Case Study- An Analytical Method Optimization Approach Based on Quality by Design

Executive Summary

Quality by Design (QbD) is a well-known pharmaceutical industry strategy for enhancing production processes, including active pharmaceutical ingredients and medicinal products. Companies may get useful insights throughout development by employing QbD concepts to build the design space and select relevant process controls. This case study shows how Renejix a QbD strategy to address an analytical method challenge involving high-performance liquid chromatography (HPLC). The approach showed fluctuating retention periods of impurity peaks, making identification and quantification difficult. Furthermore, the reported lack of consistency prompted concerns about properly detecting impurity levels, which might impair the medication product's safety, quality, identity, purity, and potency (SQIPP).

The Challenges

The analytical team encountered considerable challenges as a result of the lack of repeatability in its HPLC analytical procedure. The fluctuating retention durations of impurity peaks raised the possibility of co-elution, which might lead to inaccurate evaluations of impurity levels in the medicinal product. This condition posed an unacceptable danger to the drug's SQIPP evaluation.

The Solution

Renejix used a QbD technique and the design of experiments (DoE) tool to optimize the analytical method to handle the issues. The DoE assessed the influence of several experimental factors (X-factors), which included both continuous and categorical variables. Buffer concentration, buffer pH, percentage of organic in mobile phase A, percentage of organic in mobile phase B, flow rate, column temperature, gradient time, and hold time before gradient commencement were the continuous X-factors. The research also included

two distinct HPLC column batches as categorical X-factors. To quantify the main effects and experimental error, a resolution IV fractional factorial design with 32 unique DoE runs and four centre-point duplicates was used. Here's a table outlining the challenges faced by Renejix and the corresponding solutions implemented using the Quality by Design (QbD) approach:

Challenges	Solutions
Lack of reproducibility in the HPLC analytical method	Adopted a QbD approach to identify and optimize the factors affecting method reproducibility
Shifting retention times of impurity peaks	Utilized the design of experiments (DoE) tool to evaluate the impact of various experimental factors
Risk of co-elution leading to incorrect assessment of impurity levels	Conducted a resolution IV fractional factorial design to assess the effects of different factors on impurity resolution
Unacceptable risk to SQIPP evaluation of the drug product	Employed the QbD methodology to establish reliable and accurate analytical conditions

By addressing these challenges through the application of QbD principles and utilizing the DoE tool, the analytical team successfully optimized its HPLC analytical method, ensuring reproducibility, resolving to shift retention times, and minimizing the risk of co-elution. This enabled accurate assessment of impurity levels and ensured the safety, quality, identity, purity, and potency of their drug product.

According to the findings, eight of the nine X-factors had a statistically significant influence on the Y-metric, which was the relative resolution between the impurity peaks of interest. Column lot, buffer concentration, buffer pH, percentage of organic in mobile phase A, percentage of organic in mobile phase B, flow rate, column temperature, gradient duration, and hold time before gradient commencement were among the relevant X-factors. Gradient time was the only X-factor that did not have a statistically significant influence on relative resolution.

Conclusion

The statistical examination of the model revealed that it explained roughly 99% of the variance in relative resolution. Renejix determined the X-factor settings that consistently achieved the necessary relative resolution for the impurity peaks using the optimization tool inside the QbD method. Confirming runs were performed, which confirmed the DoE experiment findings by assuring the relative resolution between the key pair of impurity peaks. Furthermore, the adjusted conditions reduced the previously reported column lot variability. Based on the study's findings, the analytical technique was declared ready for the validation phase.

The Renejix analytical team successfully refined its HPLC analytical process by using a QbD strategy and harnessing the capabilities of the DoE tool, overcoming the hurdles associated with altering retention periods of impurity peaks. This case study demonstrates the QbD methodology's effectiveness in quickly creating ideal conditions for analytical procedures, assuring the dependability, precision, and quality of pharmaceutical goods.