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Review paper

Software-assisted analytical Quality by Design for stability-indicating method development: integration of DoE and predictive retention modeling using MODDE® and DryLab®

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Abstract

In modern pharmaceutical development, the increasing complexity of drug substances, formulations, and regulatory expectations has rendered traditional one-factor-at-a-time (OFAT) approaches to analytical method development inefficient and increasingly impractical. Consequently, analytical development in the twenty-first century is shifting toward systematic data-driven strategies based on Design of Experiments (DoE) and predictive modeling, in alignment with the principles of Analytical Quality by Design (AQbD). Software tools such as MODDE® and DryLab® exemplify this transition by enabling multivariate evaluation of critical method parameters, quantitative definition of design spaces, and prediction of chromatographic performance across wide operational ranges. Although numerous studies report the successful application of DoE-based optimization or predictive retention modeling as standalone approaches, a growing body of evidence, particularly from pharmaceutical applications, demonstrates the advantages of their integrated use for the development of robust, stability-indicating analytical methods. This review provides a comprehensive overview of AQbD-based stability-indicating method development with emphasis on the combined application of MODDE® and DryLab®, examining their roles in systematic risk assessment, statistical modeling, and predictive simulation to enhance method robustness, reduce experimental burden, and support regulatory flexibility within a scientifically justified method operable design region (MODR). In addition, emerging perspectives on artificial intelligence- and machine learning-assisted retention prediction are discussed as natural extensions of current software-assisted AQbD frameworks, highlighting future directions toward more efficient, knowledge-driven, and digitally enabled analytical method development.

Key words: Analytical Quality by Design (AQbD), Design of Experiments (DoE), DryLab®, MODDE®, stability-indicating methods

Introduction

Quality by Design (QbD) is a systematic approach in pharmaceutical development that emphasizes designing and controlling processes to ensure that products consistently meet predefined quality criteria. The QbD methodology is characterized by a comprehensive understanding of process variables and their effects on

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product quality, thereby maximizing efficacy and ensuring consistency throughout a product's lifecycle. This approach is rooted in the relationships between Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs), aiming to manage variability effectively to deliver a robust and reliable product (Pramod et al., 2016; ter Horst et al., 2021). The overarching goal of QbD is to develop products that maintain their intended quality throughout their shelf life, supported by scientific validation and proactive risk management techniques (Ameen & Pappula, 2023; Savitha & Devi, 2022).

When applied specifically to analytical method development, QbD is termed Analytical Quality by Design (AQbD) (Peraman et al., 2015). AQbD represents a systematic, science-based approach to analytical method development that emphasizes predefined analytical objectives, comprehensive process understanding, and the establishment of design spaces defining acceptable method performance across defined parameter ranges (Katekar et al., 2022). Unlike traditional one-factor-at-a-time (OFAT) approaches, AQbD integrates principles of risk management and Design of Experiments (DoE) from early stages of method development, enabling pharmaceutical scientists to establish robust analytical procedures with documented scientific understanding (Mishra et al., 2018).

Within the framework of AQbD, the Analytical Target Profile (ATP) defines the specific performance requirements a method must fulfill to be considered fit for purpose, thereby integrating uncertainty and variability management into method design (Dewi et al., 2022; Randive et al., 2024). By identifying and controlling Critical Method Parameters (CMPs) and ensuring that Critical Analytical Attributes (CAAs) meet established performance standards, scientists can improve the robustness and lifecycle performance of analytical methods (Kanthiah et al., 2025; Mahapatra & Meyyanathan, 2022). The outcomes of this systematic characterization lead to the establishment of the Method Operable Design Region (MODR), which can be defined as a multidimensional design space within which analytical methods demonstrate reliable performance and robustness under normal operating conditions. Defining the MODR within the AQbD framework may enable greater regulatory flexibility by providing a scientifically justified range of method parameters; this may reduce the extent of revalidation or regulatory oversight required for method parameter changes, although the specifics depend on regulatory acceptance and documentation (Peraman et al., 2015).

In parallel to the ATP defined within the AQbD framework, the Quality Target Product Profile (QTPP) serves as the foundational element of pharmaceutical QbD, outlining the intended quality characteristics of the drug product, from which the CQAs are derived. Establishing this QTPP-CQA linkage enables the design of manufacturing processes that are both robust and scientifically justified within the broader QbD paradigm (Verch et al., 2022).

