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Evaluating the impact of periodic product review on pharmaceutical production process improvement: A case study

Carolina Macena Glória [1], Michele Lafayette Pereira [2], Fernanda Lula Figueiredo Cambuí [3], Ygor Jessé Ramos [3,*] and Claudete da Costa-Oliveira [1, 3, 4, 5]

[1] *Universidade Castelo Branco, Faculty of Pharmacy. Santa Cruz Avenue, 1631 – Realengo, Rio de Janeiro – RJ, Brazil, 21710-255.*

[2] *Universidade do Estado do Rio de Janeiro, campus Zona Oeste, UERJ-ZO. Manuel Caldeira de Alvarenga Avenue, 1203 - Inhoaíba, Rio de Janeiro - RJ, Brazil, 23070-200.*

[3] *Terra Pharmacy Laboratory, Faculty of Pharmacy, Federal University of Bahia, Barão de Jeremoaba Street, 147, Ondina, Salvador – BA, Brazil, 40170-115.*

[4] *Faculdade de Ciências Médicas, Universidade Estadual de Campinas. Albert Sabin Street, s/nº. Cidade Universitária "Zeferino Vaz", Campinas, SP, Brazil, 13083-894.*

[5] *Didactic Laboratory of Practical Classes in Pharmaceutics, Faculty of Pharmacy, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Rio de Janeiro, RJ – Brazil, 21941-902.*

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Abstract

The aim of this study was to evaluate the impact of Periodic Product Review (PPR) on improvements in the production process of pharmaceuticals by statistically analyzing the in-process control of the parameters average weight by coating and hardness.

Methods. For this purpose, a case study was conducted in a pharmaceutical industry analyzing the statistical PPR data of a coated tablet from 2021 and 2022. Diagrams and tables based on probability and statistical theory were used for the analysis.

Results. The data analysis revealed that PPR was effective in helping to identify problems in the production process, which were then resolved. As a result, the production performance of this drug product was significantly improved, as evidenced by the reduction in the variability of analytical results and process performance indicators within the acceptable range.

Conclusion. The results of this work show that PPR is an important tool for ensuring the quality of pharmaceutical products. Statistical analysis of PPR data makes it possible to identify trends and patterns that may indicate the need for improvements in the production process.

Keywords: Periodic Product Review; Statistical Process Control; Quality Assurance; Pharmaceutical Production

1. Introduction

The pharmaceutical market is intensely competitive, with companies striving to scale up production while maintaining high standards of product quality. Compliance with standards set by ANVISA (the Brazilian Health Regulatory Agency) is critical, particularly concerning Good Manufacturing Practices (GMP). These practices have been regulated by

* Corresponding author: Ygor Jessé Ramos

Resolution of the Collegiate Board of Directors (RDC) No. 658/22 since March 2022 (1,2). Quality assurance involves monitoring and documenting all production phases, including supporting areas, to ensure adherence to these standards and the quality of the final product (3).

The pharmaceutical industry is involved in research, development, manufacture, marketing, and distribution of medications. The processes for manufacturing and packaging these products require multidisciplinary efforts, which include quality control and assurance, production, regulatory affairs, marketing, research and development, and production control planning. The overarching goal of these processes is to ensure the production of effective and safe medicinal products (4,5).

Periodic Product Reviews (PPRs) are mandatory reports providing both companies and regulatory bodies with insights into the production process, including statistical in-process control. Statistical analysis of in-process control, a legal requirement, serves as a crucial tool for global evaluation and ensuring process consistency (5). Statistical Process Control (SPC) techniques are utilized to monitor the production process, identify and correct specific deviations, encourage continuous improvement, and maintain a robust and stable process. These techniques employ probability and statistical theories, which underpin the diagrams and tables used in this analysis (6,7).

Statistical control within PPRs involves various methods and parameters, with common tools including histograms, Pareto charts, cause-effect diagrams, concentration diagrams, scatter plots, control sheets, and capability charts (8). Particularly, control charts are vital for conducting SPC analysis. Performance indices evaluate the process against critical parameters, assessing a process's capability to produce within specified limits, based on process variability. These charts include specific statistics and control limits, marked by a central line and two specification limits (lower and upper). This provides a comprehensive overview of the process, identifying trends and patterns. Any deviations outside these limits may indicate an out-of-control process, requiring root cause analysis and subsequent corrective actions (7,8,9).

