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Making Cents: QbD Must Shift Its Focus

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It has been nearly eight years since ICH first rolled out its concept paper on Pharmaceutical Development defining the framework for Quality by Design (QbD) and nearly seven since the FDA first embraced the concept in its 2004 guidance on Risk based cGMPs. During that time the industry has been warming up to the benefits of QbD. While adoption has been slow, it is gaining momentum.

At the FDA Advisory Meeting held in July, industry, academia and the Agency came together to determine where the industry was in its adoption of QbD, measure its success and understand its failures. The general conclusion from the meeting was that QbD was still in its infancy and will require more time if it is to have the transformative effect first conceived by ICH.

The factors slowing the adoption of QbD have been well documented. In a study [1] commissioned by the Agency in 2009, McKinsey & Co. was engaged to work with CDER to summarize the challenges to broader adoption of QbD across the industry. The report lumped companies into four different categories in terms of their QbD advocacy—Novice, Pilot, Rollout and Fully Implemented—and identified the following ten challenges to adopting QbD as a foundation for drug development:

Industry Impediments

- **Internal misalignment** (i.e., disconnect between cross functional areas, e.g., R&D and manufacturing or quality and regulatory)
- **Lack of belief in business case** (e.g., "There is a lot of uncertainty over timing of and investment requirements for QbD implementation.")
- **Lack of technology to execute** (e.g., difficulty managing data, limited understanding of Critical Quality Attributes [CQA] implications)
- **Alignment with third parties** (i.e., how to implement QbD with increasing reliance on suppliers and contract manufacturers?)

FDA Impediments

- **Inconsistency of treatment of QbD across FDA** (e.g., "Although a number of people in the FDA are supportive of QbD – this is not consistent.")
- **Lack of tangible guidance for industry** (e.g., "We understand what you are asking for broadly, but there are hundreds of variables–there's got to be an end in mind–a tangible one we can deliver on.")
- **Regulators not prepared to handle QbD applications** (i.e., reviewers at different levels of understanding and acceptance)
- **The way promised regulatory benefits are currently being shared does not inspire confidence** (e.g.,

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- **Misalignment of international regulatory bodies** (i.e., difficulty gaining acceptance of QbD applications in other countries)
- **Current interaction with companies is not conducive to QbD** (e.g.,"…we are treated with suspicion, it does not feel like collaboration.")

The conference concluded that tangible progress has been made against these challenges but there is still a long way to go before we see QbD as a foundation for drug development and quality.

The constant change in the marketplace cannot have helped in creating a united vision. Consolidation and acquisition have a ripple effect that lasts for years, and we are by no means done yet. Pressure on stock valuation, patent expiry and lack of access to capital markets have forced Big Pharma to buy innovation rather than invest in it. Small and mid-tier companies with developed pipelines remain the target of healthy M&A activity. Adding to this is the reality that Big Pharma is losing its grip on the marketplace. Today 75 percent of all prescriptions written in the U.S. are generic.

Generic Industry is Different in Agency's Eyes

So why haven't we shifted the focus of QbD to the issues at hand for this industry? The Office of Generic Drugs (OGD) has made decisive moves to integrate QbD concepts into its ANDA drug filing structure by implementing a Question Based Review (QBR) structure.

The problem I think is that the role of the generic industry is different in the eyes of the Agency than that of Big Pharma. While it is the joint responsibility of the industry and the OGD to support public confidence in generic drug quality, the Agency's objectives also include a business proposition to ensure generic product availability to the public. Rather than building a strategy based upon a mandate for process predictability and efficiency, the argument for QbD as a viable near-term business model for business performance has conspicuously been set aside.

The initial lure of QbD was intimately linked to the promise of Process Analytical Technology (PAT) as the carrot at the end of a long stick. It made sense to throw support behind this promise given the broad adoption of PAT by other industries, but I believe QbD has been hampered more than helped by this association. PAT may hold promise for innovator products that may enjoy a healthy market presence under patent protection, but for generic drug manufacturers who are often dealing with meaningful drug lifecycles of 3-4 years, the investment and ROI are not justified.

Complicating the discussion is the new Process Validation (PV) Guidance issued in January 2011. The new guidance is not shy about its wholesale integration of the principles of QbD as part of the new definition of PV. Despite this new guidance many companies are moving slowly or ignoring this paradigm shift for the time being. The Agency has been aggressive in its enforcement of the new guidance and this has got the industry's attention. It has also revealed a fundamental challenge to implementing QbD and the new guidance, and that is a lack of understanding of process characterization tools and methodologies.

Huge Chasm

This underlying deficiency must be addressed if the industry is to move forward. It is ironic that after five years of embracing Operational Excellence as a foundation for business improvement we find ourselves with a huge chasm regarding how to effectively use the tools and methodologies required for effective product and process development. Reliance on specialists has left the majority of the organization with a fundamental lack of appreciation of the power of methodologies such as Design of Experiments, ANOVA and Error Analysis. This chasm is further reinforced by the perception that QbD is complex and requires advanced statistics and sophisticated technology. QbD exercises employing multivariate analysis across hundreds or even thousands of variables serve to underscore the misperception. Those who have successfully implemented QbD can attest that this is the furthest thing from the truth.

If the rate of QbD adoption is going to increase in the marketplace, the emphasis behind QbD must evolve to a

QbD Links

- Chemical Research, Development and Scale-up
- Design Space and QbD Blog
- dTC's Quality by Design Blog (Spanish)
- Emerson Global Life Sciences Blog
- FDA Homepage
- ICH Homepage
- Innovative Medicines Initiative
- International Pharmaceutical Quality
- Maxiom Group Blog
- Mining Drug Space
- On Pharma Blog
- Pharmaceutical Manufacturing
- QA Pharm
- QbD Viewpoint

business proposition: one that resonates with the generics industry as a foundation for business competitiveness. To be successful QbD must facilitate a generic product development organization whose primary objective is to be first to file. Many R&D organizations within the generics industry are measured by the timing and number of ANDAs filed, not the quality of the ANDA.

If we add the Agency's activity in ensuring bioavailability claims during development is maintained in commercial products already approved and on the market, the risk of poor process and product understanding is tangible. Anyone who has operated in industries where structured development frameworks employing principles such as Design for Manufacturing, Design for Six Sigma and Toyota Product Development System understands that fast does not preclude doing things well. The integration of meaningful quality metrics such as the Cost of Poor Quality (COPQ) can substantiate the ROI of adopting the QbD mindset.

The Driving Factor

In the end, the factor that may well drive the industry toward QbD may be the new PV guidance itself. Modeling as a foundation for product and process development will demonstrate the bottom line benefits of process understanding, making scale-up and technology transfer a smooth and effective undertaking. Consolidation in the industry will continue and the pressure to shrink the innovation timeline will only increase as competition for emerging markets and within the U.S. marketplace intensifies. In many ways the success of companies in the near future may be a direct by-product of their ability to integrate the concepts of QbD. To do that it must not only make sense from a technical and compliance perspective, but also make "cents" from a business perspective.

References

1. FDA, Understanding Challenges to Quality by Design, Final deliverable for FDA Understanding Challenges to QbD Project, December 18, 2009.

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