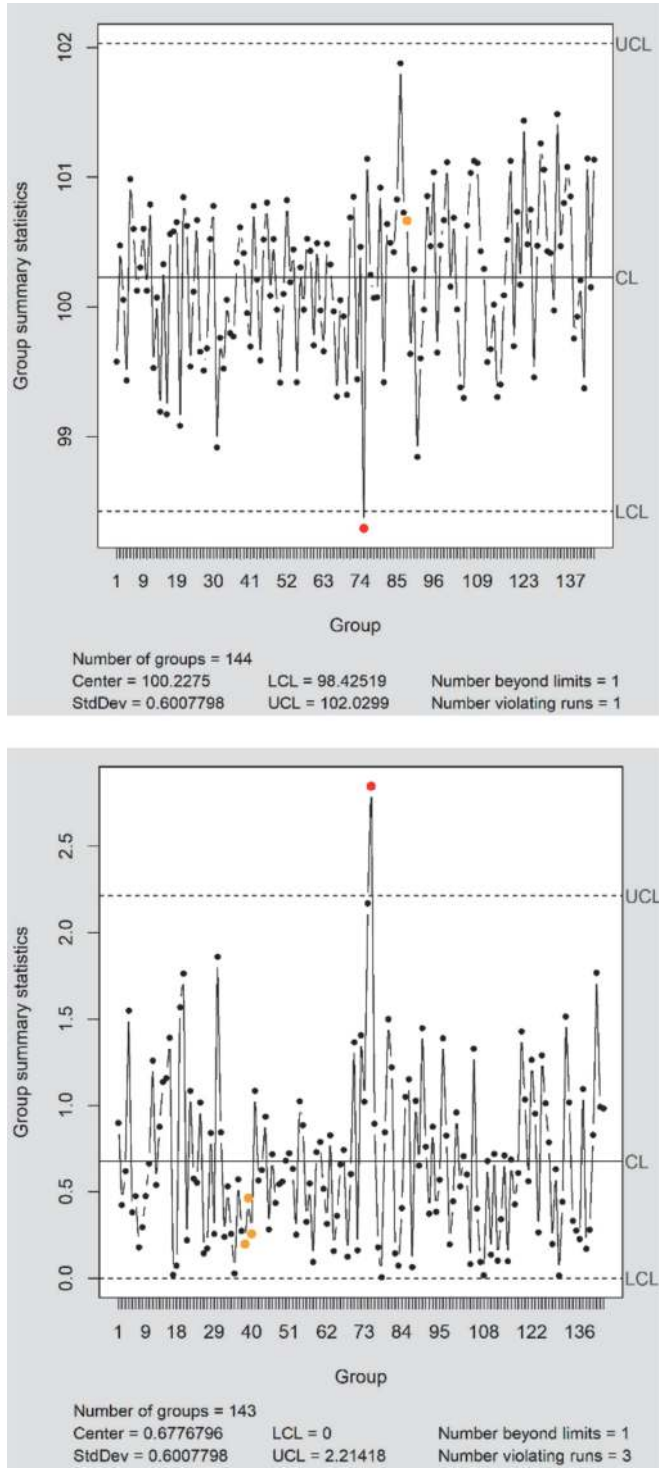

Figure 6.
Control charts for HPLC method used for the insulin quantification in pharmaceutical preparations: (upper) x-bar control chart and (lower) MR-chart. (UCL = upper control limit; LCL = lower control limit; CL = mean or average range for the MR-chart).

The ARL was 370 since the probability that any point exceeds the control limits is 0.0027.

The MR-control charts exhibit one point above the upper control limits (UCL = 2.214) as well as other forms of nonrandom variation, around the sample #40, and therefore the method should be considered out of control (**Figure 6**).

In such situation, it is necessary to search the cause and take corrective action. In the first case, the cause was assignable with a column change, whereas the second one was due to the presence of "more eight consecutive point plots on one side of the centerline."

In this case, the obtained ARL value for MR-control was 189 since the probability that any value exceeds the upper control limit was 0.0053.

3.2 Cusum and EWMA control chart

The data were analyzed using the Cusum and EWMA control charts.

The EWMA control chart shows that all plotted values fall within the control limits (**Figure 7**) using a smoothing constant of 0.2 ($\lambda = 0.2$) and control limit width fixed at three standard deviations ($L = 3.054$).

Cusum control chart, with a shift detection fixed at ± 1 SD, shows four points beyond boundaries, all of them greater than the upper control limit. The first alteration is located around the samples #84–85, whereas the second one appears close to the end of the process (#130–131). In addition, if both alterations presented an upward tendency, it indicates the process average changes, which requires a search to determine the causes. When we fixed the shift detection at ± 1.5 SD, the situation is totally different, all points fall within control limits (data not shown), and the data describe a random way with an average of zero, since the points show no evidence of an upward or downward tendency (**Figure 8**).

