QUALITY BY DESIGN: TRANSFORMING 21ST CENTURY PHARMACEUTICAL MANUFACTURING

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The quality of pharmaceutical products is the top priority for both drug makers and regulators. To ensure consistent high product quality and improve the efficiency of manufacturing and regulation, the FDA introduced quality by design (QbD) to the pharmaceutical industry in its 2002 Pharmaceutical cGMP initiative, "Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach."[1]

The QbD concept has been widely adopted as a standard of practice for manufacturers, including those in the automotive, semiconductor, electronics and chemical processing industries. Regulators have also embraced QbD as a means to modernize the regulation of pharmaceutical manufacturing and product quality through manufacturing science, based on methodologies proven across countless applications. From their standpoint, QbD-based processes hold great potential in creating the efficient, agile and flexible manufacturing systems required by biopharma to reliably deliver safe, effective high-quality drug products to patients in a secure supply chain.

REGULATORS DRIVING QBD IMPLEMENTATION GLOBALLY

Since the introduction of QbD, the FDA has taken multiple measures to promote industry-wide implementation. One step is to develop guidance and harmonize global regulation on QbD. Working with regulators in other regions (e.g., European Union) and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), the FDA has led the effort to develop international guidelines for modern pharmaceutical quality systems based on science and risk management. Four major guidelines – ICH Q8(R2) *Pharmaceutical Development*, ICH Q9 *Quality Risk Management,* ICH Q10 *Pharmaceutical Quality System*, and ICH Q11 *Development and Manufacture of Drug Substances* – provide the main regulatory guidelines for the industry to implement QbD in their operations. ICH Q12 Lifecycle Management is currently under development and will focus on post-approval chemistry, manufacturing and controls (CMC) changes.[2] Additionally, the FDA finalized its guidance on process validation (an important component in QbD paradigm) in 2011.[3]

The FDA has also actively participated in various working groups focused on QbD training and implementation. Further, several pilot programs were initiated by the FDA to encourage communications between the industry and agency, facilitate pharmaceutical companies' initial embrace of QbD and gain regulatory compliance experience. These programs include an Office of New Drug Quality Assessment (ONDQA) CMC pilot program in 2005, an Office of Biotechnology Products (OBP) pilot program in 2008 and an EMA-FDA joint pilot program of the QbD parallel assessment in 2011,[4] aimed at supporting biopharmaceutical manufacturers in integrating QbD principles into product development.

Regardless of the methodology's potential, the industry's response to QbD has been mixed. Many biopharma companies fully embrace the concept incorporating QbD approach in their development programs, while many others remain hesitant to adopt QbD and integrate its principles into their operations thoroughly. With the FDA strongly encouraging QbD elements in Abbreviated New Drug Applications (ANDA) for generic drugs since January 2013, it has become crystal clear that drug developers will have to demonstrate QbD-compliant practices in all license applications from small molecule to biologics.[5] Conventional wisdom says it is better to act now and gain practical experience with QbD before regulators mandate their wholesale adoption.

QBD FRAMEWORK

In a QbD paradigm, there are two key deliverables: a product designed to meet patient needs and a process designed to consistently deliver a product that meets the critical quality attributes (CQAs) necessary for its clinical performance.[4] Achieving these goals requires deep understanding of the product (including raw materials, excipients and intermediates) and the process (including process parameters and process performance attributes) and their impact on quality. A well-controlled and monitored process capable of continuous improvement is also a must, ultimately with potential for commercial scale-up.

Following a well-structured QbD framework, drug developers can gain a thorough understanding of the product and process. It starts with defining the quality target product profile QTPP, a summary of characteristics related to quality, safety and efficacy of a drug product including intended use, route of administration and dosage form and strength. QTPP serves as a foundation for product design (i.e., formulation) and development (i.e., analytical assay development).[6] The next step is to identify pCQAs (preliminary CQAs), through risk assessment, which ranks the importance of each product attribute based on its impact on safety and efficacy. Prior product knowledge and/or experience and relevant information from a variety of resources (similar products, literature) also contribute to this exercise. Input from clinical experts is critical for successful definition of pCQAs.[7]

After identifying pCQAs, all process parameters (inputs and outputs) in each unit operation are evaluated through risk assessment as well as preliminary critical process parameters (pCPPs), which are identified based on their correlation to pCQAs. The risk assessment mitigation matrix (RAMM) is specially designed to identify final CPPs.[7]

Once pCQAs, pCPPs and risk assessments are in place, the impact of process parameters and their interactions on pCQAs can be further studied using a design of experiments (DOEs), a structured experimental plan designed for statistical analysis. The information generated

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from DOEs can then be used to define a multidimensional design space (inputs) where each pCQA serves as a dimension (outputs). An appealing feature is that working within the approved design space is not considered a change and, therefore, will not require post-approval regulatory review or approval.[8] When DOE process characterization and more analytical data are complete, we finalize CQA and CPPs.

