Recipharm

Tackling assay variability in liquid vials to achieve product robustness

Overcoming liquid vial assay variability challenges

Ensuring consistent and accurate assay results in liquid vials is a cornerstone of product quality and regulatory compliance when developing parenteral drug products. However, many drug developers persistently face variability in assay results, often characterised by sporadic out-of-specification (OOS) events that are challenging to understand and troubleshoot. These OOS events can complicate batch release and scale-up, resulting in delayed timelines, increased costs and negative developer reputations.

This case study examines the impact of assay variability and how a data-driven approach can overcome challenges to achieve product robustness in liquid vials.

Understanding the challenge of assay variability

Assay variability is rarely the result of a single factor. Typically, it emerges from the complex and interconnected effects of critical material attributes (CMAs) and critical process parameters (CPPs), including:

- **API weighing:** Minor inaccuracies when weighing active pharmaceutical ingredients (APIs) can lead to concentration discrepancies that persist through formulation.
- **Excipient variability:** Differences in excipient grade, source or functionality can affect the solubility and stability of drug products, and ultimately assay results.
- **Fill homogenisation:** Incomplete mixing or uneven distribution of the formulation can cause dose-to-dose inconsistency in the vial content.
- **Holding time before filling:** Prolonged holding can introduce degradation or product settling that can impact assay results.
- T**ransfer conditions:** Product exposure during line setup or transfer and equipment variation can subtly alter formulation characteristics.
- **Fill volume accuracy:** Deviations in fill volume can directly influence concentration, skewing assay measurements and impacting OOS rates.
- **Assay method sensitivity:** Complex and sensitive assays, particularly those involving multiple dilutions, can introduce cumulative variability.

Each CMA and CPP can influence assay performance. However, traditional troubleshooting approaches often fall short. Conventional root cause investigations tend to examine each parameter in isolation, disregarding how these factors interact across the full product and process lifecycle. This approach can lead to overlooking all of the factors involved, resulting in prolonged troubleshooting cycles and an incomplete understanding of how to consistently meet assay targets.

Although deviations can be subtle, their unpredictability poses serious challenges for process reliability and regulatory compliance. Addressing this issue is critical to restoring confidence in the assay method and ensuring robust, reproducible performance across batches.

Developing a data-driven solution to assay variability

To reduce the likelihood of OOS results in assay readings, Recipharm developed ReciPredict, an advanced Quality by Design (QbD) and predictive analytics platform. ReciPredict applies a holistic, statistical model-driven approach that accounts for the interdependencies between formulation components and process dynamics. It allows data-driven decisions by applying data science and digital technology to develop and manufacture drug products, promising to deliver unparalleled efficiency and reliability.

Moving beyond trial-and-error experimentation, the platform employs interconnected intelligence and data driven models to identify and control the root causes of assay variability before they impact product quality at scale.

The application of ReciPredict to this assay variability challenge delivered rapid, tangible results, without the need for additional experimental trials. By harnessing existing historical data, the platform was able to quickly identify sample preparation as the root cause of the sporadic OOS results (Figure 1).

Developing a targeted approach to address this challenge not only saves valuable time and resources but also helps accelerate the journey toward a more robust, reliable manufacturing process.

First, an optimised dilution step was introduced into the QC process to reduce variability stemming from analytical procedures. Second, filling speed during the vial fill process was adjusted to improve dose uniformity and minimise disturbances in liquid dynamics. Finally, API dispensing was refined based on potency, ensuring greater consistency in concentration from the outset. Together, these targeted interventions addressed the multifactorial nature of the problem and transformed isolated variables into controlled process improvements.

