ICH Q14 Implementation: Expert Panel Discussion on Analytical Method Development

An expert panel featuring industry leaders and academics gathered to discuss practical implementation of the ICH Q14 guideline for analytical procedure development. The discussion addressed common misconceptions, shared diverse organisational perspectives, and provided practical guidance on adopting enhanced approaches for analytical method development in biopharmaceutical settings.

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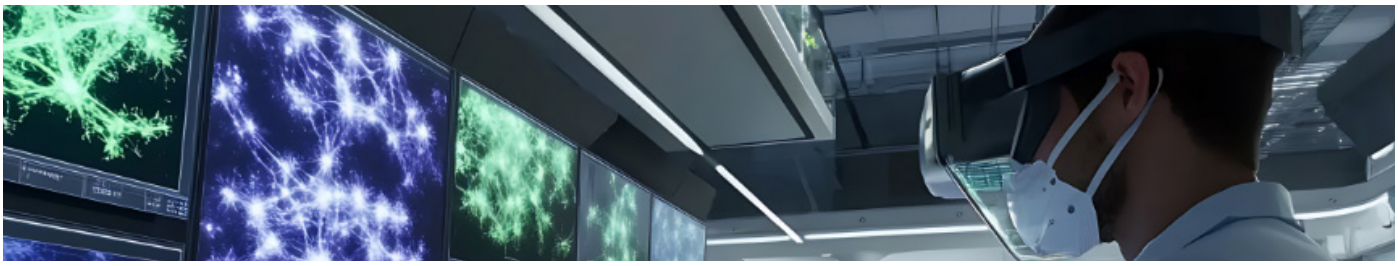
ICH Q14: Evolution Not Revolution

A central theme emerged that ICH Q14 formalises good scientific practices many organisations were already applying informally. Industry has been conducting risk assessments and systematic method development for decades, but this knowledge often remained undocumented in the minds of subject matter experts. The guideline provides visibility, rationalisation, and clear definitions that align the industry whilst creating pathways for regulatory communication about lifecycle management.

However, perspectives varied. Whilst experienced pharmaceutical companies recognised familiar concepts now formalised on paper, biopharma organisations, particularly those with scientists from biomedical rather than analytical backgrounds, welcomed the guideline as essential documentation of design thinking approaches. For these groups, ICH Q14 provides concrete guidance for creating robust methods that work reliably in routine operations, filling a gap where experimental execution was taught but not analytical method design principles.

The Continuum: Not One Size Fits All

The panel emphasised that the minimal and enhanced approaches represent a continuum rather than binary choices. Organisations should select elements based on method complexity, risk, and prior knowledge. For well-established technologies used for decades in both academia and industry, minimal approaches suffice. For complex methods with high variability, such as cell-based potency assays with numerous variability sources from dilution steps, cell culturing, and readout processes, enhanced approaches provide clear advantages



through systematic risk assessment and factor identification.

The concept of modular implementation emerged: organisations can selectively apply enhanced approach elements where they add value. Not every method requires full Method Operable Design Region (MODR) studies. The analytical target profile benefits all methods, but complete deployment of every Q14 element may be excessive for straightforward procedures. For capillary electrophoresis methods, investing in thorough risk assessment and design of experiments for robustness may provide more value than developing a full MODR.

Multivariate Optimisation: Tool Not Replacement

Multivariate optimisation is not about pushing buttons but starts with properly defining the analytical target profile to rationalise factor and response selection. ICH Q14's emphasis on risk assessment addresses a gap where developers often rely on experience and informal knowledge rather than systematic evaluation. Screening designs can inform the risk assessment step, identifying critical method parameters from initial fishbone diagrams. Response surface designs then enable detailed study of these parameters and definition of the Method Operable Design Region.

The panel agreed that multivariate development data can inform validation, particularly for robustness. ICH Q2 revision acknowledges that suitable development data can contribute to demonstrating validation, eliminating redundant robustness experiments under validation protocols when adequate datasets already demonstrate parameter robustness. However, the science must drive the approach. Multivariate methods reveal factor interactions and enable uncertainty propagation throughout the experimental domain but cannot replace fundamental understanding of the analytical system.

MODR: Practical Value Questioned

Debate intensified around MODR practical utility, particularly for physicochemical methods. For classical chromatography techniques, operational flexibility of switching flow rates or temperatures provides limited practical value. Understanding robustness remains essential, but MODR validation represents significant effort without corresponding operational benefit. For routine analysis, operators rarely need flexibility to switch instrument settings.

For biological assays, particularly cell-based methods, the discussion revealed nuance. Whilst cell stock concentrations vary, the scale remains manageable compared to bioreactor manufacturing

processes. Variability in cell-based assays is typically addressed through increased replication rather than validated operational ranges. The expense of additional replicates in analytical assays remains far lower than process-scale adjustments.