This review examines the application of AQbD principles in the development of stability-indicating methods, emphasizing the use of DryLab® and MODDE® software tools. It consolidates recent advances in AQbD implementation, highlighting how the combination of predictive retention modeling and DoE contributes to enhanced method robustness, regulatory flexibility, and lifecycle management. The aim of this work is to provide a concise, practice-oriented overview that bridges theoretical concepts with real-world analytical applications, offering guidance for scientists and regulatory professionals seeking to implement modern, science-based strategies for analytical method development.

Application of AQbD in stability-indicating method development

Stability-indicating methods are vital for evaluating how active pharmaceutical ingredients (APIs) degrade under various stress conditions, generating essential information about the shelf life, potency, and overall quality of pharmaceutical formulations (Nunsavathu & Rajaganapathy, 2024). These methods serve as critical quality control tools throughout the pharmaceutical product lifecycle, requiring comprehensive demonstration that the chromatographic separation adequately resolves the API from all potential degradation products and impurities (Karmarkar et al., 2011). They must exhibit high specificity, sensitivity, linearity, accuracy, and precision while maintaining robustness against minor variations in chromatographic parameters (Beg et al., 2015). The development of adequate stability-indicating methods requires comprehensive knowledge of drug degradation chemistry, including identification of potential degradation pathways under various environmental stress conditions (Jagadabi et al., 2018). This mechanistic understanding enables rational design of chromatographic separations that resolve all expected degradation products and support regulatory acceptance of pharmaceutical formulations (Kleinman et al., 2015).

Building on these scientific fundamentals, the guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) specify that pharmaceutical manufacturers must conduct forced degradation studies to identify potential degradation products, establish appropriate stability-indicating capability, and support overall quality-management strategies (ICH Q1A(R2), 2003). These studies systematically apply stress conditions including temperature, humidity, oxidative stress, hydrolytic stress, and photolytic stress to characterize degradation pathways (Karmarkar et al., 2011). Comprehensive documentation of degradation product structures, degradation mechanisms, and toxicology screening enables regulatory agencies to evaluate drug product safety and appropriate degradation thresholds (ICH Q3B(R2), 2006; Kakde et al., 2013). The

rigorous characterization of degradation behavior under ICH-recommended stress conditions provides the scientific foundation for establishing meaningful stability-indicating capability (Gumustas & Ozkan, 2013).

Building upon this regulatory and mechanistic framework, the application of AQbD to stability-indicating methods supports the development of analytically rigorous procedures with well-defined design spaces and improved control of variability (Vyas et al., 2021). Integrating forced degradation studies within the AQbD framework provides mechanistic insight into degradation pathways and guides the selection of chromatographic conditions that resolve all relevant degradants from the API (Kleinman et al., 2015; Randive et al., 2024). In practice, DoE, often coupled with response-surface methodology and multivariate analysis, enables efficient mapping of factor effects and interactions, facilitating identification of the analytical design space and prediction of performance across multiple critical parameters simultaneously (Lebrun et al., 2013).

Software tools such as DryLab® for retention modeling and chromatographic simulation (MOLNÁR-INSTITUTE for Applied Chromatography, n.d.) and MODDE® for statistical DoE (Sartorius, n.d.) further systematize this process by allowing quantitative exploration of parameter interactions, construction of design spaces, and objective assessment of method robustness. Compared with traditional trial-and-error screening, AQbD implementations that combine DoE with predictive modeling markedly shorten development timelines and strengthen method understanding and documentation, while developing robust, lifecycle-ready analytical methods that support continuous verification and regulatory flexibility within scientifically justified design spaces.

Regulatory context and industrial implementation

The ICH has established the foundational regulatory framework that guides the implementation of QbD and its analytical counterpart, AQbD, in pharmaceutical development. The ICH guidelines Q8(R2), Q9(R1), and Q10 collectively define scientific and regulatory expectations for product and process understanding, risk-based quality management, and integrated quality systems, thereby transforming analytical method development from empirical practice into a science-based discipline (Peraman et al., 2015; Prajapati et al., 2021). Specifically, ICH Q8(R2) emphasizes the systematic evaluation and understanding of material attributes and process parameters and their relationship to product quality (ICH Q8(R2), 2009), while ICH Q9(R1) provides a structured risk-management framework, including risk identification, analysis, evaluation, and control, that can be directly applied to analytical methods to identify and mitigate factors affecting method performance and analytical quality (ICH Q9(R1), 2023). ICH Q10 builds upon these principles by outlining a model for an effective pharmaceutical quality system implemented throughout the product lifecycle, encompassing development, technology transfer, manufacturing, and discontinuation, all of which support analytical method performance and regulatory compliance (ICH Q10, 2008). AQbD-developed methods with characterized design spaces support both initial validation and ongoing continuous verification throughout the analytical method lifecycle (Verch et al., 2022).