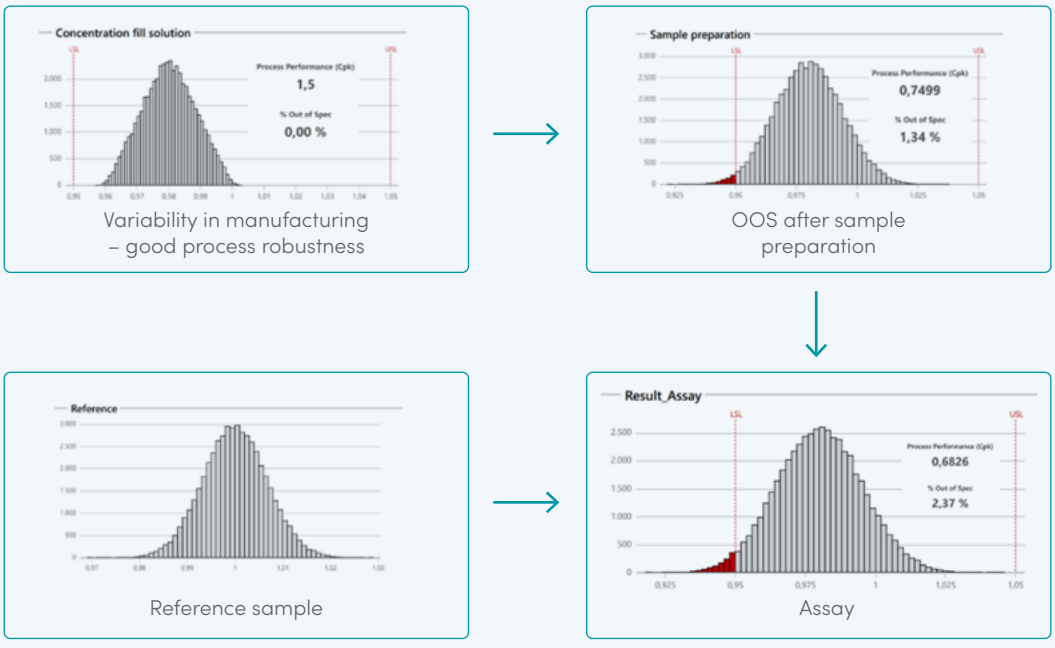

Figure 1: Applying the ReciPredict model indicated that the main driver for assay variability and OOS events was sample preparation.

ReciPredict results: Removing the "error" from trial and error

Applying the optimised changes to sample preparation resulted in the sporadic OOS events being fully eliminated (Figure 2). A complete, model-based understanding of how material attributes and process conditions influenced assay results provided full visibility into the parameters impacting product quality. As a result, batches that were previously at risk of failure could now be manufactured with confidence.

Quantitatively, the impact of ReciPredict was significant. The percentage of OOS results was reduced from 2.37% to 0.00%.

All vials produced met the required quality standards, with no recurrence of sporadic and unexplained OOS results. This translated into fewer disruptions on the manufacturing floor, reduced batch rejections and the elimination of stockouts, all of which contributed to a lower cost of production through a more robust, predictable process.

Partnering with experts to overcome assay variability

As a global CDMO with deep expertise in analytical science, process development and QbD, Recipharm combines experience with advanced tools like ReciPredict to help clients overcome complex manufacturing challenges. Here, assay variability was eliminated without additional trials, demonstrating how predictive modelling can unlock process understanding and deliver robust, reliable outcomes.

By partnering with Recipharm, companies gain access to interconnected intelligence, built on a foundation of scientific rigour, technical insight and data-driven innovation.

To learn more about how ReciPredict can support your development goals, contact us at: www.recipharm.com/contact-us

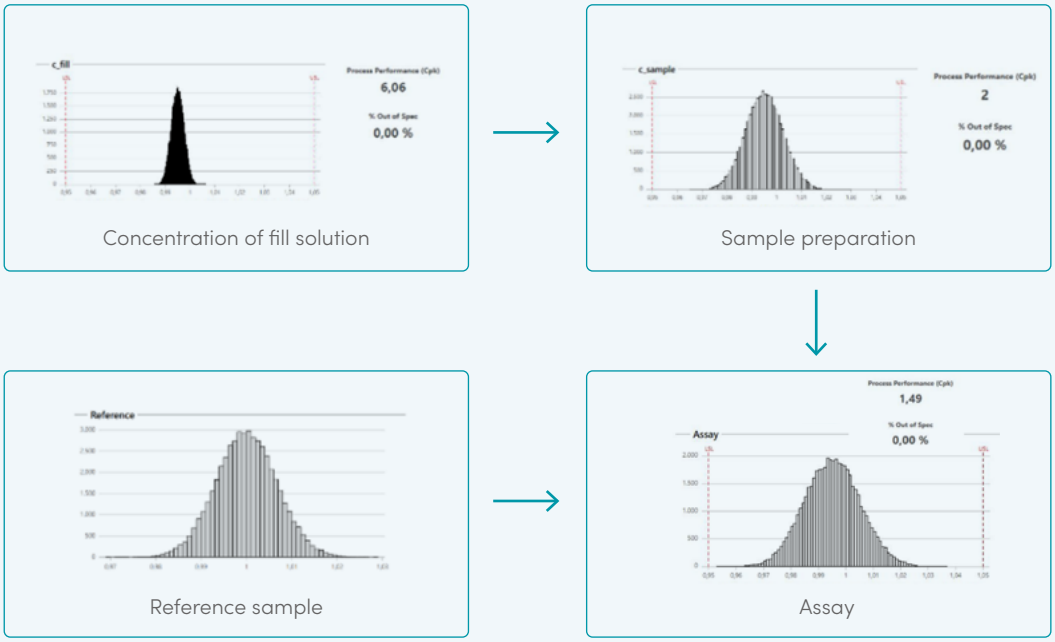

Figure 2: Optimised sample preparation resulted in complete elimination of OOS events.

About us

Recipharm is a leading contract development and manufacturing organisation (CDMO) headquartered in Stockholm, Sweden. We operate development and manufacturing facilities in France, Germany, India, Israel, Italy, Portugal, Spain, Sweden and the US and are continuing to grow and expand our offering for our customers. We are supporting pharmaceutical companies with our full service offering, taking products from early development through to commercial production. For over 30 years, we have partnered with our clients throughout the entire product lifecycle, providing pharmaceutical expertise and managing complexity, time and time again. We conduct our business as we always have and continue to deliver value for money with each customer's needs firmly at the heart of all that we do.

recipharm.com