DPT Thought Leadership
Issue 11: 1st in a Series

WHAT IS QUALITY BY DESIGN (QbD) – AND WHY SHOULD YOU CARE?

INTRODUCTION

Is your development or manufacturing operation experiencing cost over-runs and unproductive delays? Do you want to optimize your development dollars and ensure a robust commercial process? You are not alone.

The conventional development process uses an empirical approach that requires continuous end product testing and inspection to determine quality. The processes that create the end product are seen as fixed, averse to change, and focus only on process reproducibility. This approach ignores real-world variability in materials and process controls.

There is a different path. It's called Quality by Design (QbD). With QbD you will get a proactive approach to product development, potential to reduce FDA queries and review time, and the scientific data to quickly get to the root cause and resolution of any deviation.

WHAT IS QUALITY BY DESIGN?

Quality by Design (QbD) is a modern, scientific approach that formalizes product design, automates manual testing, and streamlines troubleshooting. It uses a systematic approach to ensure quality by developing a thorough understanding of the compatibility of a finished product to all of the components and processes involved in manufacturing that product. Instead of relying on finished product testing alone, QbD provides insights upstream throughout the development process. As a result, a quality issue can be efficiently analyzed and its root cause quickly identified.

QbD requires identification of all critical formulation attributes and process parameters as well as determining the extent to which any variation can impact the quality of the finished product. The more information generated on the impact – or lack of impact – of a component or process on a product's quality, safety or efficacy, the more business flexibility Quality by Design provides.[1]

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QbD has four key components:

1. Defining the Product Design Goal

In this step, you define the Quality Target Product Profile (QTPP) and identify all the critical quality attributes (CQA) for the product. The QTPP includes the factors that define the desired product and the CQAs include the product characteristics that have the most impact on the product quality. These provide the framework for the product design and understanding. The components are characterized and the compatibility of the components is evaluated.

2. Discovering the Process Design Space

Understanding your processes is the key to defining the design space. ICH Q8 defines design space as an "established multidimensional combination and interaction of material attributes and/or process parameters demonstrated to provide assurance of quality." Critical process parameters (CPPs) are identified by determining the extent to which any process variation can affect the quality of the product.[2]

When you define your design space, you are able to anticipate issues and plan how to control the process. Actual experimental data, product experience, or literature guidance can be used to define the extremes of the parameter sets to be refined.

3. Understanding the Control Space

Based on the process design space, a well-executed control space can be defined. This enables you to understand your processes in a way that ensures product quality from known variability of the production process. This disciplined approach will keep your complex production processes under control.

To illustrate the concept of a control space study, think of a reference product data set with tightly clustered data points that represent the output of a tightly controlled process. Plotting the output of your process and comparing it to such a reference will give a clear indication of whether your process is in control. One technique to help avoid such a disparity is to conduct a Design of Experiments (DOE) study on your product in the development stage. Considerable wasted effort can be eliminated with such an approach as can any unexpected adverse outcome from the lack of control space understanding.

4. Targeting the Operating Space

The operating space is the best set of parameters, determined statistically, which enable you to accommodate any natural variability in CPPs and CQAs. For generic products, the operating space should be within the control space and should allow a reference product to be tested with the same set of parameters.

For new products, the operating space should be within the design space and compliant with regulatory guidelines. Innovators can gain a competitive advantage by thoroughly exploring the design space, including testing multiple batches of formulations to truly refine their product.

THE BENEFITS OF QbD

Proper implementation of QbD can potentially provide three main benefits for development:

- More efficient use of development time and costs
- Ability to meet FDA submission guidelines and expectations
- Reduced approval times – and fewer queries – from the FDA

Likewise, QbD can potentially provide significant benefit in manufacturing. Even after your drug has gained FDA approval, routine QC testing may detect an out of specification (OOS) result. For a company that did not use a QbD approach, an OOS result can mean a seemingly endless quest to find the root cause. Absent the data that QbD provides, test results may be suspect, questions difficult

to answer, and long delays inevitable. Without knowing where to look, your team may resort to a trial-and-error approach to resolve any OOS occurrences.

One recent article presented several scenarios that could cause a 4- to 9-fold increase in testing to clear up an OOS investigation – a costly and time-consuming prospect.[3] The impact of poor quality that spirals out of control into an OOS event can be horrendous.

"For manufacturers, there are potentially huge external costs for delayed product launches or approvals, or severe actions such as consent decrees," notes one editor of an industry journal, plus "the internal costs of wasted raw materials, scrap batches, and the cost of investigation and remediation."[4]

Imagine the damage to your brand such an event would have. To add further insult, you may have to spend an enormous amount of money just to get your product back to market.

QbD minimizes these risks by mapping all the possible variables of the product attributes and processes into a known control space. This means that if any quality issues occur, your team can use specific methods to quickly pinpoint the scientific variables that are most likely causing the issues.

