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Short communication

Beyond tradition: advancing analytical procedures for drug quality control through the enhanced approach

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Introduction

The ICH Q14 guideline introduces a contemporary approach to developing analytical methods for quality control, grounded in scientific principles and a risk-based perspective (ICH, 2024). It emphasizes assessing method robustness and establishing acceptable ranges for critical parameters to ensure consistent performance and reliability. In practice, this involves using optimization strategies to identify parameter combinations that achieve adequate analytical performance. This approach increases the efficiency of quality control processes, strengthens the credibility of results, and supports ongoing refinement of analytical procedures.

The guideline distinguishes between traditional and enhanced approaches to analytical method development (ICH, 2024). The traditional, or minimal, approach has long been the standard and involves submitting only the essential data required by regulatory authorities. However, this often results in a rigid regulatory framework that limits flexibility for post-approval method changes. In contrast, the enhanced approach, known as Analytical Quality by Design (AQbD), provides a structured pathway for building and expanding knowledge throughout the lifecycle of an analytical procedure, enabling continuous optimization and improvement (ICH, 2024).

Materials and methods

When applying the AQbD framework, method development involves a series of interconnected activities (Dispas et al., 2018). These include defining the analytical target profile (ATP), conducting a structured risk assessment, establishing the desired performance characteristics of the analytical procedure across the reportable range, and identifying the relevant Analytical Procedure Attributes (APAs) to be evaluated. Design of Experiments (DoE) and modeling are then used to investigate interactions among Analytical Procedure Parameters (APPs), enabling the establishment of the Design Space (DS) and development of an appropriate analytical control strategy. Finally, the entire procedure is comprehensively documented.

Results and discussion

The AQbD paradigm is based on the ATP, which specifies what is to be measured, matrix, concentration range, and quality-related expectations, such as the level of confidence associated with reported results. APAs are also established as measurable indicators of whether the method meets the predefined performance criteria.

The next step is a structured risk assessment and identification of APPs. The process begins by identifying all variables that could influence method

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performance, typically using tools such as the Ishikawa diagram. These factors are then classified using the CNX framework into *Controlled*, *Noise*, and *eXperimental* categories (Rmandić et al., 2025). *Controlled* factors are maintained at fixed leval, while *Noise* factors are considered well-managed and low risk. *Experimental* factors are most likely to impact APAs and require detailed investigation. These are further assessed using Failure Mode and Effect Analysis (FMEA), where each factor is ranked by severity, likelihood, and detectability. Based on the resulting Risk Priority Number (RPN), critical factors are selected as APPs for further study, while less critical ones may be fixed or evaluated through quantitative robustness testing.

DoE should be used to understand the relationship between APPs and APAs, enabling systematic exploration of parameter interactions. Constructed mathematical models form the basis for defining the DS, which represents the region where the method consistently meets performance requirements with a specified probability (π). The DS is interpreted as a zone of operational robustness, where variations in APPs do not significantly compromise APAs. To increase confidence in this region, robust optimization techniques are applied, often incorporating Monte Carlo simulations to account for variability and model uncertainty. Different approaches to error propagation can be used, influencing the breadth of the DS; more conservative estimates typically result in narrower but more reliable regions. The first approach estimates uncertainty by propagating residual variance into the predicted responses, while the second approach propagates uncertainty through the regression coefficients using their standard errors. Both methods generate response distributions across all grid points in the experimental domain. (Dispas et al., 2018).

Once the DS is established, a suitable working point is selected and the method is validated. System suitability test (SST) criteria are defined to support routine application, and a control strategy is implemented to ensure consistent performance throughout the method lifecycle. This strategy relies on both qualitative robustness within the DS and quantitative robustness testing, which may include additional experimental designs such as Plackett–Burman studies (Rmandić et al., 2025).

Conclusion

In the enhanced approach to analytical method development, data quality is ensured by defining the DS, which represents the region where the criteria for APAs are met with a predefined probability (π). Qualitative robustness is evaluated, as proper application of AQbD requires robust optimization. SST parameters are established through qualitative robustness testing, and non-significant ranges for critical factors are estimated. By setting clear performance requirements and corresponding acceptance criteria in advance, the analytical procedure can be continuously adapted and refined throughout its lifecycle.

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