International Journal of Pharmaceutical research and Applications
Volume 11, Issue 3, May-June2026, pp:1921-1930 www.ijprajournal.com ISSN:2456-4494

Lifecycle Management of Analytical Procedures A Review of ICH Q14 and the Revised ICH Q2 (R2)

Mohit Raskar[1], Amit Kasabe[2], Ankita Mohite[3]

Date of Submission: 10-06-2026 Date of Acceptance: 20-06-2026

ABSTRACT:
The International Council for Harmonisation guidelines ICH Q14 (Analytical Procedure Development) and ICH Q2(R2) (Validation of Analytical Procedures), adopted in November 2023 and effective from June 2024, represent a paradigm shift in pharmaceutical analytical regulation. Together, these guidelines establish a comprehensive three-stage Analytical Procedure Lifecycle (APLC) framework encompassing prospective design via Analytical Quality by Design (AQbD), formal performance qualification aligned with updated validation parameters, and continued performance verification through statistical process control. Key innovations include the Analytical Target Profile (ATP), Design of Experiments-derived Method Operable Design Region (MODR), risk-based Established Condition designation, and Post-Approval Change Management Protocols (PACMPs). Expanded scope now covers biologics, multivariate spectroscopic procedures, and PAT-enabled real-time release testing. This review critically examines the scientific and regulatory advancements of both guidelines, analyzes implementation challenges identified in the 2024 ISPE industry survey, and discusses implications for quality assurance professionals and future regulatory directions.

Keywords: ICH Q14, ICH Q2 (R2), Analytical Procedure Lifecycle, Analytical Quality by Design, Method Operable Design Region, Analytical Target Profile

I. INTRODUCTION

The quality of any pharmaceutical product depends on the reliability, accuracy, and precision of the analytical methods used to assess identity, purity, potency, and stability across the drug development and manufacturing lifecycle. For nearly three decades, analytical method validation was governed globally by ICH Q2(R1), which treated validation as a discrete, final task with no inherent methodology for development strategy, lifecycle management, or change control. [1, 2]

The pharmaceutical industry of the 2020s differs significantly from what Q2(R1) originally anticipated. Continuous manufacturing, process analytical technology (PAT), and newer biologics (monoclonal antibodies, ADCs, cell/gene therapy) demand far greater analytical capability and flexibility. Meanwhile, QbD principles were incrementally embedded into drug substance and product development via ICH Q8–Q12, creating a contradiction: manufacturing processes followed a science and risk based lifecycle, while the analytical methods controlling them remained constrained by one-factor-at-a-time (OFAT) development and rigid, immutable submissions. [12, 13, 14, 15]

These structural weaknesses prompted ICH to form an Expert Working Group in 2018 to draft a new guideline on analytical procedure development and revise Q2(R1). Final drafts were produced in November 2018, with Step 4 adoption achieved on 1 November 2023, the updated ICH Q2 (R2) and new ICH Q14 became effective across major ICH regions in June 2024. [1,2,16,17,18] USP had already released USP <1220> “The Analytical Procedure Lifecycle” in May 2022, anticipating many of these concepts at the compendial level. [7]

This review presents a detailed analysis of ICH Q14 and Q2 (R2) and how they fit into the overall Pharmaceutical Quality System, the development of the AQbD concept, the APLC 3-stage paradigm, as well as future implementation obstacles and future pathways that would constitute analytical regulatory science in the years to come.

II. EVOLUTIONS IN THE HISTORY OF ANALYTICAL METHOD VALIDATION

1.1 From Q2A/Q2B to Q2(R1):

Regulatory analytical method validation originated with two ICH documents: Q2A (1994), covering six key characteristics such as specificity, linearity, range, accuracy, precision, and LOD/LOQ and Q2B (1996), clarifying the experimental data needed to evaluate them. These were combined into Q2(R1) (2005), which served as the global regulatory framework for nearly twenty years. [1,2]While well

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 3, May-June2026, pp:1921-1930 www.ijprajournal.com ISSN:2456-4494

established, Q2(R1)'s limitations became increasingly apparent, it addressed only conventional chromatographic and UV spectrophotometric analysis, offered no strategy for method development or optimization, defined no lifecycle beyond validation, and made no mention of biologics, cell-based bioassays, or ATMPs. [26, 32, 33]

1.2 The QbD Era and the Analytical Gap:

The ICH Q8–Q12 series progressively embedded Quality by Design principles across pharmaceutical development: Q8(R2) (2009) introduced design spaces, Q9(R1) (2023) established the current quality risk management framework, Q10 defined the pharmaceutical quality system, Q11 (2012) extended QbD to API development, and Q12 (2019) established Established Conditions and PACMPs for lifecycle management. [12,13,14,15] Borman and co-workers introduced "Analytical Quality by Design" (AQbD) in 2007, describing a systematic, science-based approach to analytical procedure development, later positioned as a tool for achieving both regulatory flexibility and robust analytical performance. [10,4] Yet until Q14, no regulatory expectations existed for AQbD-based submissions a gap later confirmed by the 2024 ISPE survey. [19, 20]