The business benefits can be significant, including:

- Fewer lost batches, typically costing $250 - $500K per batch
- Fewer manufacturing deviations, saving hundreds of costly hours and $10 - $15K per deviation
- Faster time to market and more reliable supply, when each day on the market could mean $100K (or more)
- Fewer inspections of manufacturing sites
- A many-fold ROI via cost savings and increased revenue.[5]

THE CHALLENGES OF ADOPTING QbD

Despite the many financial and operational benefits of QbD, and even with the new FDA recommendations, not all companies have adopted this approach. As the saying goes "you either pay now, or pay later." Implementing QbD beginning at the development phase requires a dedicated, disciplined, and sustained commitment by an organization. Understanding the effort necessary to implement QbD is a key component to successful adoption. Some of the most common barriers to adoption include:

- Insufficient understanding of the process and its benefits
- Organizational resistance to change
- Denial of the need ("Our process is under control")
- Competing priorities
- Lack of resources and expertise in QbD.[6]

When you consider the tremendous potential financial gain, faster time to market, process improvements, and quality assurance generated by a successful implementation of QbD, these obstacles seem to pale in comparison.

THE TIME IS NOW

As of January 2013, after nearly three years of advance notice, workshops, and consultations, all ANDA applicants are being "strongly encouraged" by the FDA to use a Quality by Design approach. The day has arrived – deficiency letters will now explicitly cite the lack of QbD.[7]

The FDA expects these QbD components in all submissions:

- Quality target product profile (QTPP)
- List of critical quality attributes (CQAs)
- List of critical material attributes of drug and excipients (CMAs)
- List of critical process parameters (CPPs)
- A control strategy that ensures the product reliability meets its predefined objectives.

The FDA clearly sees QbD as the way to enhance the quality of drug products for the benefit of everyone involved: Manufacturers will save time and money developing and producing drugs.

Regulators will save time and resources approving drug applications, conducting inspections, and troubleshooting quality issues.

Patients will be assured of more consistent, high-quality drug products that always meet safety and efficacy requirements.

In the eyes of the FDA and the many advocates of QbD, the approach represents a way to "do more with less" and gain a winning outcome for manufacturers, regulators, and patients.

TAKE THE QbD JOURNEY WITH A RELIABLE PARTNER

The challenges associated with adopting QbD can be daunting. With the FDA now squarely behind QbD, it is becoming imperative that companies find a way to adopt this scientific approach. It is not easy. It does not just happen. It takes a sustained commitment. How do you successfully complete the journey?

One way is to join forces with an experienced, knowledgeable partner who can help your team benefit from QbD with minimal disruption. A knowledgeable partner can bring together multiple sources of information, experience, and provide practical insights into issues with your product.

DPT Laboratories can help take the mystery out of QbD and get you moving toward your goal of launching a valuable drug product in the most cost-efficient and robust manner.

CONCLUSION

This paper introduces the concept of QbD and explains how it improves on conventional processes. After reading this paper you should possess the information to help you better decide how and when to implement QbD in your operation.

Proper implementation of QbD can potentially provide several benefits for development and manufacturing:

- More efficient use of development time and costs
- Ability to meet FDA submission guidelines and expectations
- Reduced approval times – and fewer queries – from the FDA
- Rapid response to any manufacturing deviation.

The impact of poor development that spirals out of control for the marketed product can be devastating. Fortunately, these costs and delays can be avoided by using QbD, a more modern, scientific approach that formalizes product design and development and eliminates troubleshooting by trial-and-error.

Despite the numerous tangible benefits of QbD, most companies do not understand the concept, appreciate its value, or know how to implement it effectively. Successful implementation of QbD requires a dedicated, disciplined, sustained commitment.

Additionally, a sense of urgency now exists as the FDA began strongly encouraging all drug product applicants to use QbD. Deficiency letters will now explicitly cite the lack of QbD.

With the new FDA recommendations for the use of QbD, how can you afford not to adopt it? And how will you do so with a minimal cost and time investment?

For more information on how DPT Laboratories can help with QbD, including gaining timely FDA approval and minimizing the cost of your development project, call 1.866.CALL.DPT or visit www.DPTLABS.com.

ENDNOTES

1: Fritz Erni, "Design Space and Control Strategy," EFPIA PAT Topic Group presentation, October 2006, p19.
2: Fritz Erni, p25.
3: John G. Lanese, "OOS: The Last Resort," Pharmaceutical Formulation and Quality, June/July 2011, p30.
4: Agnes Shanley, "From the Editor: The Cost of Poor Quality, Too High a Price?" Pharmaceutical Manufacturing, March 2012.
5: Bill Schmidt, "Implementing Quality by Design: Are You Ready, or Not?" www.pharmaqbd.com, 4 August 2010.
6: Bill Schmidt, "Implementing Quality by Design: Are You Ready, or Not?" www.pharmaqbd.com, 4 August 2010.
7: Susan Rosencrance, "QbD Status Update Generic Drugs," FDA, October 2011.

ABOUT DPT LABORATORIES:

DPT is a contract development and manufacturing organization (CDMO) providing companies the best solutions to their sterile and non-sterile pharmaceutical development and manufacturing needs through innovation, technology, and service. Specializing in semi-solid and liquid dosage forms, DPT has a reputation for quality, unmatched technical expertise, extensive manufacturing capabilities, and an exemplary regulatory compliance record. With five cGMP facilities in San Antonio, Texas, and Lakewood, New Jersey, DPT offers full-service outsourcing solutions, including stand-alone development, site transfers, state-of-the-art manufacturing, packaging, and worldwide distribution.

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