A complete QbD platform also includes a process control strategy to assure process performance and product quality as well as a strategy for process verification, life-cycle management and continual improvement.[4] In QbD framework, every component is interrelated; understanding the linkage of all of these elements to product quality (CQAs and QTPP) is fundamental to achieve QbD objectives.

With respect to regulatory filing, the following QbD components are currently expected: the QTPP; lists of CQAs, CPPs and critical material attributes of the drug and excipients (CMAs); and a control strategy that ensures the product reliably meets predefined objectives.[5]

EXPERIENCED CDMO/CMOS OFFER CONFIDENT QBD IMPLEMENTATION

The benefits brought to the industry by implementing QbD are clearly evident. First, QbD provides a holistic, structured development plan at the start of product development. It compels drug developers to rationalize product attributes to clinical performance and to investigate critical issues (such as formulation, analytics and process parameters) associated with product quality early on. Second, QbD emphasizes understanding the variables (e.g., CMAs and CPPs) and controlling uncertainties and risks.

A well-controlled, well-thought-out process will not only consistently deliver a drug product with predefined quality, but also allow easier and faster identification of root cause for an Out-of-Specification (OOS) event compared to a traditional approach. Unlike traditional development approaches, which simply focus on at-scale production, the QbD approach builds in the process capacity of scale-up manufacturing. In turn, a seamless scale-up translates to a reduced timeline for technical transfer and commercial production.

Indeed the upside potential of implementing QbD is attractive. It does, however, require significant upfront investment at the earliest stages of drug discovery and development. It also necessitates sustained commitment and tight collaboration from cross-disciplinary teams of R&D, formulation, process engineering, and regulatory affairs. Most understand that at the beginning of product development, knowledge regarding product and process is limited, particularly for first-in-class drugs. For companies with a tight budget and operational resources, these hurdles can be extremely challenging to clear while racing to market with a promising compound.

In many cases, forming a closer professional relationship with a knowledgeable and experienced contract development and manufacturing organization (CDMO) can help drug owners overcome QbD's compliance and implementation challenges while exploring the methodology's potential to accelerate drug development and successful commercialization.

There is a growing list of CDMO/CMOs offering well-structured QbD programs and relevant experience implementing QbD-based drug development. Those at the top of the list – who have embraced QbD approaches and practices – are better equipped to leverage manufacturing process knowledge and insights based on broad experience developing diverse products. In this way, valuable assessment of a drug candidate's potential and its manufacture can be initiated early, thus closing the knowledge gap as quickly as possible. By customizing the QbD approach for each product–working closely with the clients to define CQAs, assess risks and make data- and objective-based decisions–a cost-efficient, robust and QbD-compliant manufacturing process can be delivered within the targeted timeline.

Experienced CDMO/CMOs, including CMC Biologics, can take on a QbD project at any stage, but the greatest opportunity lies in engaging contract service providers at the earliest stages of a drug candidate's development. Similarly, organizations that can align themselves more closely and more strategically with knowledgeable, experienced partners will have better prospective outcomes throughout a product's potential commercial life. P

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John joined CMC Biologics in 2014 and serves as the Vice President for Process Development. Prior to joining CMC Biologics, he held director-level positions at Amgen, focused on process development and characterization, clinical and commercial technology transfer and process validation. John has a Ph.D. in chemical and biological engineering from the University of Wisconsin-Madison and a bachelors of chemical engineering from the University of Delaware.

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→ REFERENCES

1. *Pharmaceutical CGMPS for the 21st Century — A Risk-Based Approach: Second Progress Report and Implementation Plan.* Rep. U.S. Food and Drug Administration. 10 June 2015. Web.
2. "Quality Guidelines." ICH. Web.
3. *Guidance for Industry. Process Validation: General Principles and Practices.* Rep. U.S. Department of Health and Human Services Food and Drug Administration, FDA. Jan. 2011. Web.
4. Torres, Michael. "Challenges in Implementing Quality By Design: An Industry Perspective." *BioProcess International.* 16 June 2015. Web.
5. Rosencrance, Susan. "QbD Status Update Generic Drugs." GPhA Fall Technical Conference. FDA. 3 Oct. 2011. Web.
6. "Applying ICH Q8 (R2), Q9, and Q10 Principles to Chemistry, Manufacturing, and Controls Review." *Office of Pharmaceutical Quality* (2016). Center for Drug Evaluation and Research. 18 May 2016. Web.
7. Kumar, Ashok, James Schmid, Clinton Weber, Lisa Joslin, Roland Ashton, and Michael Larson. "Quality by Design: A CMO's Perspective on Gaining Knowledge Faster and Better." *BioPharm International.* 1 July 2013. Print.
8. Rathore, Anurag and Helen Winkle. "Quality by Design for Biopharmaceuticals." *Nature Biotechnology* 27 (2009): 26-34. Web.

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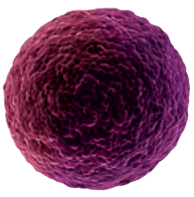

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