1.3 USP <1220>: A Lifecycle Precursor:

USP <1220>, official from 1 May 2022, was a landmark pharmacopoeial precursor to ICH Q14/Q2(R2): it first formalized the three-stage Analytical Procedure Lifecycle (Design, Validation, Continued Performance Verification) and the ATP concept at the compendial level, ahead of ICH's equivalent provisions. The forthcoming USP <1221> will provide further statistical tools for OPPV. While broadly aligned in lifecycle philosophy, ICH Q14/Q2(R2) and USP <1220> differ on OPPV monitoring frequency and EC definition for compendial procedures, requiring careful navigation for US submissions. [5, 7, 9]

III. ICH Q14: ANALYTICAL PROCEDURE DEVELOPMENT

3.1 Scope and Objectives:

ICH Q14 is the first ICH guideline dedicated solely to the development phase of analytical procedures, applying to new or revised procedures for release and stability testing of commercial drug substances and products. Its key aim is to advance science- and risk-based analytical development underpinning procedures that are fit for purpose across the entire product lifecycle, not just at initial submission. Q14 offers two development pathways - the minimal approach (similar to historical Q2 (R1) practice) and the enhanced approach (the full AQbD toolbox) - along with specific guidance on multivariate procedures for PAT applications and real-time release testing (RTRT). [1,6,21]

3.2 Analytical Target Profile (ATP):

The ATP is the conceptual basis for ICH Q14 and the key link between the analytical procedure and the quality attribute it controls. Q14 defines the ATP as a prospective summary of the quality characteristics an analytical procedure must meet to adequately control the relevant quality attribute. In practice, the ATP is developed before any experimental work and specifies the analyte(s) and sample matrix, the quality attribute to be controlled, and the required measurement range and quantitative performance criteria for specificity, trueness, precision, LOQ, and linearity. [1,11]

Critically, the ATP is technology neutral: it describes what the analytical method must do in terms of measurable performance criteria without describing the specific technique or instrument platform that is to be used. This technology agnosticism is not simply a philosophical principle – it has direct and significant regulatory consequences. A single ATP can justify post-approval technology changes (e.g., from conventional HPLC to ultra-high-performance UHPLC, or from UV detection to mass spectrometric detection) at reduced reporting categories, if appropriate ATP-based bridging studies demonstrate continued compliance with all specified performance criteria. [5,11,29]

The ATP also serves as the objective reference point against which all validation data produced in Stage 2 are compared, replacing the implicit and frequently inconsistently applied acceptance criteria of historical validation reports. Eberle et al. (2025) have noted that ATP-driven validation shifts the focus of validation away from checklist-based regulatory compliance toward confirming that ATP performance criteria are met under real conditions of use. [11]

3.3 Risk Assessment: Ishikawa Diagrams and FMEA:

Q14's enhanced development process requires formal, structured risk assessment using established quality risk management tools. Cause-and-effect

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 3, May-June2026, pp:1921-1930 www.ijprajournal.com ISSN:2456-4494

(Ishikawa/fishbone) diagrams systematically identify potential sources of variability (operator, equipment, reagents, sample preparation, environment, data processing), and FMEA assigns risk priority numbers (RPNs) to each to select critical method parameters (CMPs) for experimental study and critical method attributes (CMAs) for focused monitoring by the ACS. [1,13,23]
High-risk parameters identified by FMEA are characterized using structured DoE, while low-risk parameters may be justified by prior knowledge, platform experience, or literature precedent without further experimentation this risk-stratified investment is a key efficiency benefit over OFAT development. [22,23]

3.4 Design of Experiments and the Method Operable Design Region (MODR):

Q14 defines the MODR as a multidimensional space within which changes to analytical procedure parameters are shown to produce an acceptable reportable result the analytical equivalent of the manufacturing design space introduced in ICH Q8. The regulatory implications are similar: changes within the MODR are not subject to regulatory notification, allowing operational flexibility for routine changes such as column lot, reagent batch, or instrument platform updates. [1,12]

The MODR is typically derived using a sequential DoE approach: screening designs (Plackett-Burman, fractional factorial) identify statistically significant CMPs, followed by response surface designs (Box-Behnken, central composite) to characterise curvature and interactions. The MODR boundary is the multidimensional region where all ATP criteria are simultaneously satisfied. Chiarentin et al. (2024), reviewing ~300 published AQbD case studies, found Box-Behnken to be the most frequently used response surface design, with chromatographic resolution, peak asymmetry, plate count, and retention time as the most commonly optimised responses. [22]

