SPEEDING DEVELOPMENT AND REDUCING COSTS WITH ANALYTICAL QUALITY BY DESIGN

→ BY **ANTÓNIO RAMOS** AND **RUI LOUREIRO**, HOVIONE

Applying Quality by Design (QbD) principles to analytical method development leads to many benefits, such as a more efficient method development process, more robust and reliable analytical methods, and compliance with increasing regulatory requirements, including those pertaining to method lifecycle management.

WELL-KNOWN CONCEPT

Quality by Design (QbD) is defined in ICH Q8[1] and ICH Q11[2] for pharmaceutical development and manufacturing. It is "a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding as well as process control, based on sound science and quality risk management."[1]

At Hovione, QbD is widely applied and the company has received approvals from regulatory authorities for products developed using a QbD approach. Because analytical method development occurs alongside process development, it seemed natural to extend QbD to this activity.

WHY QBD FOR ANALYTICAL METHOD DEVELOPMENT?

Analytical control is crucial to 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 on 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 life cycle (development, validation, transfer and routine use).

Traditionally, the analytical method steps (development, validation, transfer and routine) are considered as separate entities and there is no focus on gaining

deep method understanding. Typically this approach leads to methods that present a narrow knowledge space, robustness issues and high risk of failures through their life cycles. For that reason, it is becoming a trend in the pharmaceutical industry to apply a life cycle management approach to analytical method lifecycles in order to enhance method understanding through the application of structured and scientific approaches. Herein is described the application of QbD to analytical method development.[6,7]

Application of QbD to analytical method development as part of life cycle management enables the use of well-known tools/concepts already employed during manufacturing process development. This new analytical mindset, known as Analytical Quality by Design (AQbD), provides greater process knowledge while enhancing deep method understanding and results in the development of robust methods that are compliant throughout their full life cycles.[3]

A structured and scientific approach, AQbD typically starts with the definition of the Analytical Target Profile (ATP) concept, which should state the performance requirements for the analytical method based on the selection of an appropriate technology. Through the application of prior knowledge and an initial risk assessment, it is possible to evaluate and prioritize sources of variability that may affect method performance. Design of experiments (DoE) can be used 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 (ACS) that is designed to reduce and control all sources of variability.[6]

Rather than looking at one factor at a time (OFAT), 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 leads to the definition of the optimum design space.

The greater the understanding of the impact that changes in some method parameters have on the analytical results obtained when using this structured and scientific approach, the fewer the resulting failures. As such, methods that are more robust and reliable are therefore fit for purpose throughout their life cycles.

BENEFITS OF AQbD

In addition to more efficient development of a more robust method, AQbD provides greater regulatory flexibility, because results that fall within the well-defined design space are not considered to be changes in the method.[4] Furthermore, because there is a greater understanding of these methods, the number of failures (out-of-trend (OOT) and out-of-specification (OOS) results) and transfer issues that occur over the life cycle of the method are often reduced.[5] 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.[5] Overall, therefore, AQbD is a powerful strategy for method development that leads to better, faster, greener analytical methods that reduce costs and enable resource optimization.

SCIENTIFIC AND STRUCTURED APPROACH

At Hovione, the overall AQbD process flow for analytical method development is divided into three stages. **(1) Method Design & Development**, where method performance requirements and goals are identified by a multidisciplinary team, and a technology is selected that complies with these goals. **(2) Method Understanding**, which includes gaining knowledge about the method to understand how potential sources of variability such as critical method parameters (CMPs) may impact the method performance characteristics or key performance requirements (KPRs) and critical method attributes (CMAs) using risk assessment tools; definition of an experimental strategy in which the multidimensional combination and interaction of CMPs are defined using DoEs, resulting in a space where it is possible to assure method performance, known as the method operable design region (MODR); and selection of the working point, normal operating ranges (NOR). **(3) Risk Mitigation**, where potential causes that may affect method performance during its life cycle are identified and eliminated based on the method understanding obtained during the development work. At the end, an ACS is defined in order to reduce and control all sources of variability.

WITH AQbD IT IS NO LONGER NECESSARY TO EMPLOY A TRIAL-AND-ERROR APPROACH; THE APPLICATION OF EXISTING KNOWLEDGE GREATLY FACILITATES THE EVALUATION OF POTENTIAL METHODS.

From Hovione's perspective, this approach will provide regulators and customers with a clear explanation regarding the choice of method and how it was developed. In addition, AQbD is valuable because it allows for the development of robust methods that can be used throughout the product life cycle. Improvement of analytical methods based on performance is becoming a compliance expectation. With methods developed via AQbD, the impact of possible changes over a method's lifetime has already been considered, so the need for changes is minimized.

CASE STUDY: RP-UPLC METHOD DEVELOPMENT

Reversed-phase liquid chromatography (RP-LC) is the most widely used analytical technique in the pharmaceutical industry, and thus it is well understood. At Hovione, due to technology advances, high-performance liquid chromatography (HPLC) methods are being transferred to ultra-performance liquid chromatography (UPLC) methods. UPLC is a similar but much faster technology than traditional HPLC. It also provides better chromatographic resolution and more sensitive analyses in less time, with reduced solvent consumption.[8] The combination of this

faster technology with AQbD is becoming a powerful tool for analytical method development activities at Hovione.

In one particular example, a customer brought a process to Hovione that required seven different HPLC analyses for seven different compounds using four different methods. Each analysis had a run time of approximately 30 minutes (at a flow rate of 1 mL/min). Method redevelopment was pursued with the goal of identifying one robust and reliable method for all intermediates. AQbD was applied in this case.

