Quality by Design: A Holistic Approach to Drug Development

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As the biopharmaceutical industry continues to evolve, the Quality by Design (QbD) holistic and proactive approach to drug development and manufacturing is transforming key processes. In response to increased interest from global regulatory agencies, QbD seeks to further reduce the risk associated with drug development and bring much-needed therapies to market quicker.

Sponsors who implement QbD early can save money through increased product / process knowledge, less re-work, less product deviation, less product out-of specification, fewer rejects and improved quality.

While QbD evolves from good practice to agency requirement, how can sponsors ensure that rigorous, scientific risk-based approaches are used to bring better and safer therapies to market faster? To realize the full potential of this investment, QbD must link early- and late-stage development with manufacturing and commercialization. Mostly importantly, applying QbD ensures a quality product reaches patients.

A History of QbD

Quality by Design (QbD) is a holistic and proactive approach to pharmaceutical development designed to ensure a drug product meets its desired quality specifications, and thereby, expected clinical performance. Prior to the usage of the phrase Quality by Design, the term “optimization” was more frequently used by global regulators, since it entailed optimization of drug development areas like formulation and process design.

QbD had its unofficial start in 2002 when the US Food and Drug Administration (FDA) launched the Pharmaceutical Quality for the 21st Century initiative to reduce risk and enhance the quality of pharmaceutical manufacturing. Two years later, the agency released a report “Pharmaceutical Quality for the 21st Century: A Risk-Based Approach” which noted QbD as a proven science- and risk-based approach to ensuring safe medicines reach patients in need.

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By the early 2000s, the FDA required the inclusion of more quality data in new drug application filings and stated that biopharma companies “must continue to move from a compliance mindset to quality by design.”[1] In response, the International Conference on Harmonization (ICH) provided guidance on QbD over the coming years. Following in 2013, the FDA mandated QbD implementation throughout product and process design, quality target product profile (QTPP), critical quality attributes (CQAs) and other quality elements. Today, global regulatory agencies – including the FDA, the European Medicines Evaluation Agency (EMEA), Japan’s Pharmaceutical and Medical Devices

Agency (PDMA) and the Korean Ministry of Food and Drug Safety (MFDS) – seek proof points related to QbD used during development to ensure product quality at the approval stage.

QbD in the Modern Biopharma Era

The goal of QbD is to facilitate a deeper understanding of the elements that go into creating a new therapy and designing quality into the product. At its core, the approach is "by design," which entails planning the selection of formulation and development methods to obtain a robust process. Decades ago, the mantra was "quality is not to be tested into compliance but initiated in the development phase." While quality has always been paramount in pharmaceutical development, the addition of "by design" emphasizes the importance of leveraging QbD to develop a robust process in early development in order to aid implementation in late-stage development and commercialization.

Simply put, QbD accounts for the complexities of drug formulation and drives the design of processes that result in consistent, sustained compliance with production. Across multiple areas, quality is built into a finished product. These include the raw materials employed, the drug formulation and composition, the processes involved, final packaging and even analytical testing. Consistency of the end product quality is a result of building QbD into the process early.

Applying QbD to the Drug Development Process

Quality by Design is a principle and a systemic approach that has applications throughout drug development. Understanding the critical quality parameters in any process allows developers to design procedures that support quality deliverables at any stage.

In practice, QbD principles are applied throughout the development process, including:

- Quality target product profiles (QTPPs);
- Identifying critical quality attributes (CQAs);
- Critical material attributes (CMAs);
- Critical process parameters (CPPs);
- Risk assessment and management;
- Design of experiments (DoE);
- Design space;
- Process analytical technology (PAT);
- Robust process design;
- Process control strategies; and
- Product lifecycle management.

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QbD tactics are useful in small molecule development, for example, as these products are more prone to risks that are intrinsic in the formulation or the process. For biologics, much of the risk assessment and QbD principles focus on improving the titer, purity and maintaining sterility throughout all steps and into manufacturing.

Since clinical development builds the pillar of robustness for product quality, pharmaceutical companies must perform QbD and phase-appropriate risk assessment and application of QbD principles throughout each stage of development, beginning with early development. Due to high failure rates, pharma companies too often try to get their molecule to clinic as early as possible, seeking proof of concept. As a result, they tend to invest too little in QbD, which can increase the likelihood of greater challenges later in development. Assessing risk and addressing challenges early are fundamental benefits to applying QbD. By addressing issues early, process scale-up is easier to manage, resulting in products speeding safely through development, regulatory approval and commercialization.

Use of QbD is more prevalent in late-stage development as well when sponsors have more security in the knowledge that the molecule will succeed and reach patients. At this step, pharmaceutical companies want to ensure that any outstanding issues with product robustness or process design have been resolved. This is critical, since QbD testing during late stage generates the data for the Chemistry Manufacturing and Control (CMC) package that is submitted with a new drug filing.