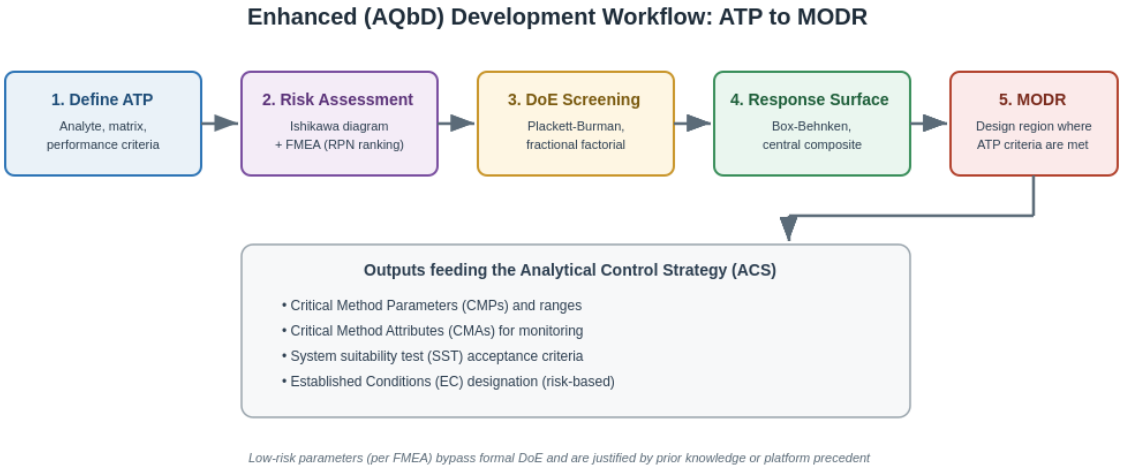

Figure 1: Enhanced (AQBD) Development Workflow From ATP Definition Through Risk Assessment and DOE to MODR Determination.

3.5 Minimal vs. Enhanced Development Approaches:

Table 1: Comparison of Minimal and Enhanced Analytical Procedure Development Approaches per ICH Q14

Feature	Minimal Approach	Enhanced Approach (AQbD)
Development Strategy	OFAT experimentation, empirical optimization	Systematic DoE (Box-Behnken, CCD, Plackett-Burman), multivariate optimization, design space definition
ATP	Not required	Mandatory, translates quality requirements into measurable performance criteria before experiments begin

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 3, May-June2026, pp:1921-1930 www.ijprajournal.com ISSN:2456-4494

Risk Assessment	Not formally required	Structured Ishikawa/FMEA to identify and prioritize CMPs and CMAs
MODR	Not defined, single set of conditions submitted	Demonstrated by DoE submitted in dossier, enables parameter flexibility within demonstrated boundaries
Established Conditions	All parameters treated as ECs, prior approval for any change	Selective EC designation by risk, non-ECs changeable without regulatory notification
Post-Approval Changes	Prior approval (Category A) for most changes	Risk-tiered reporting, low-risk changes via annual report, PACMP under Q12
Regulatory Flexibility	Limited, rigid submissions with high change burden	Greater flexibility, MODR-based submissions support continuous improvement and technology transitions

The 2024 ISPE PQLI survey found broad awareness of Q14 but limited adoption of the enhanced approach, citing DoE/statistics expertise gaps, perceived high upfront cost, and underuse of PACMP-enabled modernisation such as HPLC-to-UHPLC transitions (see Section 8.1 for detailed discussion). [19,20,21]

3.6 Multivariate Procedures and Real-Time Release Testing:

ICH Q14 gives specific guidance for multivariate procedures (NIR, Raman, FT-IR, and NMR) widely used in PAT applications and RTRT. Calibration model lifecycle follows similar principles to Q14: development on a representative sample population, validation of predictive performance with an independent test set (RMSEP, bias, SEP - not RMSECV, which applies only to cross-validation during development), ongoing predictive stability monitoring against reference standards, and systematic model updates with change documentation. [1,30]

RTRT replaces conventional end-product release testing with real-time process data and predictive models, and must meet the same three-stage lifecycle framework with particular rigour around model qualification, RTRT-specific EC definitions, and change management for model updates. BioPhorum (2024) identifies PAT-enabled RTRT as a priority application for Q14's enhanced approach, especially for biologics where batch-to-batch variability is a significant challenge. [30]

IV. ICH Q2 (R2): KEY REVISIONS AND EXPANDED SCOPE

4.1 Expanded Scope:

The revised Q2 (R2) retains Q2 (R1)'s core validation parameters i.e. specificity, linearity, range, accuracy (now resolved into trueness and precision), LOD/LOQ, and robustness but explicitly extends scope to biologics and biotechnological products, multivariate/spectroscopic procedures (NIR, Raman, NMR), and PAT-derived calibration models. This matters pragmatically: biologics now account for a majority of top-revenue pharmaceutical products, and biologics-specific procedures (cell-based bioassays, ELISA quantification, SEC for aggregates) present validation challenges entirely absent from Q2(R1). [2,30]