Although statistical methods are integral to maintaining quality in pharmaceutical production, the direct impact of these methods on enhancing production processes through regular product reviews remains underexplored, particularly within Brazilian pharmaceutical practices (9,10).

This study aims to evaluate how statistical analysis of in-process control affects regular product reviews and contributes to improvements in the production process. Conducted through a case study within a pharmaceutical company in Rio de Janeiro, the research analyzed data related to the average weights of coated tablets, seeking to highlight the benefits of a data-driven approach and how such analyses can enhance production processes. Furthermore, the study aims to identify improvement opportunities and address potential quality issues to ensure compliance with current regulations.

Tablets represent a significant segment of oral medications, with precise dose administration being crucial for safety and efficacy. This research contributes significantly to public health by aiming to enhance the safety and effectiveness of pharmaceutical manufacturing.

2. Material and Methods

This study was conducted as a case report utilizing data from the quality assurance sector of a pharmaceutical company with over 90 years of market presence, operating from a 26,000 m^2 facility in Rio de Janeiro. The focus was on analgesic tablets, specifically examining data collected from the mixing, compression, and coating stages of the manufacturing process. The data encompasses critical parameters such as average core weight and hardness.

This investigation leveraged continuous process verification records documented in the drug product procedures and reported in the periodic product reviews. Access to these records was granted on July 25, 2023, focusing specifically on retrieving in-process control data and performing statistical analyses thereof. Due to confidentiality agreements within the company, the name of the tablet under study remains undisclosed.

3. Results and Discussion

Comparing the reviews from 2021 and 2022, the average weight after coating and the hardness were analyzed, suggesting measures to enhance the process and enforce strict monitoring to ensure quality and safety. Data from eighty batches were included in the reports, emphasizing the importance of the arithmetic mean in determining the results of critical parameters based on in-process control records.

The study highlights the improvements implemented following a distribution that was out of control in 2021, showing more satisfactory results in 2022 for both average weight and hardness. Deviations from these parameters were identified as quality issues. For the target product of this study, the specification for this criterion is between 246 and 272 mg, and any result outside this range should be considered a deviation in product quality.

The hardness of the tablet is crucial for ensuring the drug's efficacy and safety and was monitored within the specification of 6 to 9 Kp for the coated tablet under study.

The performance indices PP and PPK were critical in assessing the process's ability to produce within specification, taking into account the distribution and variation of results. A PPK value greater than 1 was established as a criterion for the long-term acceptability of the process.

In figure 1, we can observe all weight data presented in 2021. The average result for that year was 259.27 mg. An analysis reveals that eight points fell outside the statistical control limits marked by the red lines. However, all these points remained within the specification limits (upper and lower bounds) indicated by the blue lines. The process appears to be trending towards the upper specification limit as observed in the long-term stability analysis, suggesting stability but not control. Overall performance during the evaluation period for coated tablet manufacturing showed the average weight after coating to be unacceptable, as reflected in the PPK value. The data exhibits significant variability and does not conform to a normal distribution, indicating potential issues with process quality. Further investigation is required, particularly concerning points near the upper specification limit, to identify any underlying causes.