The process began with the definition of the ATP, which consisted of a single method that could accurately quantify the drug substance and all intermediates to support decision-making for each step of the manufacturing process. This was in order to ensure that the final product was consistently within specifications. After considering the performance requirements, as well as business and technology drivers, RP-UPLC with a photodiode array (PDA) detector was selected as the technology of choice.

Through a knowledge-gathering process, all available information relating to the structures of the molecules was evaluated, such as pKa values and polarities. This information aided in selection of the most approriate column and pH range. CMAs of critical resolutions, least peak retention time, peak shape and signal-to-noise ratio, and potential CMPs were identified and an initial risk assessment was performed. During this process, each CMP was scored based on its potential to affect the CMAs, and this information was used to determine which parameters should be evaluated and when. As an output, the more appropriate experimental strategy was defined. The MODR was established, providing increased knowledge of method performance and leading to robust operating conditions for routine use (the NOR). The method was then assessed to ensure that it complied with all of the performance requirements when operating in the NOR.

At the end of this process, a single robust UPLC method was obtained to control and monitor all seven compounds, replacing the initial four HPLC methods and reducing analysis time by approximately 70%. The combination of UPLC and AQbD is a powerful tool for increasing productivity and reducing solvent and energy costs, while still providing for increased method understanding. Therefore, this approach results in more efficient, environmentally friendly and cost-effective analytical methods.

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. P

ABOUT THE AUTHORS

António Ramos
Analytical Chemistry Group Leader,
Process Chemistry Development, Hovione

António Ramos has a degree in Chemistry by the Faculdade de Ciências of Lisbon University, and a Ms.D. from the Universidade Aberta, Lisbon in the area of quality management. He is currently the Group Leader for Analytical Chemistry Development in the process chemistry development area with the scope of development and evaluation of all analytical procedures that are applied at Hovione Exclusives Projects.

LinkedIn www.linkedin.com/in/ant%C3%B3nio-ramos-2a1263101/
Email aramos@hovione.com

Rui Loureiro
Director of the R&D Process Chemistry, Hovione

Rui Loureiro joined Hovione in 2008 as a process chemist. After several positions, he is currently the Director of the R&D Process Chemistry area, where he is responsible for the development and scale-up of processes to produce active pharmaceutical ingredients under development. Currently his interests are scaling-up of processes to produce and purify APIs under a quality by design approach, flow chemistry and process modeling.

LinkedIn www.linkedin.com/in/rui-loureiro-59905116/
Email rloureiro@hovione.com

REFERENCES

1. *Pharmaceutical Development Q8 (R2)–ICH Harmonised Tripartite Guideline*. Rep. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Aug 2009. Web.

2. *Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities)* Q11–ICH Harmonised Tripartite Guideline. Rep. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. 1 May 2012. Web.

3. Reid, George L., James Morgado, Kimber Barnett, Brent Harrington, Jian Wang, et al. "Analytical Quality by Design (AQbD) in Pharmaceutical Development." *American Pharmaceutical Review*. 27 Aug. 2013. Web.

4. Tang, Yubing. Quality by Design Approaches to Analytical Methods - FDA Perspective. *AAPS*, Washington, DC, 25 Oct. 2011. U.S. Food and Drug Administration. Print.

5. Kochling, Jianmei, Wei Wu, Yimin Hua, Qian Guan, Juan Castaneda-Merced, et al. "A Platform Analytical Quality by Design (AQbD) Approach for Multiple UHPLC-UV and UHPLC-MS Methods Development for Protein Analysis." *Journal of Pharmaceutical and Biomedical Analysis* 125 (2016): 136. Web.

6. Martin, Gregory P., Kimber L. Barnett, Christopher Burgess, Paul D. Curry, Joachim Ermer, et al. "Proposed New USP General Chapter: The Analytical Procedure Lifecycle (1220)." U.S. Pharmacopeial Convention. Web.

7. Martin, Gregory P., Kimber L. Barnett, Christopher Burgess, Paul D. Curry, Joachim Ermer, et al. "Lifecycle Management of Analytical Procedures: Method Development, Procedure Performance Qualification, and Procedure Performance Verification." U.S. Pharmacopeial Convention. Web.

8. Kumar, Ashok, Gautam Saini, Anroop Nair, Rishbha Sharma. "UPLC: A Preeminent Technique in Pharmaceutical Analysis." *Acta poloniae pharmaceutica* 69.3 (2012): 371-80. Web.

9. Musters, Jacky, Leendert van den Bos, Edwin Kellenbach. "Applying QbD Principles To Develop a Generic UHPLC Method Which Facilitates Continual Improvement and Innovation Throughout the Product Lifecycle for a Commercial API." *Organic Process Research & Development* 17.1 (2013): 87-96. Web.

10. Hanna-Brown, Melissa, Kimber Barnett, Brent Harrington, Tim Graul, James Morgado, et al. "Using Quality by Design to Develop Robust Chromatographic Methods." *Pharmaceutical Technology*. 2 Sep. 2014. Web.

11. Monks, Kate, Imre Molnár, H-J Rieger, B. Bogáti, E. Szabó. "Quality by Design: Multidimensional Exploration of the Design Space in High Performance Liquid Chromatography Method Development for Better Robustness before Validation." *Journal of Chromatography A* 1232 (2012): 218-230. Web.

12. Ermer, Joachim, John H. McB. Miller. *Method Validation in Pharmaceutical Analysis: A Guide to Best Practice*, 2nd Edition. Germany: Wiley-VCH, 2014. Web.

The Leader in Commercial Spray Drying

Combining the largest capacity, the best scale-up science and the most experienced team you can trust Hovione to take your project from development to market.

SOLUTIONS FOR

Solid Dispersions
Taste Masking
Modified Release
Lung Delivery

In it for life

Hovione

www.hovione.com • +351 219 829 000