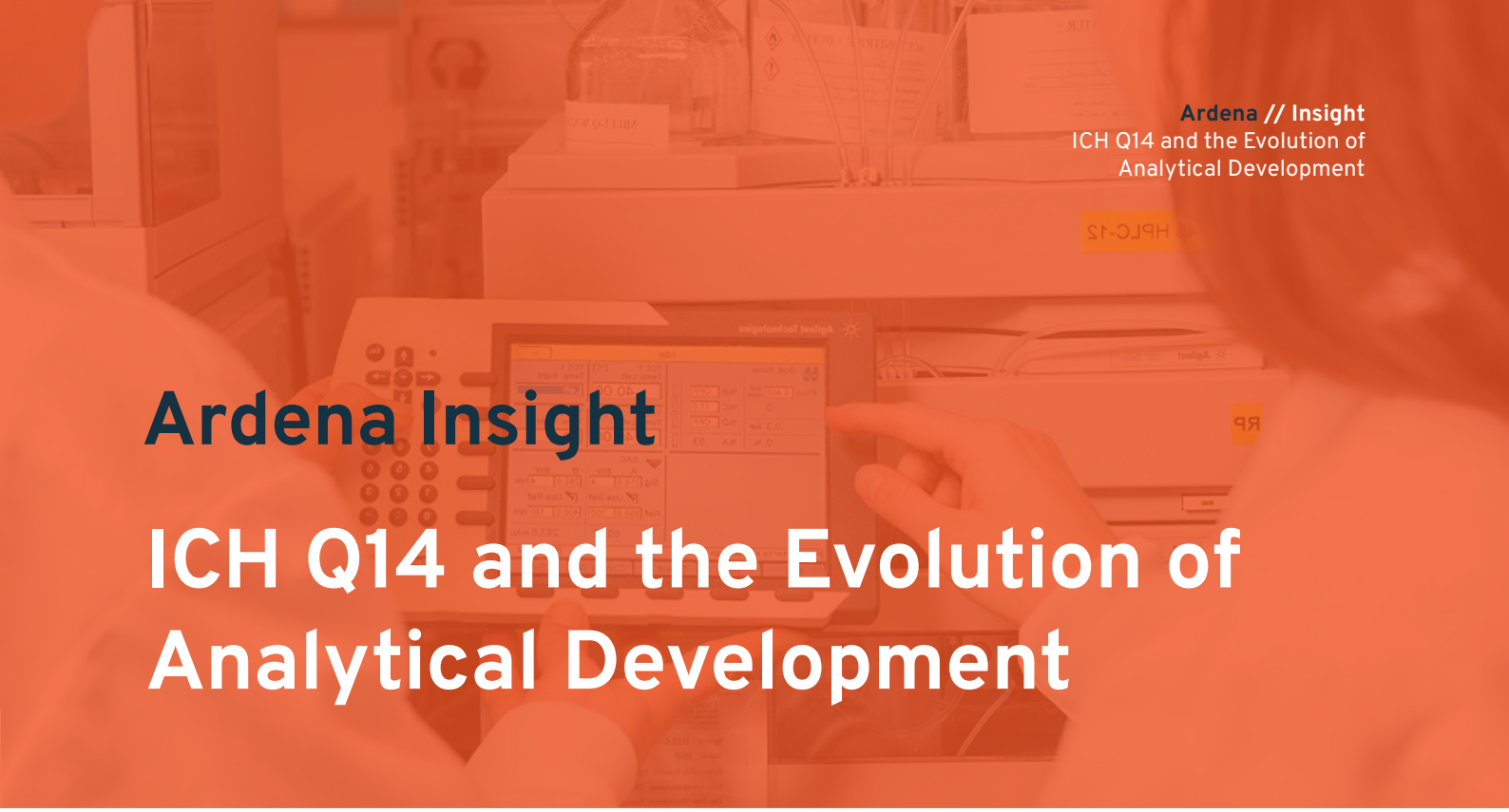


Ardena Insight

ICH Q14 and the Evolution of Analytical Development

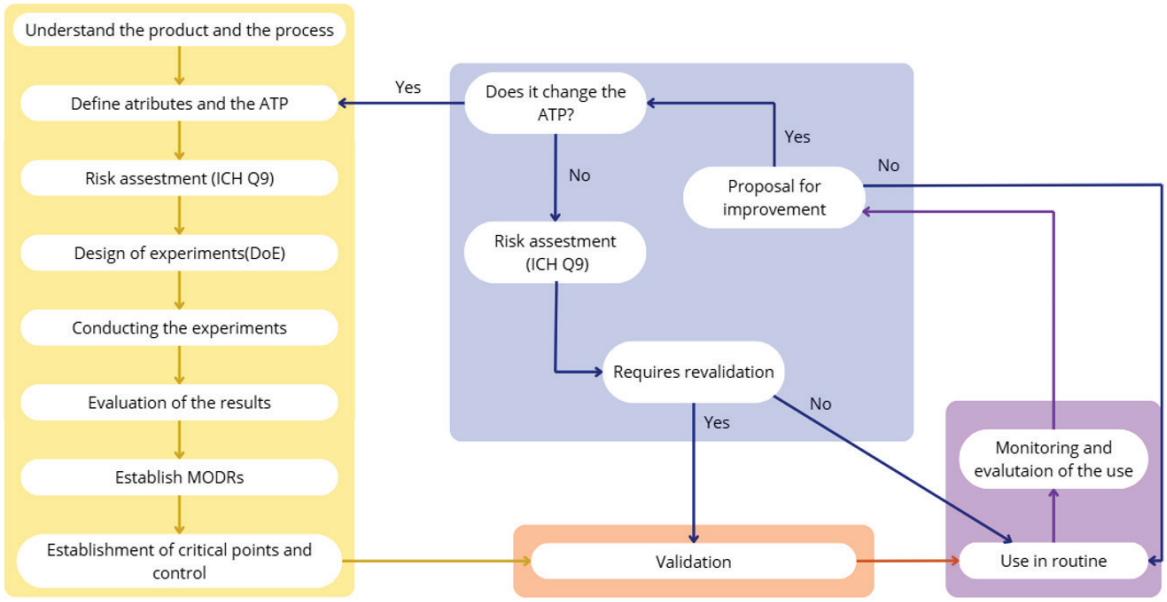
Pharmaceutical development has progressively embraced a holistic and systematic approach to quality, embedding robustness into processes and products from the earliest stages. The concept of Quality by Design (QbD) established the principle that quality must be built into a product rather than verified retrospectively. Building on this paradigm, the ICH Q14 guideline (2022) extends QbD into analytical science through Analytical Quality by Design (AQbD), promoting lifecycle management of analytical procedures and a risk-based framework for regulatory flexibility.