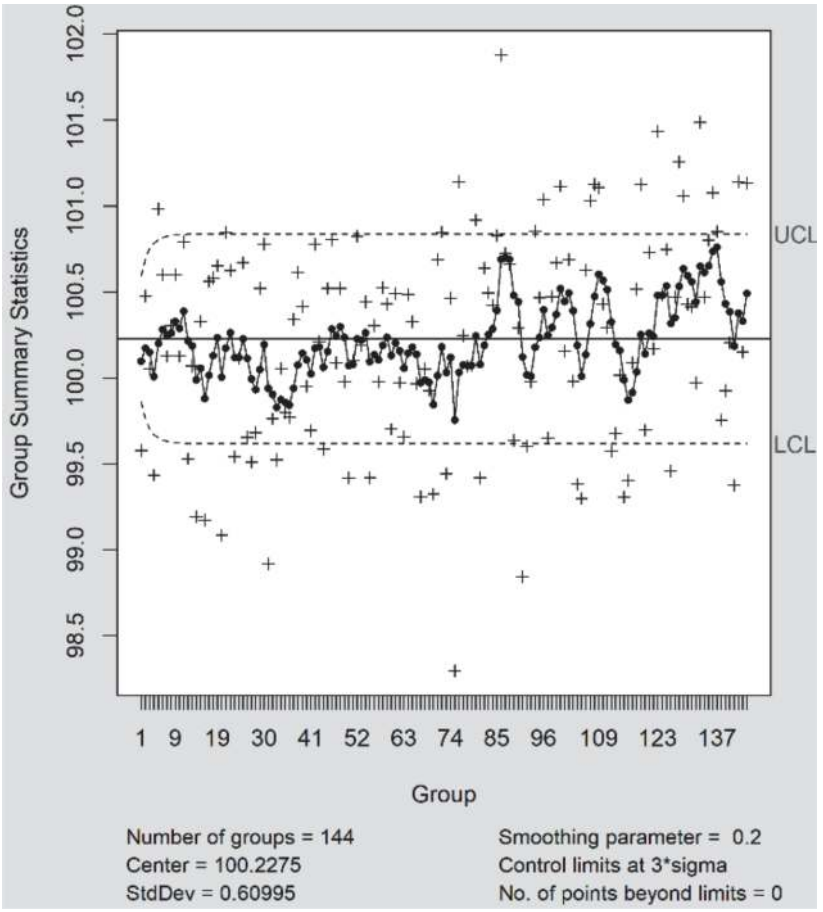

Figure 7.
EWMA control chart for HPLC method. All points fall within control limit for $\lambda = 0.2$ and $L = 3.054$.

3.3 Process capability and specification limits

Since the analytical method is in control and stable, capability indices can be computed. **Table 2** shows the estimated C_{pk} and C_{pm} indices to analyze the capability of our analytical method. The index C_{pm}, sometimes called the Taguchi index, adequately reveals the ability of the method to cluster around the target. This reflects the degree of method targeting (centering). For this, C_{pm} incorporates the variation in the method with respect to the target value and the specification limits preset by the analyst/customer [26]. This index conveys critical information regarding whether a method (or process) is capable of reproducing items satisfying a requirement that would be preset by the analyst [30]. If the prescribed minimum capability fails to be met, the method is considered incapable.

To calculate the C_{pm}, the method mean and variability must be estimated relative to the method target and specification limits [27]. In our case, the target value T corresponds to standard solution concentration (T = 100 U/mL). The analysis of the measurements during this period shows the accuracy; the average error between