ICH Q11, meanwhile, provides complementary guidance for the development and manufacture of drug substances, reinforcing the same science- and risk-based principles central to QbD (ICH Q11, 2012). For analytical methods specifically, the validation parameters that must be demonstrated to ensure analytical reliability are being refined through the recently updated ICH Q2(R2) and the new ICH Q14 guideline, which jointly establish harmonized international standards for analytical procedure development and validation (ICH Q2(R2), 2023; ICH Q14, 2023). Within this framework, AQbD-based approaches inherently address these expectations by systematically characterizing method performance across the design space and ensuring consistency with the ATP defined during method development (Orlandini et al., 2014). This integrated regulatory landscape ensures that pharmaceutical and analytical quality are not tested into products but scientifically designed, controlled, and continuously improved across the entire lifecycle.

An overview of the ICH guidelines relevant to QbD and AQbD implementation is provided in Table 1.

Beyond ICH guidance, regulatory agencies, including the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), actively encourage the implementation of QbD and AQbD principles and recognize that analytical methods developed within an established design space may qualify for regulatory flexibility (Simões et al., 2024). Both agencies have explicitly promoted AQbD-based approaches through guidance documents, scientific workshops, and regulatory pilot programs, emphasizing that analytical procedures supported by well-defined design spaces can enable post-approval method adjustments without the need for supplemental regulatory submissions (FDA and EMA, 2017). The FDA has already approved multiple new drug applications incorporating AQbD-developed analytical methods with such flexibility provisions, demonstrating that method changes made within a justified MODR or design space can be implemented without prior approval (Peraman et al., 2015). This regulatory flexibility not only strengthens lifecycle management of analytical procedures but also reduces time-to-market for manufacturing and analytical modifications while preserving high assurance of product quality, providing a clear economic incentive for pharmaceutical companies to adopt AQbD-based method development (Jagan et al., 2021).

Table 1. ICH guidelines supporting QbD and AQbD implementation

ICH Guideline	Core Focus	Relevance to AQbD
Q2(R2)	Validation requirements	Definition of analytical performance criteria
Q8(R2)	Design space concept	Scientific basis for systematic method design
Q9(R1)	Risk management	Identification and control of critical method risks
Q10	Pharmaceutical quality system	Lifecycle management and continuous improvement
Q11	Drug substance development	Alignment of analytical control with QbD principles
Q14	Analytical procedure development	Framework for AQbD-based method development

Implementation of AQbD reduces the frequency of out-of-trend (OOT) and out-of-specification (OOS) results in routine quality control operations compared to traditionally developed methods, directly supporting pharmaceutical quality system objectives (Peraman et al., 2015). The pharmaceutical industry has progressively adopted AQbD as a strategic quality initiative, increasingly integrating AQbD with process analytical technology (PAT), pharmaceutical analytical technology, and overall quality systems management (Mishra, 2018). This adoption reflects industry recognition that AQbD enables development of scientifically robust methods with documented design spaces that demonstrate reliability across foreseeable operational variations, reducing method development time, ensuring regulatory compliance, and supporting continuous improvement initiatives throughout the product lifecycle (Bairagi et al., 2024).

Integration of DoE and risk management in AQbD

DoE represents a fundamental statistical methodology enabling simultaneous optimization of multiple analytical method parameters through systematically designed factorial designs, central composite designs, and response surface methodology, effectively replacing inefficient OFAT screening approaches (Dar et al., 2024). When integrated with AQbD principles, DoE empowers pharmaceutical scientists to characterize relationships between CMPs and critical attributes, establishing mathematical models describing method performance across the entire design space (Prajapati et al., 2021). Response surface methodology generates multidimensional response surface predictions that reveal not only main effects of individual parameters but also interaction effects where parameter combinations produce unexpected performance consequences (Sha'at et al., 2022). This comprehensive method understanding, derived through statistical modeling rather than empirical trial-and-error, enables prediction of analytical performance across defined operational ranges that single-point OFAT approaches cannot achieve.

