Applying QbD Principles to Analytical Development

By Shawn Watson, Head of Research and Development

Stephen R. Covey said a principle is a natural law, determining action and outcomes. The second principle of his 7 Habits of Highly Effective Leaders is to start with the end in mind. This happens to be the guiding principle behind Quality by Design (QbD). Quality must be designed into the product, or in pharma's case, the drug or the process. Pharma has successfully been applying QbD to developing safe and effective medicines, and is now looking to harness the power of the principle to Analytical Method Development by building quality into the design of an analytical test method. Analytical Quality by Design (AQbD) is indeed an extension of QbD, offering a systematic and robust approach to the development of analytical procedures involving all the stages of the product's lifecycle.

Those who have read my QbD series of articles know my passion for QbD, and this passion expands to AQbD because it is the key to method accuracy and precision. AQbD benefits include identifying and minimizing sources of variability that may lead to poor method robustness and ensuring that the method meets its intended performance requirements throughout the product and method lifecycle. As the term suggests, the analytical procedure lifecycle is a cyclic process that should result in continuous method improvement.

Regulators Are Embracing AQbD

Deploying AQbD has been hindered by regulations, or, more specially, a lack thereof. As recently as 2017, there were no specific guidelines showing how to implement AQbD concepts.

Then, in 2018, ICH Q14: Analytical Procedure Development was proposed to harmonize scientific approaches, and was published just this year. Q14 that lays out the concept and application of Quality by Design in relation to the development of analytical methods. Before ICH Q14, it was common for only analytical validation results to be reported and few presented a performance evaluation with analytical development results. This made communication with the regulatory authorities more difficult, especially when unconventional analytical methods are used (i.e. real-time release testing and multivariate models for process control). In addition, the lack of guidelines excluded the possibility for providing a scientific basis for flexible regulatory approaches, like QbD, to change analytical methods after approval. According to ICH, the new Q14 directive is proposed to harmonize the scientific approaches to analytical process development and to provide the principles for the description of the analytical development process. The new guideline should improve communication between industry and regulators and allow for more efficient, scientifically sound and risk-based authorization and change management for post-approval changes to analytical methods.

This year also brought the revision of ICH Q2(R1) for validating analytical procedures. ICH Q2(R2) develops a new quality guideline and provides principles relating to analytical development procedures. Applying this guideline will also aim to improve regulatory communication between industry and regulators include validation principles that cover analytical use of spectrometric data (i.e. near infrared spectroscopy or Raman spectroscopy, and Nuclear Magnetic Resonance).

In parallel with the activities outlined in ICH Q14 and ICH Q2 (R2), the first draft of USP <1220> Analytical Procedure Life Cycle was published in 2020.[1] The main focus is on the ATP (Analytical Target Profile), and the draft states that ATP is an essential part of the life cycle approach. The ATP serves as a prospective description of the desired performance of an analytical method used to measure a quality characteristic and is defined, for example, in quantitative or semi-quantitative methods, among other things, by the requirements for precision and accuracy. The ATP thus focuses on the design objectives for a new analytical method and serves as a basis for validation and monitoring of the method during its life cycle.

Additionally, this past April, the British Pharmacopeia (BP) published a supplementary chapter on The Application of AQbD to Pharma Methods.[2] In its role at the Medicines and Healthcare products Regulatory Agency (MHRA), the BP claims the chapter is not designed to be mandatory and is to be provided as selective guidance for the application of AQbD principles and across the entire analytical method lifecycle. The chapter is meant to be fluid so that the BP can add and revise the guidance as more information becomes available and further international standards are developed.

The AQbD Process

With guidance clarification now available, how should QbD be applied to Analytical Development? Based on FDA[3] and USP[4] suggestions, the following AQbD approach can be taken:

- Define the analytical target profile (ATP). This is a predefined objective of the method that stipulates the performance requirements. Determine what to measure and where/when to measure it based on critical quality attributes (CQAs).

- Determine the method design. These are the critical procedure attributes (CPAs) and analytical responses that you will be monitoring during the design. The responses should reflect the method of quality and work performance of the method.

- Identify critical method parameters (CMPs), These are the analytical conditions that significantly impact method performance. How to analytical condition changes impact analytical responses. Here you can rely on prior knowledge and risk assessment tools to help select those critical parameters.

- Screen and optimize using design. Here, you can use Design of Experiments (DoE), data acquisition, regression analysis or prediction model validation. DoE can help to understand the effect of CMPs on performance and then aid in selecting the best performance conditions for method optimization. This leads to what is called the “knowledge space.” This is the space where

we know how analytical responses will behave based on changes in analytical conditions. The ultimate goal is to optimize performance. Determine the operating range for good performance of the method.