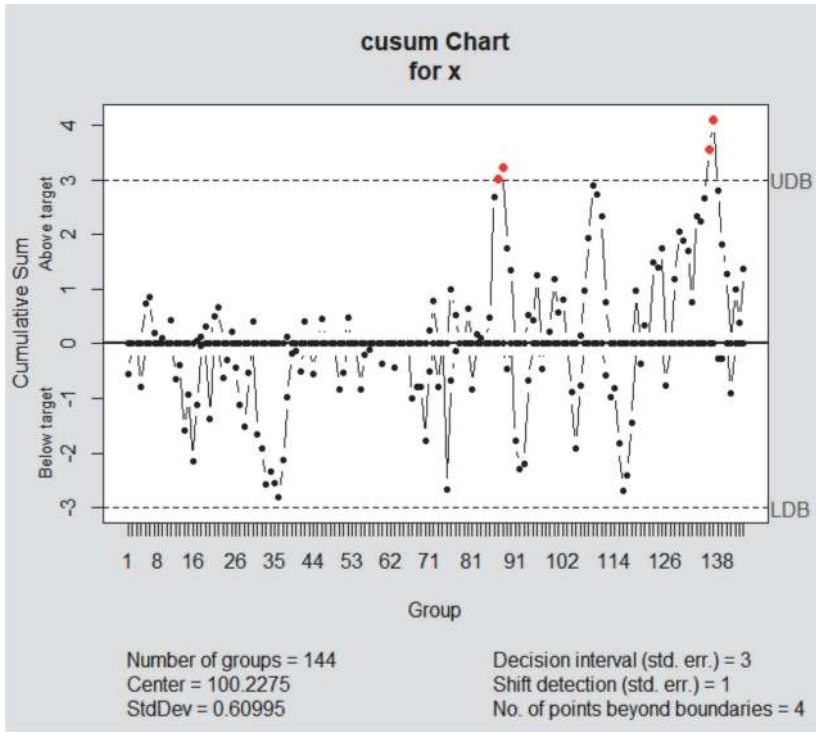

Figure 8.
Cusum control chart for HPLC method. The number of samples beyond limits was four for shift detection fixed at ±1 SD with an upward tendency. The cause of this alteration is unknown.

USL-LSL	C_{pm}	Co	C_{pk}	Co	Method capability
±3SD	0.95	1.08	0.79	1.095	Inadequate
±2.5%	1.30	1.08	1.26	1.095	Capable
±3%	1.56	1.44	1.54	1.45	Satisfactory
±5%	2.60	2.16	2.65	2.18	Super

Table 2.
C_{pk} and C_{pm} values as a function of the specification limit (USL-LSL). The method capability is based on the critical values (Co).

the mean and target concentration $(\mu - T)^2$ was 0.052 U/mL, whereas the precision calculated from the MR-chart was 0.36 U/mL. The overall uncertainty, calculated as the sum of the uncertainty of each component's contribution (precision and accuracy), was 0.41 U/mL. The expanded uncertainty was 0.82 U/mL, using a coverage factor of 2. The calculated concentration is thus 100 ± 0.82 U/mL.

If the specification limits are set at ±5% of the T value, according to Bouabidi et al. [8] criteria, the C_{pm} index was 2.60 (n = 100) with a lower confidence bound C on C_{pm} (i.e., the value used to measure method capability) of 2.48 (**Figure 9**). We therefore conclude that the true value of the method capability C_{pm} is no less than 2.48 with a 95% level of confidence. This result indicates that the method is "super" ($C_{pm} > 2.0$), and no further stringent precision control is required.

If the specification limits are reduced to ±3% of T value, the C_{pm} was 1.56 with a lower 95% confidence limit of 1.47. This result implies that the method is considered "satisfactory" ($1.33 < C_{pm} < 1.50$). The method is inadequate for specification limits lower than ±2% of the T value, since the lower 95% confidence limit for the C_{pm} is less than 1. A similar result was obtained when the specification limits and the control limits were of equal width. Thus, the number of observations out of specification in the method was zero when the specification limits are greater than ±3% of the T value, and the proportion of nonconforming results was less than 1, giving a process yield of 100%. When the reference limits and the specification