Risk assessment methodologies, as specified in ICH Q9 guidelines, provide systematic frameworks for identifying and prioritizing CMPs that significantly impact analytical performance (Prajapati et al., 2021). Failure Mode and Effects Analysis (FMEA), when combined with risk priority number (RPN) ranking, enables systematic identification, evaluation, and prioritization of potential failure modes, helping to distinguish parameters requiring stringent control from those that allow operational flexibility (El-Awady, 2023). This risk-based prioritization ensures that experimental resources focus on characterizing relationships between the most critical parameters and analytical performance, maximizing information generation from limited development budgets while effectively allocating quality control resources. Integration of risk assessment with DoE through sequential parameter screening creates a highly efficient development pathway where risk assessment guides experimental design priorities, subsequent DoE characterization confirms parameter criticality, and response surface modeling enables definition of control strategies.

AQbD implementation systematically integrates DoE and risk assessment from method development initiation, generating comprehensive understanding of relationships between method parameters, operational conditions, and

analytical performance (Mishra et al., 2018). This integrated approach enables establishment of the MODR and associated control strategies that maintain method robustness across manufacturing variations, environmental fluctuations, and instrumental variations inherent in real-world analytical operations (Peraman et al., 2015). The resulting documentation supports regulatory submissions by demonstrating not only that methods produce acceptable results, but that pharmaceutical companies comprehensively understand method performance drivers and can reliably predict analytical behavior across defined operational ranges, substantially strengthening regulatory confidence in method robustness and transferability.

Software-assisted implementation of AQbD

Software-assisted analytical method development has become integral to AQbD implementation, with chromatographic modeling platforms, DoE software, and statistical analysis as tools enabling rapid exploration of complex parameter spaces (Tome et al., 2019). Predictive software such as DryLab® utilizes minimal scouting experiments to build retention models enabling simulation of chromatographic performance across multiple parameter combinations, dramatically reducing experimental burden while maintaining scientific rigor (Makey et al., 2020). This computational capability enables pharmaceutical scientists to explore method optimization scenarios rapidly, identify robust operating regions, and establish design spaces with substantially fewer experiments than traditional approaches. The integration of predictive retention modeling with High-Performance Liquid Chromatography (HPLC) systems through automated workflow platforms significantly compresses development timelines and enhances reproducibility by eliminating manual experimental manipulation and transcription errors inherent in conventional workflows.

DoE software such as MODDE® streamlines implementation of complex experimental designs, enabling visualization of relationships between method parameters and performance attributes through response surface plots, interaction diagrams, and optimization contours (Azcarate et al., 2020). Statistical modeling capabilities in DoE software generate predictive equations describing method performance as functions of critical parameters, enabling quantitative establishment of design space boundaries (Dar et al., 2024). These mathematical models reveal parameter interaction effects that single-factor optimization approaches cannot identify, facilitating identification of robust method regions resistant to minor variations in temperature, mobile phase composition, and instrumental conditions (Alves et al., 2025). Integration of DoE software with Laboratory Information Management Systems (LIMS) further reduces development timelines and enhances data quality through automated experimental workflow management and elimination of manual transcription errors.

The combination of predictive retention modeling and DoE software provides synergistic advantages for stability-indicating method development, enabling rapid establishment of robust analytical procedures with well-defined design spaces and comprehensive supporting documentation (Makey et al., 2020). Integrated software platforms substantially reduce the experimental workload compared with traditional OFAT approaches by enabling virtual simulation, optimized experimental planning, and more efficient exploration of multidimensional parameter spaces (Mannochio-Russo et al., 2020). The electronic development records generated by these platforms, covering design rationale, experimental design matrices, statistical evaluations, and design-space justification, provide transparent and regulator-ready documentation that facilitates assessment and supports post-approval flexibility for methods operating within established design spaces (Colloud et al., 2023).

DryLab® software: retention prediction and method optimization

DryLab® functions as a predictive modeling tool that leverages minimal scouting experiments to construct retention models for analytes, simulating chromatographic behavior as a function of gradient and column conditions (Liu et al., 2002). Rather than conducting extensive parameter screening, DryLab® builds quantitative relationships between chromatographic variables and retention behavior using a minimal set of strategically designed pilot experiments (approximately 2–12 inputs), thereby enabling prediction of chromatographic behavior across a broad experimental space (Fekete & Molnár, 2018). This software-assisted development approach substantially accelerates the transition from exploratory method development to systematic optimization, enabling investigators to identify optimal separation conditions without exhaustive empirical screening. The software's ability to model retention as a mathematical function of controllable parameters transforms the method development process from trial-and-error experimentation into rational design guided by predictive algorithms, a capability emphasized by Rácz & Kormány (2018), who describe DryLab® as a retention time-based computational tool implementing solvophobic theory-derived equations to predict chromatographic behavior across variable conditions.