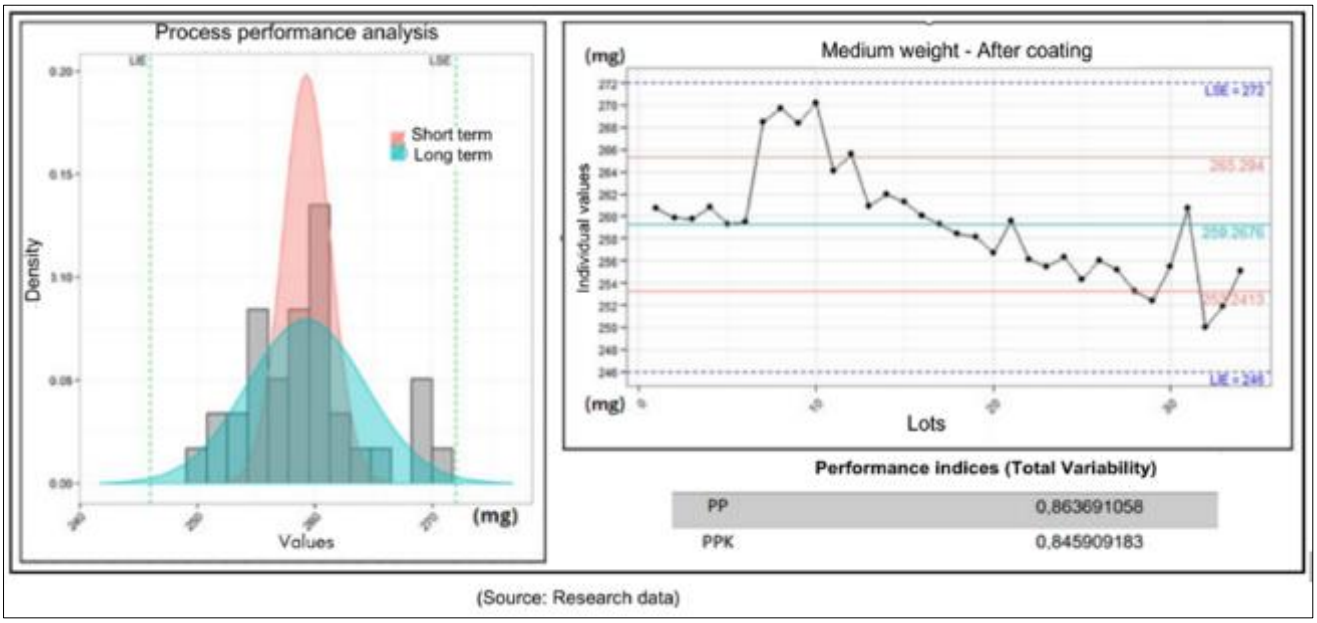

Figure 1 Weight control 2021

The data presented in 2022, in figure 2, it is noticeable that the values did not vary so significantly. All the points met the specification limits (upper and lower), indicated by the blue dotted lines. The average value of the results was 256.62 mg. It can therefore be concluded that this parameter is under control.

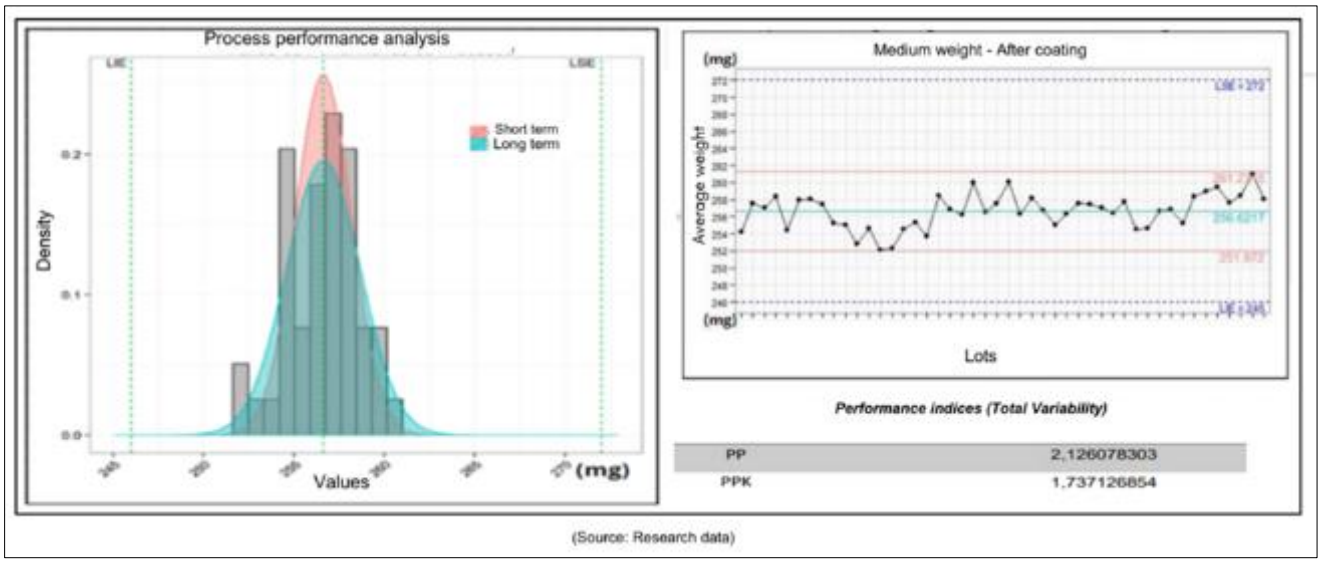

Figure 2 Weight control 2022

Evaluating the two periods shows a significant improvement in the distribution of results. In figure 2, the process for average weight after coating is considered acceptable, which can be seen from the PPK value (1.737126854), which indicates that despite showing a trend closer to the lower limit of the specification, the green dotted line on the left shows that the results come from a normal distribution. It is important to note the significant improvement in the process.

