Analytical Procedure (Method) Lifecycle Management Drives Method Development at Innovative CDMO

Waters ACQUITY UPLC with PDA/QDa technology and Empower Software are integral to the early adoption of method lifecycle management at Hovione

Technology: ACQUITY UPLC System, ACQUITY PDA/QDa Detectors, Empower Chromatography Data Software

ANALYTICAL PROCEDURE (METHOD) LIFECYCLE MANAGEMENT AT HOVIONE

"Start with the end in mind..." says António Ramos, Principal Analytical Chemist for Analytical Development, *"...and you will find your development and manufacturing processes can be faster, more efficient, and less costly."*

Bold claims, but claims that are born out of the company's dedication to innovation, uncompromising quality, and the understanding and early adoption of new regulatory themes such as Analytical Procedure Lifecycle Management (also known as Method Lifecycle Management or MLCM).

Since 1959, contract development and manufacturing organization (CDMO) Hovione has helped its customers bring new and off-patent drugs to market. More than 1600 employees across four sites – in Portugal, USA, China, and Ireland – provide services for the development and compliant manufacture of new drug products.

As a global CDMO, Hovione has built a reputation for excellence and integrity, and the majority of the company's customers contract for a complete package – across both development and manufacturing. Mr. Ramos comments: *"Hovione has applied QbD, continuous improvement, change management and lifecycle management approaches in our manufacturing operations for many years – our customers expect nothing less. So, for me, it is a logical extension to integrate these ideas into the earlier stages of development too."*

Hovione's laboratory in Lisbon, Portugal.

WORKING WITH WATERS

Hovione has standardized on Waters™ instrumentation across many of its locations – particularly ACQUITY™ UPLC™ Systems and ACQUITY PDA and QDa™ Detectors, which support Hovione's proactive approach to method lifecycle management. The CDMO prides itself on acquiring the best in analytical instrumentation, with accuracy, precision, and reliability being the key performance parameters that are assessed. This has led to the company's long-standing relationship with Waters.

Alexandra Silva, Director of Analytical Chemistry, describes her company's instrumentation investment strategy: *"It's all about the data quality, we buy the equipment that best fits our purposes and our high standards. We also ensure we have the right amount of support from our suppliers and, in my experience, Waters is one of the best in the business."*

The pharmaceutical regulatory bodies have also begun to champion method lifecycle management (MLCM) as they expand and update industry regulations.

The USP has published a series of 'stimuli articles' that inform a proposed USP General Information Chapter <1220> 'The Analytical Procedure Lifecycle'. The articles discuss how the lifecycle concept described for process validation in ICH guidelines Q8, Q9, and Q10 can be applied to analytical procedures. In addition, ICH Q12 'Pharmaceutical Product Lifecycle Management' is in draft; and is expected to be complemented by a revision of Q2(R1) on method validation and new guideline Q14 on method development.

Mr. Ramos sees this rapidly developing regulatory framework as extremely important: *"Many people don't realize that the existing guidelines are already seen in the context of MLCM, but ICH Q12 and Q14, the latter of which will be dedicated to method development, should be the game-changers that really give people confidence to transform the way things are done."*

Importantly, the FDA (and other regulators around the world) are calling for companies to shift the drug discovery process away from simply collecting data to generating knowledge about a potential new drug.

A scientist at work at Hovione.

"Overall, Quality-by-Design is a good fit for analytical method development because it involves such a structured and scientific approach. This well-understood and systematic tactic makes it much easier to discuss why and how a method was developed with customers – including chemists, engineers, and others involved in the development process."

ALEXANDRA SILVA
Director of Analytical Chemistry

THE THREE STAGES OF THE ANALYTICAL LIFECYCLE

- **Stage 1: Method design and development**
  The Analytical Target Profile (ATP) is used to drive activities. Risk assessment tools and statistical methods used to facilitate understanding of the method (e.g. robustness, design of experiments) and its performance characteristics (e.g. accuracy and precision). ATP is a statement that defines the method's purpose and is used to drive method selection, design, and development activities. It's a key parameter that facilitates greater continuous improvement of analytical methods and their choice.
- **Stage 2: Method performance qualification**
  Confirms that the analytical procedure is capable of delivering reproducible data which consistently meet the ATP. This includes the finalization of the Analytical Control Strategy (ACS), for example: a science-based definition of the allowable replication level of the reportable value. This stage also considers analytical transfer and implementation of compendial procedures.
- **Stage 3: Continued method performance verification**
  The ongoing assurance that the analytical procedure remains continuously in a state of control. This includes an ongoing program for routine monitoring of analytical performance data, as discussed in the FDA Method Validation Guideline from July 2015, and the systematic evaluation of changes.