4.2 Terminology Harmonization: Trueness, Precision, and Accuracy:

One of the most practically relevant revisions in Q2 (R2) is the formal adoption of ISO/VIM vocabulary to resolve the long-standing ambiguity around "accuracy" in Q2 (R1). Under Q2(R2): 'trueness' is the systematic conformity between the mean of a series of measurements and the accepted reference value, expressed as mean % recovery from spiked samples or comparison with a reference standard; 'precision' is the random variation among repeated measurements under the same conditions, expressed as %RSD for repeatability, intermediate precision, and reproducibility; and 'accuracy' remains a qualitative umbrella concept (ISO 5725) comprising both trueness and precision not a separate, measurable parameter in Q2(R2). [2]

This terminology clarification directly affects validation reporting: reports under Q2 (R2) must separately report trueness (mean % recovery with confidence intervals across concentration levels) and precision (%RSD with variance component analysis), and must define the 'reportable range' the concentration interval where all accuracy criteria are simultaneously met which matters most for non-linear models such as the 4PL function used in potency assays. [2,3]

4.3 Updated Guidance for Core Validation Parameters:

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 3, May-June2026, pp:1921-1930 www.ijprajournal.com ISSN:2456-4494

Q2 (R2) raises specificity requirements: chromatographic methods now need peak purity assessment by PDA or MS detection, while multivariate methods use spectral prediction residuals and leverage diagnostics to flag samples outside the model's applicability domain. Linearity now requires residual analysis (residuals vs. concentration) to detect systematic departures masked by a high r^2 value alone, which Q2(R2) explicitly states is insufficient evidence of linearity. [2]

Precision moves from descriptive statistics to variance component analysis (via ANOVA), separating total variability into repeatability, intermediate precision, and reproducibility to enable expanded measurement uncertainty calculations. LOD/LOQ now also use uncertainty-based approaches alongside the traditional signal-to-noise and SD/slope methods, with LOQ tied directly to the lower limit of the reportable range. Robustness is formally linked to the ACS and MODR: CMPs from DoE-based robustness studies must be incorporated into the ACS and controlled within validated ranges. [2,23,24]

4.4 Biologics-Specific and Multivariate Validation Guidance:

The Q2 (R2) extension to biologics includes cell-based bioassays with defined precision criteria (%geometric CV ≤ 30% for typical potency assays), ELISA quantitation with sigmoid calibration models, and purity determination by size-exclusion chromatography (SEC) or capillary electrophoresis. BioPhorum's (2024) best-practice document elaborates on robustness testing, platform validation for monoclonal antibody processes, and considerations specific to potency, binding, and HCP immunoassays. [30]

Table 2: Comparative Analysis of ICH Q2 (R1) and ICH Q2(R2)

Aspect	ICH Q2(R1) [2005]	ICH Q2(R2) [2023]
Scope	Chemical drug substances/products chromatographic and UV spectrophotometric methods only	Expanded: biologics, bioassays, multivariate/spectroscopic methods (NIR, Raman, NMR), PAT models
Terminology	Accuracy used collectively for trueness and precision ambiguous	Formally distinguishes trueness (mean recovery) from precision (variability), ISO/VIM harmonized
Linearity	r^2 and y-intercept as primary criteria	Residual analysis mandatory, reportable range concept introduced for non-linear models
Precision	Repeatability, intermediate precision, reproducibility described qualitatively	Variance component analysis, measurement uncertainty from each precision source required
Robustness	Evaluated but not mandatory in all submissions	Linked to ACS and MODR, critical parameters must be defined and controlled
Lifecycle	No mention; validation a one-time, terminal event	Aligned with ICH Q14, validation as Stage 2 of 3-stage APLC, continuous monitoring mandated
Multivariate	Not addressed	Comprehensive: calibration model lifecycle, RMSEP/bias/SEP metrics, model update management

V. THE THREE-STAGE ANALYTICAL PROCEDURE LIFECYCLE (APLC)

The lifecycle concept of analytical procedures, formalised in USP <1220> (2022) and now integrated into the ICH Q14/Q2(R2) framework, replaces the linear terminal validation model with a continuous, iterative, and evidence-based framework consisting of three formally defined stages. This approach fundamentally re-conceptualizes the relationship between analytical development, validation, and routine use: rather than considering validation as the last milestone before commercial use, the lifecycle model considers validation as the evidence-generating confirmation of performance criteria set prospectively in Stage 1. [7, 11]

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 3, May-June2026, pp:1921-1930 www.ijprajournal.com ISSN:2456-4494