- Risk assessment and robust testing. Risk assessments (RA) are an integral part of the AQbD process. Their use facilitates identification and ranking of parameters that could impact method performance and conformance to the ATP. Risk assessments are often iterative throughout the lifecycle of a method, and are typically performed at the end of method development, with product changes (e.g., route, formulation or process) and as a precursor to method transfer. Risk assessments at the development to commercial transfer stage typically focus on parameters from a ruggedness perspective. These RAs focus on potential differences (e.g., laboratory practices, environment, testing cycle times, reagents sources). Major differences (e.g., equipment availability) should be identified and factored in at the technique selection and method development stages. AQbD risk assessments start with deconstructing the analytical method into Analytical Unit Operations. Unit operation Inputs and the Analytical Actions related to the particular process steps are identified.

- Method verification. Validation of the method in line with ICH Q2(R2) guidelines is typically carried out at a set point (normal operating condition - NOC) within the chromatographic spaces evaluated. In addition to validating the method characteristics as per regulatory guidance, verifying the accuracy and precision provides additional understanding of the method's measurement uncertainty and confirms conformance to the previously defined method performance requirements (ATP).

- Define the method operable design region (MODR). The MODR, also known as the control space, is established based on CMP models and robustness simulations. MODR is the operating range for the critical method input variable, producing results that consistently meet the goals set out in the ATP. MODR permits the flexibility in various input method parameters to provide the expected method performance criteria and method response without resubmission to FDA. It is based on a scientifically-sound, risk-based, and multivariate approach to evaluate effects of various factors on method performance. FDA has suggested conducting MODR together with method validation. Once this is defined, appropriate method controls can be put in place and method validation can be carried out.[5]

- Control strategy. A meaningful method control strategy is established based on the wealth of data collected during the method development and verification stages. Correlations can be made between method attributes and the ability to meet ATP criteria, which will ensure a strong link between method purpose and method performance. The control strategy should include method parameters that influence method variability.

- Continuous monitoring/lifecycle management. Once a method is established for routine use, method performance should be monitored over time to ensure it remains compliance with the ATP criteria. Periodically monitor the method's performance to address gaps, and, as needed, update the process and analytical technology.

Contract development and manufacturing organizations (CDMOs) with QbD experience can effectively apply AQbD to method development and navigate the existing and recently updated guidelines. A CDMO

will draw from its QbD experience to develop a robust method at the beginning, but always keeping the end in mind.

About Pii

Pharmaceutics International, Inc. (Pii) is a contract development and manufacturing organization (CDMO) with a passion for solving problems efficiently with the highest quality standards. Pii's Analytical Research & Development scientists pride themselves on their experience and ability to expedite method development and tech transfer in support of complex sterile fill/finish projects.

Pii's Hunt Valley, Maryland campus includes 70 manufacturing suites with 4 integrated aseptic filling lines delivering quality, safety, and efficiency. Our professionals have extensive experience with small and large molecule compounds, developing and manufacturing complex parenteral drugs, extended-release formulations, non-aqueous injectable drug products, and lyophilization. Learn more at https://www.pharm-int.com/

About the Author, Shawn Watson

Shawn Watson joined Pii in July 2020 and is responsible for all product development, including sterile, non-sterile, oral, and topical dosage forms, as well as analytical methods development.

Shawn has over twenty years of leadership experience in the pharmaceutical industry in specialty, generic and contract development and manufacturing organizations (CDMOs). His wealth of knowledge spans Research and Development, Quality, and Technical Services.

Prior to joining Pii, he served as the Vice President of Quality and Laboratory Operations at Lupin Pharmaceuticals, Vice President of Compliance at Sigmapharm Laboratories, and Supervisor of Analytical R&D at Teva Pharmaceuticals. Additionally, he has held a variety of other key positions including Vice President of Quality, Senior Director of Chemistry & Manufacturing services, and Senior Manager of Analytical Research and Development. Shawn's passion for working in the pharmaceutical industry began with his very first job as a quality control chemist with a CDMO and included work with Pii.

Shawn earned a Masters of Business Administration from the Fox School of Business at Temple University, a Master of Science in Chemistry from Villanova University, and a Bachelor of Science in Chemistry and Biology from Heidelberg University. He also obtained a six sigma green belt from Villanova University.

References

1. The British Pharmacopoeia
2. Quality by Design Approaches to Analytical Methods -- FDA Perspective, Yubing Tang, PhD, AAPS, Oct. 25, 2011.
3. Introduction to Analytical Quality by Design (AQbD) principles, Amanda Guiraldelli, Scientific Affairs Manager, USP, April 15, 2021.
4. USP publishes draft of new chapter <1220> Analytical Procedure Life Cycle, ECA Academy, Sept. 9, 2020.
5. Analytical Quality by Design: A Tool for Regulatory Flexibility and Robust Analytics, Int J Anal Chem, Feb. 2, 2015.