In figure 3, we can begin to analyze the available hardness data. In the year 2021, the values presented also showed a lot of variation in the limits. Like the critical parameter of average weight after coating, hardness also showed a very high variation in values in the 2021 periodic review. The excessive variability can be seen in the statistical control lines which are very close to the specification limits, thus indicating a risk of some items going out of specification, even though the process is operating within specifications.

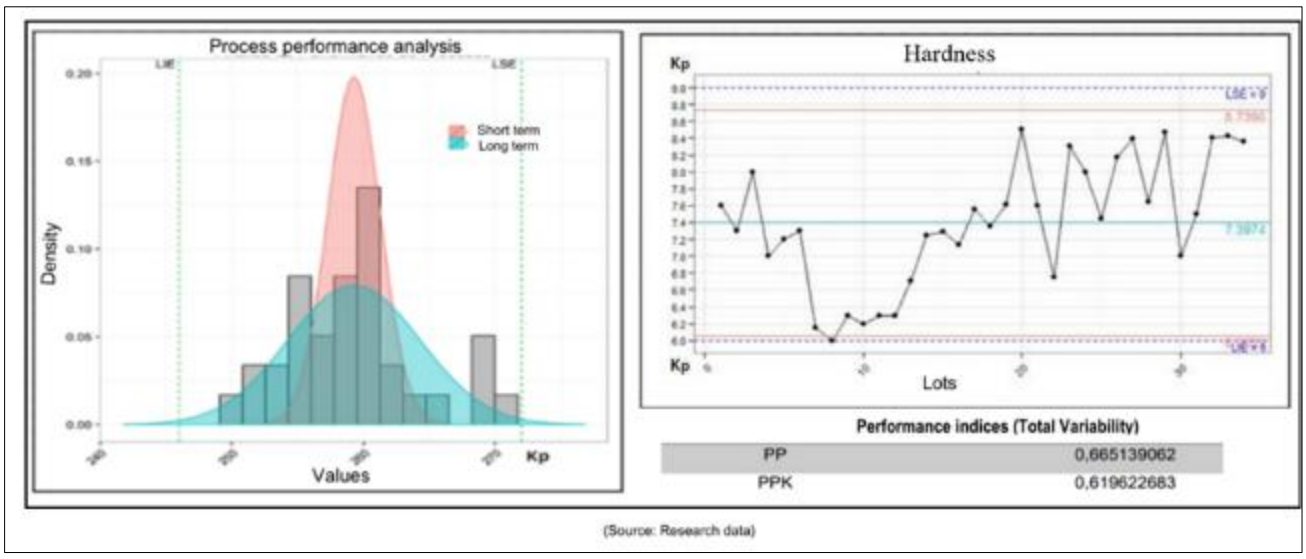

Figure 3 Hardness control chart 2021

The long-term curve indicates that the process is subject to a high level of variability, which makes it more susceptible to generating batches outside the specified range. In addition, the process is not centralized and tends towards the right side of the figure, i.e. it is closer to the upper limit of the specification.

Comparing the 2022 figures with the previous ones, shows a significant improvement in the distribution of points with a reduction in the statistical control range.