The software employs multivariate modeling to simulate chromatographic performance across multiple parameter combinations simultaneously, creating a quantitative design space that encompasses hundreds or thousands of potential method configurations (Ahmad et al., 2021). This *in silico* exploration capability significantly reduces both experimental runs and reagent consumption compared to traditional sequential approaches. When integrated with HPLC systems for direct data capture, DryLab® enables seamless feedback between simulation and experimental validation, with published studies

demonstrating that model predictions typically agree with experimental retention times within less than 3.5% (Makey et al., 2020). The high fidelity of these predictions permits confident method transfer and reduces the risk of failed implementations during technology transfer to quality control laboratories.

For stability-indicating method development, DryLab® accelerates the optimization phase by predicting resolution, peak capacity, and selectivity across the design space, facilitating rapid identification of robust method conditions that maintain adequate separation even with specified parameter ranges, consistent with the systematic optimization capabilities described for DryLab® applications in chromatography (Terzić et al., 2014). The software generates resolution maps and multidimensional optimization contours that provide visual guidance for selecting optimal operating points that balance multiple performance objectives, such as analysis time minimization and peak resolution maximization (Huang, 2016; Velichkovska et al., 2022). These computational outputs enable analytical scientists to move beyond single-point optimization toward establishment of wider design spaces that demonstrate inherent method robustness (Latrous, 2022). By integrating forced degradation data with predictive modeling, DryLab® establishes the quantitative foundation necessary for regulatory submissions that demonstrate both separating capacity and analytical method suitability.

MODDE® software: DoE and statistical organization

MODDE® provides comprehensive DoE functionality that enables systematic investigation of CMPs through multiple efficient experimental design approaches (Sartorius, n.d.). DoE software packages, such as MODDE®, implement fractional factorial, central composite, and Plackett-Burman designs, generating experimental templates that guide investigators through structured parameter screening and optimization phases (Fukuda et al., 2018). By simultaneously evaluating multiple variables rather than sequentially optimizing individual factors, MODDE® substantially reduces experimental burden while enhancing the quality of statistical inference (Yeğen et al., 2023). The platform's integrated analytical response analysis tools enable direct measurement and interpretation of how CMPs (mobile phase pH, organic solvent composition, column temperature, and flow rate) influence CAAs including peak resolution, retention time, theoretical plate count, and peak tailing factor (Peng et al., 2022).

Statistical modeling capabilities within MODDE® incorporate response surface analysis and multivariate optimization algorithms that identify optimal factor settings satisfying multiple performance criteria simultaneously (Zakrajšek et al., 2015). The software constructs mathematical models quantifying relationships between independent method parameters and dependent analytical performance metrics, enabling visual representation through contour plots and response surface plots that facilitate rational decision-making during method optimization (Popovska Jakimovska et al., 2023). MODDE® calculates design space boundaries defining the multidimensional region where CAAs remain within predefined acceptance ranges, establishing the analytical MODR that characterizes method robustness across controlled parameter variations (Peraman et al., 2015; Popovska Jakimovska et al., 2023; Zakrajšek et al., 2015). These computational outputs transform analytical method development from isolated single-point optimization toward establishment of wider operating regions demonstrating inherent robustness and regulatory compliance.

Integration of MODDE® with risk assessment workflows streamlines the identification and prioritization of critical parameters requiring tighter control strategies based on their statistical significance and practical impact on method performance (Deidda et al., 2018). The software facilitates systematic navigation of the MODR by quantifying the relative influence of each parameter on analytical performance, enabling pharmaceutical scientists to focus control strategy resources on parameters with the greatest impact on quality attributes (Deidda et al., 2018; Popovska Jakimovska et al., 2023; Zakrajšek et al., 2015). By documenting the quantitative relationships between method parameters and performance outcomes, MODDE® provides the scientific foundation necessary for establishing robust control strategies, defining specification limits, and supporting regulatory submissions that demonstrate comprehensive process understanding and method suitability for stability-indicating applications throughout the pharmaceutical product lifecycle Bairagi et al., 2024 ; (Ellwanger et al., 2020).

