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## Review Article

# Chromatographic Method Development and Validation in the ICH Q2(R2)/Q14 Era: A Critical Review of Analytical Quality by Design-Driven Approaches

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## ABSTRACT

Chromatographic method development and validation entered a distinct new regulatory phase with the International Council for Harmonisation's split of the long-standing ICH Q2(R1) guideline into two documents: Q14 (Analytical Procedure Development), reaching Step 4 in November 2023, and Q2(R2) (Validation of Analytical Procedures), finalized on the same timeline. Both were adopted by the European Medicines Agency in January 2024 and became legally effective on 14 June 2024, with the US FDA issuing aligned final guidance in March 2024. This bifurcation formally separates the historically conflated activities of method development and method validation, and embeds Analytical Quality by Design (AQbD) — Analytical Target Profile definition, risk assessment, Design of Experiments-based Method Operable Design Region mapping, and a defined control strategy — as the expected route to a validated procedure, rather than as an optional enhancement. This review synthesizes the post-2023 chromatographic method development and validation literature across HPLC, RP-HPLC, and capillary electrophoresis platforms, evaluates industry readiness based on a 2024 ISPE PQLI survey of over 100 stakeholders, and identifies where AQbD-Q14 practice is converging and where it remains inconsistent — particularly around confidence-interval-based accuracy/precision reporting and integration of green- and white-analytical-chemistry metrics.

## INTRODUCTION

For nearly two decades, chromatographic method development and validation in pharmaceutical analysis were governed by a single document —

ICH Q2(R1) — which addressed validation parameters (specificity, linearity, accuracy, precision, robustness) without formally prescribing how a method should be developed in the first place. This left method development

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largely empirical: one-factor-at-a-time optimization of mobile phase, column, flow rate, and detection wavelength, followed by a validation exercise bolted on afterward. The rise of Quality by Design (QbD) in manufacturing, formalized in ICH Q8(R2), prompted a parallel analytical movement — Analytical Quality by Design (AQbD) — that sought to apply the same risk-based, design-space logic to analytical procedures themselves.

This movement was formally recognized by the International Council for Harmonisation with the split of Q2(R1) into two purpose-built guidelines: ICH Q14, governing analytical procedure development, and ICH Q2(R2), governing validation. Both reached Step 4 (final harmonised text) by November 2023, were adopted by the EMA in January 2024, and became legally effective across the EU on 14 June 2024; the US FDA issued a combined Federal Register notice and aligned final guidance in March 2024. This regulatory bifurcation is the central organizing event for this review: it converts AQbD from a research-literature enhancement into the anticipated default pathway for developing a chromatographic method destined for regulatory submission.

## 2. Regulatory Relevance: The Q2(R1) to Q2(R2)/Q14 Transition

The practical significance of this transition is substantial. ICH Q14 introduces the Analytical Target Profile (ATP) as the predefined performance objective against which a method is designed, and formalizes the Method Operable Design Region (MODR) — the multivariate space, mapped through Design of Experiments, within which the method reliably meets its ATP. Q2(R2), in turn, becomes the formal verification step confirming that the developed method satisfies its ATP, and extends validation guidance to non-chromatographic techniques (NMR, ICP-MS,

dissolution, XRPD) for the first time. A 2024 industry survey by the ISPE Product Quality Lifecycle Implementation (PQLI) group, covering more than 100 stakeholders, found that 76% had concerns about the new confidence-interval-based approach to accuracy and precision reporting introduced in Q2(R2) — with 40% citing a need for more replicates and only 15% already using confidence-interval methods in practice. By late 2025, jurisdictions including the EU, USA, Switzerland, China, Egypt, Argentina, Turkey, and Saudi Arabia were at various stages of adopting Q2(R2)/Q14, underscoring the immediate, practical relevance of this review to any laboratory currently developing or revalidating a chromatographic method for regulatory submission.