ANALYTICAL QUALITY BY DESIGN – THE ESSENTIAL FIRST STEP

Implicit in an MLCM approach is the application of Analytical QbD as analytical methods are developed. AQbD benefits include more efficient development of a more robust method, and greater regulatory flexibility because results that fall within the well-defined design space are not considered to be changes in the method.

Furthermore, because there is a greater understanding of these methods, the number of failures and transfer issues that occur over the lifecycle of the method are often reduced. For commercial processes, the high quality of the data provided by AQbD methods may allow for more timely data release, reduced regulatory risk, and lower costs.

Mr. Ramos explains: *"AQbD has a lot of benefits, and you need to start when you are at the beginning of the development stage, so you can put these processes into place and get those benefits in the future. We work with our customers to see how it can help them later on, when they need to transfer methods, for example."*

Hovione sees the key advantages offered by AQbD in the following ways.

Method performance: AQbD typically starts with the definition of the ATP, which should state the performance requirements for the analytical method. Through the application of prior knowledge and an initial risk assessment, AQbD makes it possible to evaluate and prioritize sources of variability that may affect method performance. Researchers use the design of experiments as a systematic tool to understand the real impact of each variable. This process results in the definition of a planned set of operational controls referred to as the analytical control strategy, which is designed to reduce and control all sources of variability.

"If you need to develop something from scratch, the features of AQbD will help you guide you through the process. The real benefits are at the end when you have documentation of all the steps that were developed and the decisions that were made."

ANTÓNIO RAMOS
Principal Analytical Chemist for Analytical Development

Hovione scientists in the laboratory.

Method robustness: Quality-by-design based method development can also result in increased method robustness – which can lead to decreased effort needed for method performance verification and post-approval changes, as well as minimized risk of method-related out-of-specification results.

This approach also strongly contributes to reducing the costs of the method during its lifecycle. Rather than looking at one factor at a time, which typically involves optimization of one factor while the others remain constant, AQbD introduces multivariate analysis. This approach allows an overall understanding of method performance based on the multidimensional combination and interaction of these factors to be obtained, and it leads to the definition of the optimum design space.

The greater the understanding of the impact that occurs because of changes in method parameters, the fewer the resulting failures. As such, methods that are more robust and reliable are therefore fit for purpose throughout their lifecycles.

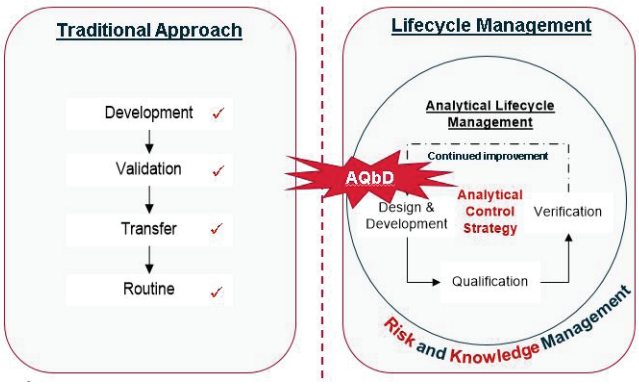
Mr. Ramos describes these benefits: *"Typically, CROs and contract manufacturing organizations (CMOs) transfer methods frequently – from customers, or to customers, or to other locations. Many problems are related to moving methods and the need to change those methods when they move. That's because you often need to make small adjustments for something that is not working. So, there's an advantage if you can build more robustness into the method and avoid those problems. At Hovione, we regularly transfer methods between sites and this methodology helps us to take a structured approach wherever the method is used."*

Risk management: Managing and mitigating risk is extremely beneficial in the pharmaceutical industry, where risk is ever-present. AQbD helps identify potential issues that may affect method performance during the lifecycle, as well as eliminating these issues based on the method understanding obtained during the development work. The overall goal is to reduce and control all sources of variability.