Integration of DryLab® and MODDE® for stability-indicating method development

Combined utilization of DryLab® and MODDE® creates a synergistic approach in which systematic DoE-based exploration using MODDE® is complemented by predictive retention modeling in DryLab®, enabling efficient identification of optimal conditions within the defined design space while minimizing experimental requirements (Velichkovska et al., 2022). DryLab® and MODDE® are employed as illustrative examples; however, the described AQbD workflow is not software-dependent and may be reproduced with other DoE and chromatographic modeling platforms offering comparable functionality. This integrated workflow reduces development timelines from weeks to days while maintaining scientific rigor and regulatory compliance (Mannochio-Russo et al., 2020). The workflow begins with MODDE®-facilitated risk assessment and factorial screening to identify CMPs, followed by central composite or Box-Behnken design to establish quantitative relationships between factors and analytical performance (Fukuda et al., 2018; Sartorius, n.d.). Subsequently,

DryLab® leverages experimentally generated data from structured method development studies to construct predictive retention models and generate multidimensional resolution maps, enabling exploration of optimization scenarios without additional experiments (Jayaraman et al., 2011). This sequential integration ensures that every experimental resource contributes to comprehensive process understanding, while effectively eliminating redundant parameter screening and trial-and-error optimization cycles characteristic of traditional method development.

The complementary strengths of both tools enable comprehensive method understanding: MODDE® provides statistical confidence in parameter effects and interactions (Zakrajšek et al., 2015), while DryLab® offers predictive capability for rapid exploration of optimization scenarios (Makey et al., 2020). MODDE® quantifies the magnitude and significance of each parameter's influence on CAAs through rigorous statistical analysis, generating the empirical foundation necessary for establishing control strategies and defining design space boundaries (Popovska Jakimovska et al., 2023). DryLab®'s multivariate modeling and *in silico* simulation capabilities enable simultaneous exploration of numerous potential method configurations derived from design space corners and center points, identifying robust conditions that balance competing objectives such as resolution maximization and analysis time minimization (Jayaraman et al., 2011). This combination ensures both knowledge-rich development through DoE and resource-efficient optimization through predictive modeling, creating a methodologically rigorous yet practically efficient workflow. This integration further enables bi-directional validation, whereby MODDE®-predicted optimal factor settings are experimentally verified to confirm DryLab® predictions, while unexpected experimental outcomes inform iterative refinement of the predictive models.

Despite these advantages, practical implementation of the integrated software-based DryLab®–MODDE® AQbD workflow may be limited by the need for specialized DoE/modeling expertise and rigorous model validation, with potentially reduced predictive reliability for highly complex or novel analytical systems or when extrapolating beyond the studied factor ranges.

Table 2. Key advantages and limitations of the integrated DryLab®–MODDE® software approach in AQbD-based method development

ADVANTAGES		LIMITATIONS	
Aspect	Integrated Software Approach	Aspect	Integrated Software Approach
Experimental efficiency	Reduced number of experiments through statistically guided DoE and predictive modeling	*Training requirements*	Need for expertise in DoE and modeling principles
Design space definition	Rapid establishment of a multidimensional design space	*Initial investment*	Software and infrastructure costs
Development timeline	Shortened method development time compared with traditional approaches	*Data dependency*	Prediction accuracy dependent on quality of input data
Method robustness	Improved robustness through multivariate optimization	*Model applicability*	Limited predictive reliability for highly complex or novel systems
Regulatory support	Structured documentation supporting lifecycle management	*Verification needs*	Experimental confirmation required before implementation
Resource consumption	Lower solvent, reagent, and waste generation	*Implementation complexity*	Integration into existing laboratory workflows