A reconceptualisation emerged: MODR need not represent maximum combination of all factors in multidimensional space. Simpler implementations combining just two factors, perhaps allowing temperature adjustment when changing instruments based on robustness data, could provide practical benefit without excessive validation burden. The distinction between MODR and critical reagent control strategies became a point of discussion, with recognition that many approaches fall under the broader umbrella of analytical procedure control strategy.

The panel acknowledged splitting hairs in some discussions. Enzyme activity determination from batch to batch, validated through intermediate precision studies using different enzyme sources, could be labelled MODR or simply considered part of the method with critical reagent controls. What matters is having good understanding during development and appropriate controls based on risk, whether formalised as MODR or managed through other control strategy elements.

Implementation: Training and Change Management

Organisations approach Q14 implementation through guidance documents rather than standard operating procedures, recognising that enhanced approaches represent recommendations rather than mandatory requirements. Companies are developing practical templates, risk analysis fishbones, and method-specific examples showing how to deploy Q14 principles for typical analytical techniques.

Risk assessment receives particular formalisation, as ICH Q9 already mandated risk-based development approaches across pharmaceutical companies. Application to analytical procedures represents extension of existing practices. Other concepts require training but also strategic decisions about where application provides value, where establishing a comprehensive ATP from the beginning guides development of specific measurements effectively.

Change management emerges as critical, particularly for growing biopharma companies transitioning from small startup cultures to larger organisations requiring systematic knowledge capture. External training support provides value, particularly practical hands-on training rather than purely theoretical overview. Implementation guidance, having experienced practitioners review approaches and identify gaps between current state and needed capabilities, accelerates adoption.

Documentation and Knowledge Capture

A recurring theme emphasised documentation value. Many scientists initially resist formalisation, believing they already practise good science intuitively. However, organisational memory proves fragile. Subject matter experts join and leave organisations. Without documentation, subsequent scientists lack context for parameter choices and development decisions. Even single-sentence justifications preserve

crucial reasoning that would otherwise disappear.

The formalisation process enables organisational learning. Risk assessments evolve across projects. Version one gets updated for second and third projects, adding information and revising rankings without starting from scratch. Templates for specific technologies capture accumulated knowledge, creating institutional memory whilst maintaining flexibility for new information from literature or experience.

Initial template development requires time investment, but formalises work already being performed informally. Meeting minutes traditionally captured stakeholder discussions about critical quality attributes, technology selection considerations, and method destination. Converting these discussions into systematic ATP templates ensures consistent coverage without representing fundamentally new work.

Enhanced Approach: Investment and Return

Concerns about enhanced approach time and resource requirements received direct responses. The fundamental question asked: what happens if organisations do not invest in understanding their methods and technologies? Inadequate knowledge leads to unexplained problems, potential manufacture of materials outside clinical scope, and possible patient harm. Every problem not solved during development costs at least double when addressed later.

The ATP specifically illustrates this principle. Organisations have always discussed method purpose, stakeholder requirements, technology selection, and destination in meetings. This information existed in meeting minutes. The investment lies in creating proper templates ensuring systematic consideration rather than ad hoc coverage. Robustness studies have always been performed, with parameter selection residing in expert judgement. Documentation difficulty, backing up mental reasoning into structured documents, required initial investment. Once proper templates and building blocks exist, however, the work becomes formalisation of existing practice rather than additional burden.

The payoff accumulates through organisational learning cycles. Each project using similar techniques or facing similar questions adds to the knowledge bank. Best practices become captured in evolving templates. This growing institutional memory represents significant value, preventing rediscovery of known issues and accelerating development for subsequent products.

Future Evolution

The panel considered whether ICH Q14 represents a starting point or mature framework. As analytical technologies evolve, development tools and guidance will likely evolve correspondingly. Modelling approaches will gain importance. AI-supported development tools will emerge. These technological advances may drive updated tools for analytical procedure development and modified guidance frameworks.

Regulatory interaction also shapes evolution. As organisations communicate more extensively about development approaches and tools with health authorities, expectations may crystallise. This interaction between industry practice

and regulatory expectations creates motivation for evolving tools and frameworks beyond the current Q14 foundation.

Academic input emphasised that Q14 represents both a good starting point and, considering the journey from early AQBD concepts, a significant achievement. The connection between companies, universities, and research communities provides the mechanism for improving guidelines through continued dialogue. One area identified for potential emphasis: multivariate optimisation could receive greater stress in future guideline iterations.

Conclusion

Implementation of ICH Q14 centres on clarity of purpose and disciplined thinking rather than compliance exercises. The guideline provides systematic approaches ensuring analytical procedures reliably support their intended decisions. Success requires recognising the continuum between minimal and enhanced approaches, selecting appropriate elements based on method complexity and risk, and investing in documentation that captures organisational knowledge for long-term benefit. The journey begins with fundamental questions: what is this method for, what decision must it support, and what performance is genuinely needed? These answers, properly captured in analytical target profiles, guide all subsequent development work towards robust methods serving product quality and patient safety.

Meet the Panel

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Watch the full expert forum:
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