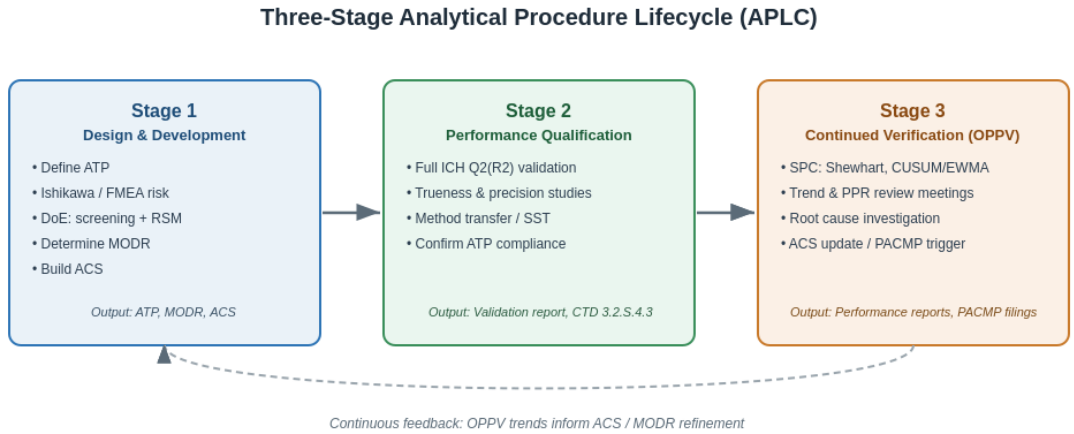

Figure 2: The three-stage Analytical Procedure Lifecycle (APLC), showing the continuous feedback loop from Stage 3 monitoring back to Stage 1 design refinement.

5.1 Stage 1: Procedure Design and Development:

Stage 1 begins with ATP definition, followed by structured risk assessment (Ishikawa diagrams and FMEA) to prioritise CMPs for experimental study. Statistically significant factors are identified via DoE screening, then response surface methodology generates the MODR. The resulting Analytical Control Strategy (ACS) defines MODR operating boundaries, SST parameters and SPC-based acceptance criteria, column qualification and reagent specifications, and the Stage 3 monitoring program design. In a typical RP-HPLC assay, the MODR generally spans mobile phase pH (±0.2 units), organic modifier content (±3% v/v), column temperature (35 ± 5°C), and flow rate (±0.1 mL/min). [1,22,23]

5.2 Stage 2: Procedure Performance Qualification (Validation)

Stage 2 is formal validation under Q2 (R2), providing statistically sound evidence that the procedure meets all ATP performance criteria under actual conditions of use, including variability from analysts, instruments, and laboratory environments. Unlike the historical gatekeeping model, validation here explicitly benefits from Stage 1 knowledge: DoE data guides the validation design, directing resources to the highest-risk parameters and confirming robustness across the MODR boundaries. [2,11] Method transfer via full validation at the receiving site, comparative testing, co-validation, or a justified transfer waiver is also part of Stage 2, and Stage 1's MODR evidence greatly eases this process by showing that inter-laboratory differences within the MODR do not affect ATP compliance. [3,29]

5.3 Stage 3: Continued Procedure Performance Verification (OPPV)

In Stage 3, statistical process control (SPC) is applied throughout the procedure's operational lifetime using routine system suitability data. Shewhart and CUSUM/EWMA charts monitor SST parameters plate count, peak asymmetry, resolution, retention time against SPC control limits derived from validation precision data. A clear distinction must be maintained between SPC control limits (set at ±3σ from the process mean, reflecting inherent variability) and specification limits (compendial or internal acceptance criteria for product release). [7,24]

Periodic Procedure Performance Review (PPR) meetings quarterly or semi-annually provide a structured forum for trend analysis, out-of-control signal assessment, root cause investigation, and decisions on ACS updates or PACMP activation. Borman et al. (2024) proposed a risk-based OPPV approach that prioritises monitoring intensity by procedure criticality and process stability, improving resource allocation. [24]

VI. ESTABLISHED CONDITIONS, PACMPS, AND ICH Q12

6.1 Established Conditions and Risk-Based Designation:

Established Conditions are defined in ICH Q12 (2019) as approved regulatory commitments that require regulatory submission if changed. Under Q2(R1), all submitted method parameters were implicitly treated as ECs, so any change regardless of its impact on performance required prior

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 3, May-June2026, pp:1921-1930 www.ijprajournal.com ISSN:2456-4494

approval. This blanket EC designation was a major driver of the regulatory burden Q14 was designed to address. [15]

Within the enhanced approach, the MODR fundamentally changes the EC landscape: parameters shown experimentally to yield acceptable results throughout the MODR are not ECs, since their variation has been demonstrated not to affect ATP compliance. EC designation applies only to parameters with acceptable ranges narrower than the MODR, or those tied to critical attributes requiring tight control. This targeted, risk-based designation significantly reduces the post-approval change burden for enhanced-approach procedures. [1,15]