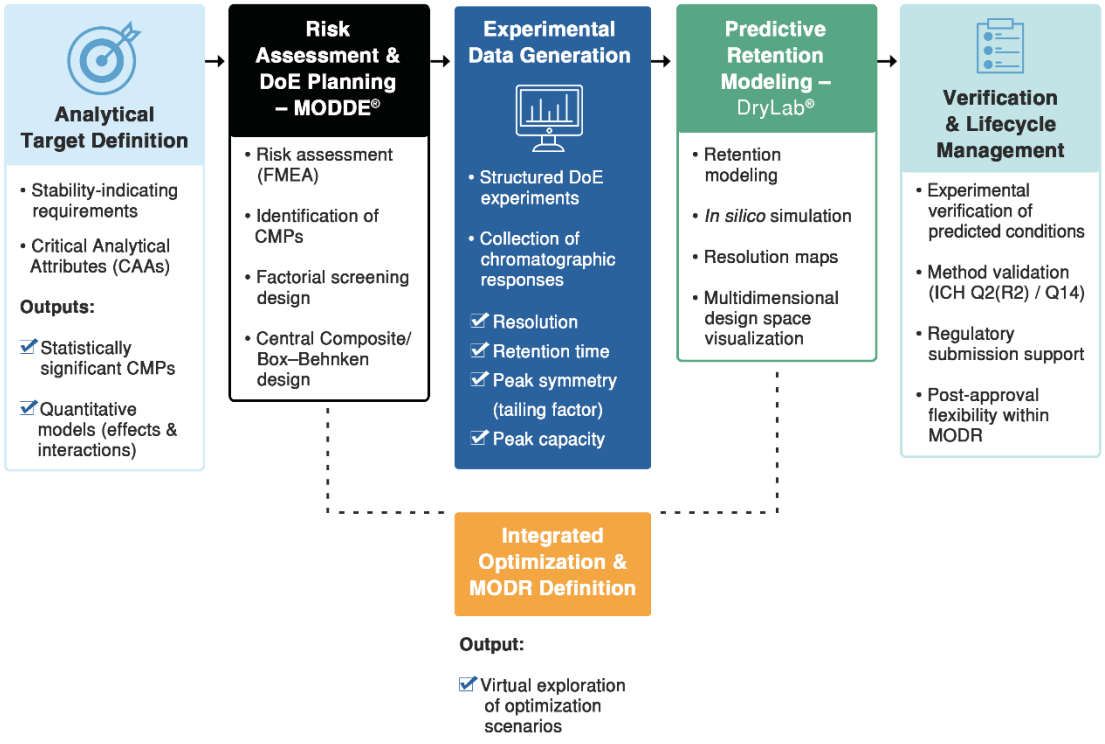

Fig. 1. Integrated AQbD workflow for stability-indicating method development using MODDE® and DryLab® (Workflow concept based on published descriptions of the MODDE® and DryLab® approaches; created with Adobe Photoshop).

The key practical advantages and limitations associated with the integrated DryLab®–MODDE® software approach are summarized in Table 2.

For stability-indicating methods, the integrated approach streamlines troubleshooting during method transfer and scale-up by documenting critical parameters, control strategies, and design space boundaries established through combined modeling (Jayaraman et al., 2021; Losacco et al., 2021). The documented design space serves as the analytical foundation for all subsequent work: technology transfer to quality control laboratories includes resolution maps and predicted performance across operational ranges, enabling rapid confirmation of method suitability without the need for redundant screening experiments (Agrawal & Kotadiya, 2024; Jayaraman et al., 2021). During stability testing program execution, the design space documentation facilitates rapid response to analytical method performance variations by identifying which parameters require monitoring and corrective adjustment to maintain method performance, consistent with multivariate and probabilistic design space concepts proposed for analytical methods under the AQbD framework (Agrawal & Kotadiya, 2024; Lebrun et al., 2013). Real-time monitoring capabilities enabled by this integrated framework support continuous verification of method performance within defined operating ranges, with MODDE®-identified critical control points providing targets for analytical quality assurance throughout the method lifecycle (Deidda et al., 2018; Lebrun et al., 2013; Popovska Jakimovska et al., 2023). Integration of forced degradation study results with both MODDE® statistical models and DryLab® predictive simulations ensures comprehensive demonstration of method specificity across the full range of potential degradation scenarios, providing regulators with confidence that the developed method will reliably detect and quantify all anticipated impurities under real-world storage conditions (Agrawal & Kotadiya, 2024; Jayaraman et al., 2021).

Future perspectives and method development integration

Artificial intelligence (AI) and machine learning (ML) approaches are increasingly recognized as valuable complements to traditional DoE and retention prediction methodologies in analytical method development (Singh et al., 2023). Advanced ML algorithms are capable of processing complex chromatographic datasets and identifying non-linear relationships between separation variables and analytical performance that may not be fully captured by classical statistical models, particularly in mixed-mode and other complex chromatographic systems (Gritti, 2021). The integration of AI-driven retention

prediction with established AQbD workflows thus represents a natural evolution toward data-enriched analytical method development, enabling improved prediction accuracy and broader applicability, particularly for compounds with limited structural precedent (Alves et al., 2025). In this context, AI-enriched quantitative structure–retention relationship (QSRR) models provide a powerful extension of retention modeling by linking molecular structure to chromatographic behavior with improved accuracy and an expanded applicability domain (Xie et al., 2025).