## 3. AQbD Framework for Chromatographic Methods Under Q14

The Q14-aligned AQbD workflow recurring across the literature reviewed proceeds through five stages: (i) definition of the Analytical Target Profile, specifying required specificity, sensitivity, and reportable range; (ii) risk assessment — typically Ishikawa/fishbone analysis followed by Plackett-Burman or fractional-factorial screening — to shortlist critical method parameters (CMPs) from a larger candidate list (mobile-phase composition, pH, flow rate, column temperature, wavelength); (iii) response-surface optimization, most often via Box-Behnken or central composite design, modelling critical analytical attributes (resolution, tailing factor, theoretical plates, retention time) as functions of the shortlisted CMPs; (iv) establishment of the Method Operable Design Region and a normal operating region within it; and (v) a defined control strategy, followed by full Q2(R2) validation. A comprehensive bibliometric review cited within the Q14 secondary literature identified more than 180 AQbD research articles published between



2019 and 2024 alone, spanning small molecules, biologics, and herbal products, with further growth anticipated following Q14's formal adoption.

#### 4. Literature Review

Representative recent applications illustrate how Q14-aligned AQbD principles are being implemented across chromatographic platforms.

A Q2(R2)/Q14-aligned RP-HPLC/DAD related-substances method was developed and validated for venetoclax, a BCL-2 inhibitor used in chronic lymphocytic leukemia, using gradient elution on an X-Bridge Phenyl column with forced-degradation-based impurity profiling — an example of AQbD-Q14 implementation for an oncology small molecule with degradation-product complexity (PMC, 2025).

Beyond conventional HPLC, AQbD-Q14 principles have been extended to capillary electrophoresis: a cyclodextrin-modified micellar electrokinetic chromatography method for trimecaine and its impurities was developed against a defined Analytical Target Profile using Q14/Q2(R2) recommendations, and a separate review addressed chiral capillary electrophoresis method development for enantiomeric purity control under the same framework — indicating that the Q14 development paradigm is platform-agnostic rather than HPLC-specific.

Integration of sustainability metrics into the AQbD workflow is illustrated by a harmonized Design of Experiments framework combining green and white analytical chemistry principles for synchronous chromatographic assay of anti-diabetic drug combinations (Prajapati et al.), and by a stability-indicating RP-HPLC method for a fixed-dose combination that explicitly integrated green chemistry into its AQbD development (RSC Sustainability, 2026) — both signalling a shift toward sustainability-aware method development running in parallel with the Q14 transition.

A practical-implementation review of ICH Q14 tools for capillary electrophoresis method development (PMC, 2025) noted that, despite Q14's formal adoption, implementation remains challenging in practice due to a shortage of complete worked examples and training resources — a gap directly relevant to the training and case-study needs of academic and industrial analytical laboratories transitioning from Q2(R1)-era to Q2(R2)/Q14-era practice.

#### 5. Identified Gaps and Novelty Statement

Three gaps recur across the post-2023 literature surveyed. First, despite Q14 and Q2(R2) becoming legally effective in mid-2024, published worked examples explicitly structured around the full ATP-to-MODR-to-control-strategy workflow remain scarce relative to the volume of AQbD papers that use Box-Behnken/CCD optimization without formally invoking Q14 terminology — creating a disconnect between AQbD practice and Q14-aligned documentation. Second, the confidence-interval-based accuracy/precision approach introduced in Q2(R2) is inconsistently applied, with the 2024 ISPE PQLI survey indicating most laboratories are not yet using it in practice. Third, integration of green- and white-analytical-chemistry scoring into the AQbD control strategy remains the exception rather than the norm across the chromatographic method literature reviewed, despite growing individual examples.

#### 6. CONCLUSION

The split of ICH Q2(R1) into Q14 (development) and Q2(R2) (validation), effective across major regulatory jurisdictions from mid-2024, marks a structural change in how chromatographic methods are expected to be built and documented. AQbD tools — Analytical Target Profile definition, risk-based parameter screening, Design



of Experiments-based Method Operable Design Region mapping, and confidence-interval-based validation — are moving from optional best practice to the anticipated regulatory default. The literature reviewed here shows steady platform-agnostic uptake of AQbD principles across HPLC, RP-HPLC, and capillary electrophoresis, but reveals continuing gaps in confidence-interval implementation, green-chemistry integration, and availability of complete Q14-aligned worked examples — representing the principal opportunities for near-term analytical method development and training literature in this field.

### Conflict of Interest

The authors declare no conflict of interest.

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