6.2 Post-Approval Change Management Protocols (PACMPs):

Within ICH Q12, PACMPs are prospectively incorporated into the dossier at initial marketing authorization, pre-approving anticipated future analytical changes at lower reporting categories. For example, a PACMP for an HPLC-to-UHPLC transition normally requiring Category A prior approval in most jurisdictions can pre-authorize the change at a Category B (annual report) level if it includes an ATP-based bridging study protocol demonstrating equivalent performance. [15,16,17]

Global Q12 implementation is proceeding at different speeds: FDA published final implementation guidance in March 2024, EMA's adoption took effect in June 2024, and PMDA and Health Canada continue their respective national schedules. This variability requires jurisdiction-specific PACMP strategies. [16,17]

VII. AQBD CASE STUDIES: PRACTICAL APPLICATION:

The AQbD workflow in Sections 3.3–3.5 is validated by published case studies. Nagar et al. (2022) showed that DoE-based MODR optimization for RP-HPLC assay methods reliably produces more robust procedures than OFAT approaches with fewer experimental runs, while Lopes et al. (2024) applied FMEA and Box-Behnken RSM to a stability-indicating HPLC method for nevirapine, confirming ATP compliance across the MODR. These studies confirm the enhanced approach is feasible for routine analytical applications, not just large innovator settings. [1, 22, 25, 28]

VIII. IMPLEMENTATION CHALLENGES

8.1 Industry Readiness: Evidence from the 2024 ISPE Survey:

In 2024, the ISPE PQLI Analytical Methods Strategy Team conducted an industry survey (published in Pharmaceutical Engineering, September/October 2025) assessing readiness for Q14/Q2 (R2) rollout, building on an earlier ISPE lifecycle guidance document outlining practical approaches to development, validation, and change management under the new framework. Awareness was widespread across company sizes and sectors, but actual adoption of the enhanced approach remained limited, with most respondents still following minimal-approach practices similar to Q2(R1)-era standards. [19,20,27]

The three most cited barriers were: (i) a lack of in-house expertise in DoE design, data analysis, and ACS development; (ii) a perception of prohibitively high upfront investment relative to the minimal approach, without clear quantification of long-term savings from MODR and PACMP mechanisms; and (iii) a communication gap, with many respondents not pursuing modernizations such as HPLC-to-UHPLC transitions despite PACMP being designed to support exactly this. Borman et al. (2025) argue that this 'high investment' perception significantly underestimates cumulative lifetime savings from reduced prior-approval filings. [19,20,21,29]

8.2 Regulatory Harmonization across ICH Regions:

FDA issued final implementation guidance for Q14 and Q2(R2) in March 2024, addressing simultaneous Q14/Q2(R2)/Q12 PACMP submissions; EMA's adoption took effect in June 2024; and PMDA and Health Canada continue their national schedules, with the concurrent revision of USP <1225> and drafting of USP <1221> adding further alignment requirements for US submissions. [7,8,9,16,17] Rignall and Borman (2026) note that while ICH Q14/Q2(R2) and USP <1220> share a harmonised lifecycle philosophy, provisions on OPPV monitoring frequency, control chart selection, and compendial EC definitions remain divergent, requiring careful navigation for multi-region submissions. [5]

8.3 Organizational and Training Requirements:

Successful enhanced-approach implementation demands a cross-functional capability build spanning DoE, RSM, FMEA, ACS/PACMP management, and SPC for OPPV a significant challenge for smaller companies and CROs. Structured training, CRO partnerships, and engagement with industry forums (ISPE, CASSS,

International Journal of Pharmaceutical research and Applications
Volume 11, Issue 3, May-June2026, pp:1921-1930 www.ijprajournal.com ISSN:2456-4494

BioPhorum) are the most recommended pathways to close this gap, complemented by ICH's own training curriculum released to support harmonised interpretation of the new guidelines. [19,20,21,31]

IX. FUTURE DIRECTIONS

The technology-agnostic architecture of ICH Q14 makes the APLC framework a natural host for emerging technologies. AI/ML offers potential across all three stages: models trained on chromatographic databases could reduce Stage 1 DoE burden, while ML-based anomaly detection on Stage 3 data may flag instrument or column deterioration before Shewhart violations occur. Q14's multivariate guidance also offers the clearest pathway for PAT-enabled RTRT and biosimilar comparability work requiring HDX-MS, circular dichroism, and MALS. However, AI/ML-specific regulatory guidance remains limited, and organizations must invest in digital CMC infrastructure integrating ATP, DoE, MODR, and OPPV data across procedures' 2–3 decade lifetimes. [1, 22, 29, 30]

