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Short communication

Enhancing the sampling process in suspension manufacturing using Lean Six Sigma tools

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Introduction

The pharmaceutical industry operates in a highly complex and regulated environment driven by global competition, sustainability requirements, and rapid technological advancement. Digitalization and artificial intelligence (AI) are increasingly integrated into manufacturing systems to enhance process performance through real-time monitoring and data-driven decision-making. Nevertheless, manufacturing processes remain the fundamental systems responsible for converting raw materials into finished products. Therefore, the optimization and continuous improvement of processes remain critical for achieving consistent product quality and regulatory compliance (ICH Q10, 2008). In this context, Lean, Six Sigma, and their integrated methodology—Lean Six Sigma—are widely recognized as effective approaches for reducing waste, minimizing process variability, and improving overall process capability (George, 2002; Montgomery, 2019). The aim of this study was to improve the sampling process during suspension manufacturing by applying Lean Six Sigma methodology, with focus on reducing re-sampling and re-analysis rates, minimizing variability in active substance content, and improving overall process stability.

Materials and methods

The project followed the DMAIC (Define–Measure–Analyze–Improve–Control) methodology (ASQ, 2026; George, 2002; Montgomery, 2019; Pyzdek and Keller, 2018):

Define phase: A comprehensive process flow diagram was developed to map the entire suspension manufacturing process, including stages such as raw material preparation, mixing, in-process control, sampling, quality control (physico-chemical and microbiological testing), filling, packaging, and storage. A Gemba Walk analysis was conducted to identify inefficiencies and non-value-added activities within the process. The results indicated that the most critical areas of waste were associated with sample preparation, sampling procedures, sample transfer, quality control analysis, and interpretation of analytical results. Additionally, a Voice of the Customer (VOC) analysis was performed to capture internal stakeholder requirements. The key issues identified included delayed sampling, repeated sampling and analysis, analytical errors, and variability in the active substance content. A value analysis matrix prioritized the following improvement targets: Reduction of repeated analyses; Reduction of re-sampling; Process stabilization; Reduction of variability in active ingredient content

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Measure phase: Key performance indicators (KPIs) were established, including: Percentage of re-analysis; Percentage of re-sampling; Process capability indices (Cp, Cpk, Pp, Ppk); Active substance content (%). Data were collected from 40 manufactured batches of suspension. The parameter "assay of active substance" was identified as the most critical quality attribute (CQA), as it directly reflects process stability and performance.

Analyze phase: Statistical analysis was performed using I-MR control charts, enabling visualization of process variability and stability over time. The results indicated significant variability, with control limits wider than specification limits (95%–105%), suggesting a risk of out-of-specification (OOS) results. Process capability analysis using Minitab software yielded the following results: Cp = 1.20; Cpk = 0.76; Pp = 1.09; Ppk = 0.68. These values indicate that the process was not centered nor capable, with a mean shifted toward the upper specification limit (mean ≈102%). The findings confirmed the presence of systematic variation and highlighted the need for process improvement.

Improve phase: A multidisciplinary team comprising experts from Quality Assurance, Quality Control, Production, and R&D conducted a structured brainstorming session using the 6-3-5 method. Several improvement ideas were proposed, including: Modification of the sampling method; Expansion of specification limits; Elimination of intermediate product testing; Re-evaluation of the analytical method. After evaluation using a portfolio matrix (considering impact, cost, and implementation effort), the selected solution was modification of the sampling approach. The new sampling strategy involved: Sampling during the mixing phase instead of filtration; Collecting representative samples from both upper and lower zones of the mixing equipment (OLSA); Combining samples to obtain a homogeneous representative sample. The change was implemented through a formal Change Control procedure, supported by a documented risk assessment in compliance with GMP requirements.

Control phase: Process performance was monitored using Product Quality Review (PQR) and Ongoing Process Verification (OPV) reports, ensuring continuous statistical evaluation and compliance with standard operative procedures.

Results and discussion

Following implementation of the improved sampling strategy, a reduction in variability of the active substance content was observed. The process mean shifted closer to the target value (100.5%), indicating improved centering. Control charts demonstrated enhanced process stability, and a decrease in re-sampling and re-analysis was achieved.

Conclusion

The application of Lean Six Sigma methodology proved effective in identifying and eliminating inefficiencies in the sampling process. The implemented improvements resulted in enhanced process capability, reduced process variability, and improved product quality. These findings confirm that structured, data-driven approaches are essential for achieving reliable and efficient pharmaceutical manufacturing processes.

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