From a lifecycle perspective, the convergence of predictive modeling tools with PAT concepts enables continuous verification of analytical method performance throughout routine use (Mishra et al., 2018). Software-defined design spaces generated using DryLab® and MODDE® can serve as the scientific basis for real-time monitoring strategies, enabling proactive identification of method drift and targeted adjustment of critical parameters during routine quality control and manufacturing scale-up. Such integration has the potential to transform analytical methods from static procedures into dynamic, knowledge-driven control tools aligned with modern pharmaceutical quality systems.

Future regulatory acceptance and broader industrial adoption of AI-enriched AQbD approaches are likely to depend on continued standardization of design space documentation, model validation practices, and reporting formats. Harmonized presentation of software-generated models, confidence intervals, and robustness assessments in regulatory submissions would reduce ambiguity and facilitate consistent interpretation across agencies. Collectively, the integration of AQbD principles with predictive software, AI-based modeling, and lifecycle management frameworks represents a forward-looking pathway toward more efficient, robust, and digitally enabled analytical method development, consistent with recent perspectives on data-driven and AI-supported analytical innovation (Alves et al., 2025).

Conclusion

The combined application of MODDE® and DryLab® represents a mature and efficient AQbD-based strategy for the development of robust, stability-indicating analytical methods, particularly suited to the needs of the pharmaceutical industry. By integrating statistically guided DoE with predictive modeling, this approach enables rapid design space establishment, improved method robustness, and substantial reductions in experimental workload, solvent consumption, and development timelines compared with traditional trial-and-error methodologies. These advantages directly support lifecycle management, technology transfer, and regulatory flexibility within a scientifically justified MODR.

Although the implementation of integrated software-based workflows requires initial investment and specialized expertise, these limitations are progressively offset by long-term resource savings, enhanced process understanding, and reduced risk of method failure during routine use. The growing incorporation of AI and ML into retention prediction and AQbD workflows firther strengthens this paradigm by extending predictive capabilities beyond conventional modeling domains. Wider adoption of such tools, supported by increased integration into academic curricula and professional training, will be essential to ensure that future analytical scientists are adequately prepared for data-driven, digitally enabled pharmaceutical development. Collectively, the integration of DoE, predictive modeling, and emerging AI technologies establishes a forward-looking framework for efficient, robust, and sustainable analytical method development.

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Резиме

Софтверски потпомогнат развој на методи за следење на стабилноста според принципите на аналитички квалитет во дизајн: интеграција на DoE и предиктивно моделирање на ретенцијата со примена на MODDE® и DryLab®

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Клучни зборови: аналитички квалитет во дизајн (AQbD), дизајн на експерименти (DoE), DryLab®, MODDE®, методи за следење на стабилноста

Во современиот фармацевтски развој, сè поголемата сложеност на активните супстанции и формулациите, како и зголемените регулаторни очекувања, ги прават традиционалните пристапи „еден фактор во дадено време“ (one-factor-at-a-time, OFAT) за развој на аналитички методи неефикасни и сè помалку применливи. Како резултат на тоа, аналитичкиот развој во XXI век се насочува кон систематски стратегии базирани на дизајн на експерименти (Design of Experiments, DoE) и предиктивно моделирање, во согласност со принципите на аналитички квалитет во дизајн (Analytical Quality by Design, AQbD). Софтверските алатки, како MODDE® и DryLab®, ја овозможуваат оваа транзиција преку мултиваријантна евалуација на критичните параметри на методот, квантитативно дефинирање на простори на дизајн и предикција на хроматографските перформанси во широки оперативни опсези. Иако бројни студии потврдуваат успешна примена на DoE-базирана оптимизација или предиктивно моделирање на ретенцијата како самостојни пристапи, растечкиот корпус на докази, особено во фармацевтската пракса, укажува на предностите од нивната интегрирана употреба за развој на робусни аналитички методи за следење на стабилноста. Овој труд обезбедува сеопфатен увид во AQbD-базираниот развој на методи за следење на стабилноста, со фокус на комбинираната примена на MODDE® и DryLab®. Притоа, се анализира улогата на овие софтверски алатки во систематската проценка на ризик, статистичкото моделирање и предиктивната симулација, со цел унапредување на робусноста на методот, намалување на обемот на експериментална работа и поддршка на регулаторната флексибилност во рамки на научно оправдана работна област на дизајн на методот (Method Operable Design Region, MODR). Дополнително, се дискутираат перспективите за предиктивно моделирање на ретенцијата со примена на вештачка интелигенција и машинско учење, како природно продолжение на постојните софтверски потпомогнати AQbD рамки, при што се истакнуваат насоките кон поефикасен пристап базиран на знаење и дигитално овозможен развој на аналитички методи.