X. IMPLICATIONS FOR QUALITY ASSURANCE PROFESSIONALS

Quality assurance involvement in analytical method management was primarily retrospective in the Q2 (R1) paradigm: review of completed validation reports, audit of compliance with validated procedures and deviation management. Q14 and Q2(R2) suggest a lifecycle framework that necessitates significantly earlier, more continuous, and more technical QA involvement across all three APLC phases. [1,2]

Stage 1 Engagement: QA reviews and approves the ATP to ensure performance criteria align with the drug product's control strategy, participates in FMEA risk assessment to confirm failure modes are properly identified and ranked, and reviews the ACS to ensure MODR boundaries are well-defined and operationally feasible. [1]

Stage 2 Engagement: QA ensures the validation design is statistically sufficient to prove ATP compliance adequate sample size (at least six analyses per concentration for repeatability; at least three analysts or three days for intermediate precision), full residual analysis for linearity claims, and proper statistical evaluation of LOD/LOQ data then checks Q2 (R2) compliance and prepares the corresponding CTD dossier sections. [2,3]

Stage 3 Engagement: QA plans and controls the OPPV process control chart selection, SPC limit computation, monitoring frequency, PPR meetings, and escalation for out-of-control situations and must clearly distinguish common from special causes, and SPC control limits from release specification limits. [7,24]

This requires an operational framework of ATP, FMEA, DoE protocol, MODR validation, ACS, PACMP, and OPPV monitoring plan templates, plus validated SPC software all needing adequate lead time for development and validation before initial submissions. [19,29]

XI. CONCLUSION

ICH Q14 and ICH Q2 (R2), adopted in November 2023 and effective June 2024, represent a consequential transformation of pharmaceutical analytical regulation. Together they establish an integrated, scientifically rigorous lifecycle philosophy: prospective ATP definition anchors Stage 1 AQbD-based development and MODR characterization, Q2(R2)-governed validation confirms ATP performance in Stage 2, and statistically robust OPPV provides continuous evidence generation throughout Stage 3. [1, 2, 7]

The enhanced approach requires greater upfront investment in DoE expertise and knowledge management infrastructure, but offers substantially reduced lifetime regulatory burden through risk-based EC designation and PACMP pre-authorization. The ISPE survey evidence shows a persistent gap between awareness and implementation, driven by expertise deficits and cost-benefit misperceptions; nonetheless, the enhanced approach is set to become the expected standard for new marketing applications as regulators gain experience with Q14 submissions. [19, 20, 21, 29]

Remaining implementation challenges jurisdictional harmonization, workforce expertise gaps, and digital infrastructure development will require sustained collaboration among regulators, industry bodies (ISPE, BioPhorum, CASSS), and the academic analytical science community. For QA professionals, the lifecycle framework expands both responsibility and opportunity; organizations that invest proactively in enhanced-approach capability now will be best placed to realize its benefits as global adoption accelerates. [5, 29, 30]

REFERENCES

[1]. ICH Q14: Analytical Procedure Development. Step 4, November 2023;