Then, supply chain QbD comes into play. Can I manufacture my product on a routine basis? Can I meet the demand forecast? At this point, pharmaceutical companies realize the need to have a robust drug manufacturing process, and QbD fulfills this requirement.

The Benefits of QbD

In response to increased interest by global regulatory authorities, pharmaceutical companies are embracing the use of QbD principles throughout drug development. Regulators are asking questions as to what quality assurance work has been done, which includes elements of QbD. Pharmaceutical industry stakeholders are also understanding the benefits of QbD application in the different phases of drug development.

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Pharmaceutical companies benefit from implementing QbD in numerous ways:

- Meeting clinical trial timelines;
- Creating less waste of time and resources;
- Faster approval as regulatory agencies look for QbD elements;
- Continuous process improvement;
- Reducing manufacturing issues;

- Challenging bad methods or processes;
- Sharpened focus on procedures;
- Quicker batch release and stability study generation;
- Faster commercialization through the ability to scale up with no inherent defects; and
- Consistent sustained processes that can be Right First Time.

Sponsors who implement QbD at the outset can save money through increased product / process knowledge, less re-work, less product deviation, less product out-of-specification, fewer rejects and improved quality. Most importantly, applying QbD ensures a quality product reaches patients – the end goal for all healthcare providers and manufacturers of pharmaceutical products.

The Risks of Delaying QbD

For some pharmaceutical clients, the worst-case scenario for not implementing QbD early enough can mean going back to the drawing board with a product after learning a formulation cannot be manufactured consistently. This revelation jeopardizes timelines, costs and the approval process. Many companies choose to bypass investment in early development by using fit-for-purpose formulations for early clinical development. While initially effective, these simple drug formulations may lead to discoveries later about efficacy that compromise the product.

Biopharma companies also delay investing in QbD due to reasons, including concerns over the high percentage of attrition in drug development. By not applying QbD early, sponsors assume they are taking less financial risk. This may prove true in the short term, but can be costly in the long run. Patheon encourages early adoption of QbD principles as a way of increasing the value of the drug asset, by confirming its overall quality and enhancing its chances for success. This is especially important for companies hoping to outlicense a molecule once early development testing indicates a clear opportunity for commercialization.

The perceived increased costs associated with QbD keeps other pharmaceutical companies from early adoption of QbD. Higher quantities of the active pharmaceutical ingredient (API) may be needed to achieve QbD objectives, for example. These elements lead to more labor cost, as well – for the work, analytical testing, statistical analysis, interpretation, data reports and other needs.

Pharmaceutical developers may also fear the unknown with QbD and not understand how it is relevant to their product. As more regulatory agencies utilize and enforce QbD, companies that do not leverage a proper risk – and science-based development process face challenges. These include:

- Product rejections and timeline delays;
- Regulatory questions and concerns;
- Inconsistent drug performance;
- Adverse impacts to clinical trial endpoint data;
- Risk of failure during commercial scale up; and
- Risk of regulatory deficiencies that could delay or deny their drug application.

Today, more pharmaceutical companies are willing to implement QbD, but the larger appetite for investing still rests with companies that have solid funding and a high level of confidence in progressing their molecule. By not investing in QbD, pharmaceutical companies may create a product and process that cannot be scaled up or manufactured consistently for commercial markets. By its nature, QbD seeks to reduce the risk associated with drug development and bring much-needed therapies to market quicker.

Moving the Industry Forward

As the industry enters the next phase of formulation complexity and technological advancement, QbD continues to benefit those drug developers who capitalize on its approach. Soon, all major regulatory agencies will require documented proof that QbD principles were used throughout the development process.

As QbD evolves from good practice to requirement, it presents a distinct advantage during the final regulatory filing from patient safety, technical capability and regulatory perspectives. To reach its full potential, however, QbD must link earlyand late-stage development with manufacturing and commercialization. Through early adoption and application of QbD, key pharmaceutical industry stakeholders can ensure that rigorous, scientific risk-based approaches are used to bring better and safer therapies to market faster.

With more than 50 percent of all new products outsourced to CDMOs and a majority of NDA/MA approvals supported by CDMOs[2], it is important and critical that the outsourced partners have the skill set and experience in implementing QbD for future drug products.

1 August 2002, Food and Drug Administration, Pharmaceutical Current Good Manufacturing Practices (cGMPs) for the 21st Century, initiative announcement.

2 LifeScience Leader, March 3, 2014, “Outsourcing Solid Dose Manufacturing Trends in 2014” by Kate Hammeke, Director of Marketing Intelligence, Nice Insight.

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