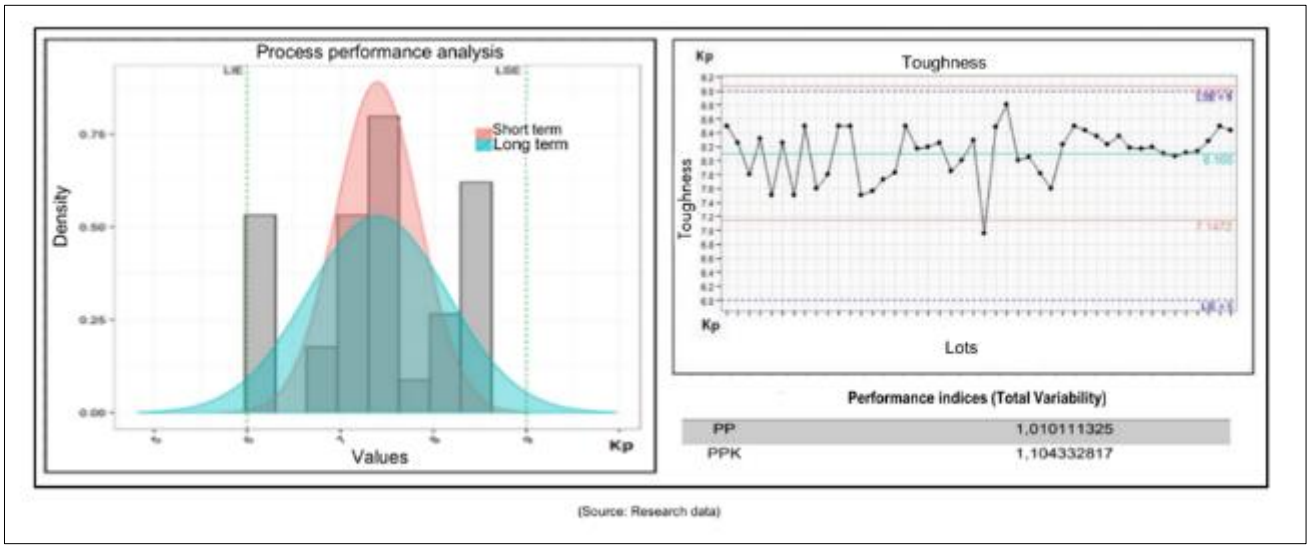

Figure 4 Toughness control chart 2022

Considering the average weights of 250 mg for the core and 259 mg after coating, it can be inferred from Table 1 that the batches classified as unacceptable for the critical parameter of average weight after coating showed higher results in the compression stage. Additionally, greater process variability can lead to tablets of varying sizes and hardnesses. For proper compaction, precise punching force and uniform powder quantity are necessary.

Table 1 Batch process control results considered unacceptable

LOTS	AVERAGE NECLEUS WEIGHT (mg)	AVERAGE NECLEUS WEIGHT (mg)
7	257,60	268,50
8	258,40	269,70
9	257,40	268,40
10	259,50	270,20
11	258,60	264,10
12	255,30	265,60
26	245,70	256,00
27	244,70	255,20
28	244,70	253,30
29	244,90	252,40
32	242,50	250,00
33	244,00	251,90
34	245,10	255,10

Source: Research data.

The root cause of the unsatisfactory results was identified as variations in the average core weight due to operator changes between batches. To enhance the robustness of this process, two improvement measures were implemented: firstly, the revision of the manufacturing process instructions (PI) for all products to include a specified range in the average core weight in the in-process control tables. This allows the compression manager to maintain a statistical

range around the average weight. A comprehensive study was conducted across all drugs manufactured at the facility to determine the ideal operational ranges for each product.

The second improvement involved retraining all operators involved in tablet compression, which subsequently mitigated the impact of labor changes on result uniformity.

Statistical analysis enabled the identification and correction of production issues, proving to be an effective tool. By defining values during the production flow, it is possible to minimize quality deviations and comply with critical legislative requirements. Tôrres et al. (6), highlights that the major advantage of these reports is their ability to provide an overview of performance and ensure compliance with established parameters.

Statistical analysis enhances the reliability of production processes, thereby ensuring product quality. Batista et al. 2021 (7), points out that Statistical Process Control (SPC) decreases the likelihood of quality deviations by identifying special causes, facilitating the creation of action plans to adhere to specification limits and produce quality medicines through a stable process.

4. Conclusion

This case study demonstrated how statistical analysis of data from periodic reviews can elucidate product performance and identify improvement opportunities, substantially enhancing not only the product quality but also the overall production process. The findings underscore the pivotal role of statistical control in periodic product reviews (PPRs), decisively addressing the core research question concerning the impact of statistical process control on production enhancements.

The analysis revealed that after implementing targeted improvements, there was a marked enhancement in product quality. The performance indices showed a significant increase between the two periods analyzed. This progression indicates that the implementation of corrective actions based on statistical insights can lead to substantial improvements in manufacturing outcomes.

Moreover, this research not only contextualized the practical application of statistical tools but also assisted in pinpointing specific process deficiencies, validating process changes, and supporting data-driven decision-making. Ultimately, contributes to advancing the pharmaceutical industry by reinforcing the efficacy of statistical analyses in sustaining regulatory compliance and elevating production standards.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that they have no conflict of interest.

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