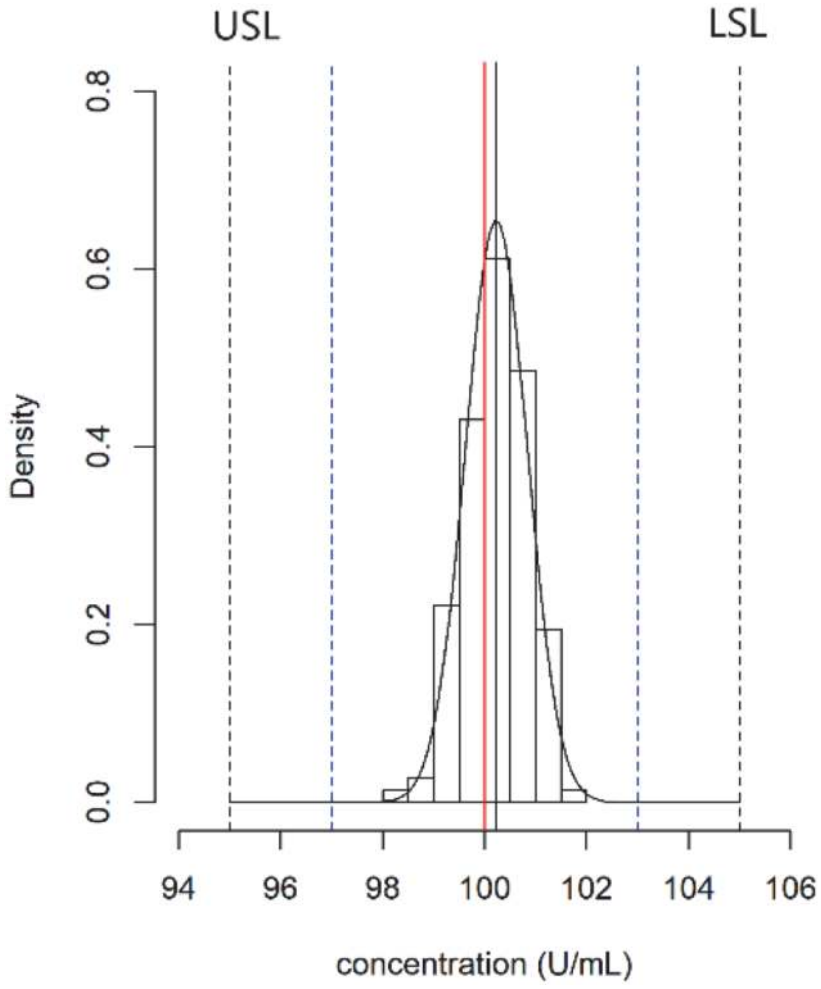

Figure 9.
The black-dashed line shows the specified limits (USL and LSL) established at ±5% of T value, whereas the blue-dashed line corresponds to ±3%. The red line is the T value.

limits are of equal width, only 0.27% of the expected observations will be out of specification in the long term, and the process yield is 100%.

The results obtained showed that we cannot use the control limits as specification limits, since the method is considered "inadequate" according to the criteria proposed by Pearn and Shu [24]. However, the control limits can be used in the development of the specification limits. In this example, a level of variability ±2.5% of T can be enough to declare the method capable ($1.0 < C_{pm} < 1.33$), as seen in **Table 2**.

All these aspects were also analyzed using the C_{pk} index. The results are summarized in **Table 2**. To determine if the method meets the capability requirement, we must calculate the critical value Co for C_{pk} based on α risk, sample size, and C value (i.e., the required method capability) [25]. We find the critical value Co = 1.081, based on C = 1.0, α = 0.05, and sample size n = 200. When the specification limits are set at ±2.5% of T value, the estimated C_{pk} value is 1.30 and exceeds the critical value of 1.081, demonstrating that the method meets the capability requirements. Furthermore, if the limits are increased to ±5% of the T value, the C_{pk} increases to 2.65 with a critical value of 2.18 (based on C = 2.00; α = 0.05; n = 200), indicating that the capability is "super." The obtained quality requirements were similar in both cases.

The use of C_{pk} is clearly preferable when the limits are not equidistant, whereas the C_{pm} index can be overly conservative in this scenario. In our case, the target is at the center of the specification range, and if the aim of our method is to achieve a measure close to the target value with minimum variation, then C_{pm} is the most sensitive capability index. Given two analytical methods with different performances (i.e., precision and accuracy) and the same method departure, a simple comparison between both C_{pm} is sufficient to select the better, although similar results were obtained with the C_{pk} index. This fact was analyzed by Oliva and Llabrés [29].

4. Conclusions

The traditional x-chart and moving range chart represent the first option to monitor the analytical method or process over a long time. The EWAMA and Cusum are two good alternatives in those situations where it is important to detect small process shifts. The capability indices are calculated to evaluate whether the process or analytical method under study is able to provide sufficient conforming results when it is operating under statistical control. To calculate the PCIs, it is necessary to know the actual performance of the process or analytical method (using the control chart) and the customer requirements in terms of specification limits. The specification limits should be determined externally from previous knowledge of inherent process variability. However, different criteria have been proposed to fix these limits. The C_{pm} and C_{pk} indices were used as part of the control strategy. C_{pk} is the best option because it is not dependent on the process or method being centered. However, C_{pm} is more sensitive to departure from the method target than C_{pk} is. Independent of the criteria used to establish the specification limits, computation of the capability indices depends on the analyzed response, and their application is limited to each particular situation and is not general.

Acknowledgements

The authors wish to thank Dr. José B. Fariña from University of La Laguna, Tenerife, Spain, for providing the compaction process data. This research was financed by Instituto de Salud Carlos III, Ministerio de Ciencia, and Innovación y Universidades y FEDER as part of Project PI18/01380.

Conflict of interest

The authors declare no conflict of interest.

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