AQbD integrates statistical design, risk management, and knowledge management tools to ensure predefined quality attributes are consistently achieved. By identifying and controlling sources of variability, QbD enhances both product quality and process efficiency. Regulatory guidance has reinforced this concept through ICH Q8 (Pharmaceutical Development), Q9 (Quality Risk Management), Q10 (Pharmaceutical Quality System), Q11 (Drug Substance Development and Manufacture), and Q12 (Lifecycle Management). Together, these guidelines provide a harmonized foundation for science- and risk-based pharmaceutical development.

The publication of ICH Q14 represents a major step in aligning analytical method development with lifecycle principles and intends to improve regulatory communication between industry and regulators and facilitate more efficient, sound scientific and risk-based approval as well as post-approval change management of analytical procedures.

One of the key concepts in ICH Q14 is that, once validated, an analytical method for a product is not fixed permanently. The lifecycle approach establishes a risk-based framework that ensures the quality of the method throughout its use and allows greater flexibility for post-approval change management.

The following diagram illustrates the lifecycle of an HPLC analytical method following the enhanced approach described in ICH Q14. The yellow section shows the different steps in procedure development, the orange section shows validation, the purple section shows routine use and monitoring, and the blue section outlines the process to follow when a method change is required.



During the development of one analytical method, the first step is to understand both the product and the selected technique, in this case HPLC. From the outset, it is essential to define the intended purpose of the method in alignment with product requirements and applicable regulatory expectations.

Once the objectives are established, the **Analytical Target Profile (ATP)** is defined. The ATP describes the required performance of the analytical procedure to ensure it is fit for its intended purpose, by specifying the performance requirements for characteristics such as accuracy, precision, specificity, and range.

ICH Q14 emphasizes identifying those analytical procedure performance characteristics that are critical for meeting the ATP. These measurable aspects of method performance, commonly referred to in the literature as Critical Analytical Attributes (CAA), ensure that the method is fit for its intended purpose. For an HPLC method, relevant examples may include resolution, peak symmetry, theoretical plate number, peak area repeatability, and signal-to-noise ratio.

The ATP and these critical analytical performance attributes are considered early in development, as they form the foundation of a science- and risk-based approach to analytical method design. In line with ICH Q14, a risk assessment is performed using available knowledge of the product and analytical technique to identify and prioritize parameters that may affect analytical procedure performance.

The risk evaluation highlights the parameters that need to be studied further to ensure analytical method quality. This evaluation can be performed using a **Design of Experiments (DoE)** approach.

Following experimental evaluation, a **Method Operable Design Region (MODR)** is established. The MODR represents the multidimensional space within which the ATP criteria are consistently met, and method quality is assured. Movement within the MODR does not require regulatory notification, provided performance remains within the established boundaries.

With prior knowledge and the information obtained in the risk assessment process and experimentation, an **analytical procedure control strategy** is established.

Once the risk assessment is complete and the method is established, the method is validated and used in routine operations. This control strategy ensures method performance and product quality are maintained throughout the analytical method lifecycle.

If a change to the method is required during the product lifecycle, it needs to be studied to determine its potential impact. If the change concerns a variable that has been evaluated in the DoE and remains within the limits of the MODR, it does not need to be reported. If the change is not covered by the MODR, further assessment is required. Depending on whether the change affects the ATP, different pathways may apply. If the ATP is not affected, a risk evaluation should be performed and the method revalidated if necessary. If the change affects a parameter in the ATP, the process may need to begin again.

ICH Q14 reinforces the importance of method lifecycle management, in which analytical procedures are seen as dynamic assets rather than static deliverables. The analytical control strategy becomes a living framework, incorporating performance trends, robustness assessments, and real-world learnings from early clinical phases.

For Ardena, ICH Q14 represents more than a regulatory update. It is an opportunity to deepen scientific dialogue with clients, strengthen analytical strategies from first principles, and deliver methods that are not only phase-appropriate but also forward-looking. By embedding AQbD into our analytical development approach, we help innovative drug developers build analytical procedures that are robust, compliant, and responsive to the realities of modern drug development.