effective June 2024. Geneva: International Council for Harmonisation.
[2]. ICH Q2(R2): Validation of Analytical Procedures. Step 4, November 2023; effective June 2024. Geneva: International Council for Harmonisation.
[3]. Bhattachar SN, Morrison JS, et al. Navigating ICH Q2(R2) compliance: a gap analysis toolkit. J Pharm Sci. 2025;114(5). doi:10.1016/j.xphs.2025.03.012
[4]. Peraman R, Bhadraya K, Padmanabha Reddy Y. Analytical quality by design: a tool for regulatory flexibility and robust performance. Int J Anal Chem. 2015;2015:868727. doi:10.1155/2015/868727
[5]. Rignall A, Borman PJ. Analytical procedure lifecycle approaches per ICH Q14 and Q2(R2): convergences and remaining divergences with USP <1220>. LCGC Int. 2026 Apr.
[6]. Cauchon N, Pelletier MB. Overview of ICH Q2(R2)/Q14 and implementation considerations. CASSS Analytical Methods Symposium Proceedings. 2023.
[7]. USP <1220> The Analytical Procedure Lifecycle. United States Pharmacopeia–National Formulary 2022, Issue 1. Official 1 May 2022.
[8]. United States Pharmacopeial Convention. (2024). Validation of compendial procedures⟨1225⟩. In USP–NF. United States Pharmacopeial Convention. https://doi.usp.org/USPNF/USPNF_M99945_04_01.html
[9]. United States Pharmacopeial Convention. (2025). Proposed revision: Validation of analytical procedures⟨1225⟩ [Draft general chapter]. Pharmacopeial Forum, 51*(6)*.
[10]. Borman P, Chatfield MJ, Nethercote P, et al. The application of quality by design to analytical methods. Pharm Technol. 2007;31(10):142–152.
[11]. Eberle M, Wasylenko JT, Kostelac D, Kiehna S, Schellinger A, Zhang Z, Ehrick JD. A modern framework for analytical procedure development and lifecycle management based on ICH Q14 principles. Anal Chem. 2025;97(1):12–21. doi:10.1021/acs.analchem.4c04521
[12]. ICH Q8(R2): Pharmaceutical Development. Geneva: International Council for Harmonisation; 2009.
[13]. ICH Q9(R1): Quality Risk Management. Geneva: International Council for Harmonisation; 2023.
[14]. ICH Q10: Pharmaceutical Quality System. Geneva: International Council for Harmonisation; 2008.
[15]. ICH Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management. Geneva: International Council for Harmonisation; 2019.
[16]. FDA. Q14 Analytical Procedure Development and Q2(R2) Validation of Analytical Procedures: Guidance for Industry. Silver Spring, MD: US Food and Drug Administration; March 2024.
[17]. EMA. ICH Q14 Guideline on Analytical Procedure Development. EMA/CHMP/ICH/195040/2022. London: European Medicines Agency; 2024.
[18]. Saxena A, Kulkarni P. ICH Q14 and Q2(R2): a comprehensive review of analytical lifecycle management. Int J Pharm Sci Res. 2023;14(8):3619–3630.
[19]. ISPE PQLI Analytical Methods Strategy Team. Readiness for ICH Q2(R2) and Q14: industry survey results and implementation barriers. Pharm Eng. 2025 Sep/Oct.
[20]. ISPE PQLI. Streamlining post-approval analytical procedure changes: industry insights on ICH Q14 PACMP applications. Pharm Eng. 2025 Sep/Oct.
[21]. Borman P, Rignall A, Chatfield MJ. Analytical procedure development with ICH Q14: practical challenges and organizational opportunities. Pharm Outsourcing. 2025.
[22]. Chiarentin L, Orlandini S, Furlanetto S, Noe CR, Quaglia F. Digging into the 'quality by design' approach for analytical methods: a systematic review of published AQbD case studies. Crit Rev Anal Chem. 2024;54(8):3478–3519. doi:10.1080/10408347.2023.2253321
[23]. Verch T, Campa C, Holzgrabe U. Analytical quality by design, life cycle management, and method control strategy. AAPS J. 2022;24(1):16. doi:10.1208/s12248-021-00665-5
[24]. Borman PJ, Guiraldelli AM, Weitzel J, Thompson S, Ermer J, Roussel JM, Marach J, Sproule S, Pappa HN. Ongoing analytical procedure performance verification using a risk-based approach to determine performance monitoring requirements. Anal

Chem. 2024;96(3):966–979. doi:10.1021/acs.analchem.3c03708
[25]. Nagar P, Garg M, Chauhan C, Kumar R, Chaudhary AK. Analytical quality by design (AQbD) approach for HPLC method development, method optimization and validation. Int J Pharm Qual Assur. 2022;13(2):103–110. doi:10.25258/ijpqa.13.2.2
[26]. Ermer J, Weitzel MLJ, eds. Method Validation in Pharmaceutical Analysis: A Guide to Best Practice. 2nd ed. Weinheim: Wiley-VCH; 2015.
[27]. ISPE PQLI. Streamlining analytical procedure development, validation, and change management: a lifecycle guidance document. Pharm Eng. 2024 May.
[28]. Jesus do Nascimento Lopes I de, Kazumasa Fujimori S, de Carvalho Mendes T, Adrielle Dias de Almeida R, Furtado de Mendonça de Sousa F, Areias de Oliveira C, Dibo do Nascimento D, Rebello Lourenço F, Isabel Rodrigues M, Deris Prado L. Application of analytical quality by design (AQbD) for stability-indicating method development for quantification of nevirapine and its degradation products. Microchem J. 2024;199:109939. doi:10.1016/j.microc.2024.109939
[29]. Borman PJ, Rignall A, Chatfield MJ, et al. Advancing implementation of innovative analytical technologies through the ICH Q14 lifecycle framework. J Pharm Sci. 2025;114(1). doi:10.1016/j.xphs.2024.11.009
[30]. BioPhorum Working Group on Analytical Procedures. Best practices for development, validation, and registration of analytical procedures for biologics: implementation of ICH Q2(R2) and Q14. BioPhorum; 2024.
[31]. ICH Q2(R2)/Q14 Implementation Working Group. Training Modules 1–7 on ICH Q2(R2) Validation of Analytical Procedures and ICH Q14 Analytical Procedure Development. Geneva: International Council for Harmonisation; released 9 July 2025. Available from: https://www.ich.org
[32]. FDA. Analytical Procedures and Methods Validation for Drugs and Biologics: Guidance for Industry. Silver Spring, MD: US Food and Drug Administration; July 2015.
[33]. EMA. Guideline on Bioanalytical Method Validation. EMEA/CHMP/EWP/192217/2009. London: European Medicines Agency; 2011.