Risk assessment identifies the parameters that impact the ATP. Once the technique is identified, AQbD focuses on method development and includes detailed assessment of the risks associated with variability such as analyst, instrument, sample preparation, analytical method parameters, and environmental conditions.

"If you follow the AQbD process, the scientific knowledge will be there and will help to make the decisions. In method development, for instance, you'll know why you're in this position now and what decision will fit the purpose that you want for a particular method. In terms of risk, it makes you more aware of the problems you will be having or the problems that you can overcome. AQbD puts you in a very good position for solving problems and preventing problems in the future."

ANTÓNIO RAMOS
Principal Analytical Chemist for Analytical Development



A traditional approach to method development compared with Hovione's MLCM approach.

One of Hovione's scientists working on Waters instruments in the laboratory.

Data trending: Data is the backbone of MLCM. Data trending is a proactive approach that enables timely identification and actions, controls variability and risk, and serves as the basis for continuous improvement during the product lifecycle. Data trending provides better knowledge about the method to understand how potential sources of variability such as critical method parameters may impact the method performance characteristics or key performance requirements.

Data trending in MLCM impacts all aspects of development and contributes to reducing risk, lowering costs, and improving regulatory compliance.

Data trending is one reason why Hovione puts so much emphasis on its need for high-quality tools like Waters™ Empower™ Data Chromatography Software to generate data, to retrieve data, and to ensure data integrity.

"Method development through AQbD requires more focus on data trending and how to evaluate big data. It contributes to all aspects of MLCM."

ANTÓNIO RAMOS
Principal Analytical Chemist for Analytical Development

EMBRACING CHANGE

Analytical control is a vital part of the success of drug development and manufacturing programs from the earliest discovery phases through process development to commercialization. Appropriate and effective analytical methods provide information about the impact of process changes on the quality of pharmaceutical products and play a vital role in decision-making. Therefore, the quality of analytical methods must be assured throughout their lifecycle, including development, validation, transfer, and routine use. Method lifecycle management incorporates the entire process.

By embracing AQbD, scientists have the potential to directly affect the pharmaceutical method development process by:

- Reducing the risk of making a wrong decision
- Controlling the method throughout the lifecycle
- Increasing method understanding
- Increasing flexibility to change.

"These are big changes for the industry, and they don't happen in just one day. It takes a lot of time to introduce these concepts. It's clearly a different way of approaching method development when compared to the traditional ad-hoc development that is common in most companies."

ANTÓNIO RAMOS
Principal Analytical Chemist for Analytical Development

Hovione provides services for the development and compliant manufacture of new drug products.

WORKING WITH WATERS

Hovione has equally high expectations for Waters Empower Chromatography Data Software, which the company uses across all of its sites. Ms. Silva explains: *"Empower is more robust, more user-friendly, and gives us the best advantages in terms of managing data and data integrity. That's essential for analytical procedure lifecycle management."*

Overall, Hovione has determined that the combination of Waters instrumentation and AQbD is a powerful strategy for method development that leads to better, faster, greener analytical methods, as well as reduces costs and enables resource optimization. Hovione plans to actively pursue AQbD because of the significant benefits to its customers – and to the company's business strategy.

António Ramos in the laboratory at Hovione.

Hovione has proactively adopted MLCM and AQbD methodology to help their customers gain efficiencies, and improve the quality of their drug products, and the adoption of Waters UPLC and PDA/QDa technology has contributed to its success.

LOOKING AHEAD

The interest in MLCM and AQbD methodologies continues to grow and Mr. Ramos and Ms. Silva expect that firm regulatory guidelines will be in place in the next few years. With that, industry standardization can follow.

As Hovione's customers have begun to recognize these new concepts, the company has seen a gradual shift in the conversations it is having at the beginning of a project. Around 20 percent of the company's clientele have already begun specifically requesting AQbD, and Hovione is actively proposing the approach with the other 80 percent of customers.

"It's an added value for our customers when they understand that we are able to provide this new and improved way of method development. It's good for them in terms of compliance, and it encourages them to use our capabilities in this area. That's good for our business."

ANTÓNIO RAMOS
Principal Analytical Chemist for Analytical Development

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