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Review Article

QUALITY BY DESIGN (QBD) IN PHARMACEUTICAL INDUSTRY

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ABSTRACT

In 2004 US Food and Drug Administration (FDA), as part of the Process Analytical Technology Guidance, introduced the idea of Quality by Design (QbD). The core objective was to design quality into the process and product rather than try to check quality of the product at the end of production. It has been known since long time that "quality by testing" is a low-yield and costly strategy. ICH, in 2005, outlined the concept of design space in its Q8 guideline related to development of pharmaceuticals. Since that time, pharmaceutical companies, despite depending on innovation for their livelihood, have been adopting QbD for new drug applications (NDA) and as well as for Abbreviated New Drug applications (ANDA). In nutshell it has been observed that, now QbD is becoming mainstay of development of pharmaceutical products.

Key words: Quality, pharmaceuticals, FDA, ICH, industry

INTRODUCTION

QbD has its origins dating back to the 1950s when the initial ideas of the operating window (now called as "design space") in the Pharma and Biotech world were put forth (Box and Wilson 1951). Later in 1992, Juran popularized the term "Quality by Design" in his book. Some of the experts says that pharma and biotech are behind the times while others see that the 'glass is half-full' and that pharma and biotech can come up the learning curve much more quickly than other industries[1].

FDA's emphasis on QbD

In January 2011 FDA announced their new process validation guidance which leans heavily on the ICH documents, Q8, Q9 and Q10 stating, in the introduction that, "this guidance aligns process validation activities with a product lifecycle concept and with existing FDA guidance, including the FDA/International Conference on Harmonization (ICH) guidances for industry, *Q8 (R2) Pharmaceutical Development*, *Q9 Quality Risk Management*, and *Q10 Pharmaceutical Quality System*". Although this guidance does not repeat the concepts and principles explained earlier, FDA encourages the use of modern pharmaceutical development concepts, quality risk management, and quality systems at all stages of the manufacturing process lifecycle[2].

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In June 2011 FDA Center for Drug Evaluation and Research (CDER) updated its "Manual of Policy and Procedures" (MAPP 5016.1) to read regarding applying ICH Q8 (R2), Q9, and Q10 Principles to CMC Review[1,2].

The MAPP outlines and clarifies how the chemistry, manufacturing, and controls (CMC) reviewers in the Office of Pharmaceutical Science (OPS) should apply the recommendations in the ICH Q8 (R2), Q9, and Q10 guidance to industry. OPS CMC reviewers will consider ICH Q8 (R2), Q9, and Q10 recommendations when reviewing applications that may or may not include QbD approaches[3,4].

In 2012 FDA commented on the use of QbD in development of generic drugs.

"We encourage you to apply Quality by Design (QbD) principles to the pharmaceutical development of your future original ANDA product submissions, as of January 1, 2013. A risk-based, scientifically sound submission would be expected to include the following: Quality target product profile (QTPP), critical quality attributes (CQAs) of the drug product, product design and understanding including identification of critical attributes of excipients, drug substance(s), and/or container closure systems, process design and understanding including identification of critical process parameters and in-process material attributes control strategy and justification. Figure 1 portrays how FDA has implemented QbD in generic drugs[5-7].

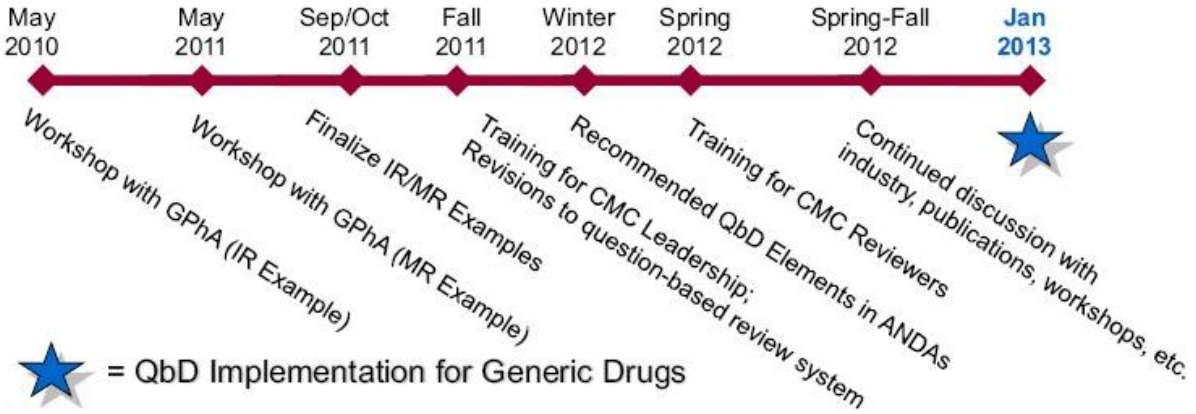

Figure 1: Implementation of QbD by FDA

Resistance to QbD

Resistance to any new idea is a natural human reaction; resistance happens to all new ideas, not just QbD. In order to create and sustain use of QbD, it must be recognized that using QbD is a culture change and a well-planned initiative using a culture change strategies and models like that proposed by John Kotter (1996) must be utilized. Some critical building blocks include a strategy, a plan, QbD demonstration projects and periodic management review at several levels in the organization – strategic, managerial and operational[7,8].

Companies, large and small are adopting QbD and progress is being made. There continues to be conferences on the subject in the US, India and Europe. The subject is discussed frequently in the literature. ISPE (International Society for Pharmaceutical Engineering), among other organizations have developed best practices to guide its deployment. But there is much work to be done[8].

QbD provides a common language for outsourcing partnerships. One area that needs attention is outsourcing to CMOs (contract manufacturing organizations) which is on the increase. Some companies want to develop

partnerships to increase the effectiveness of CMO relationships. Partnerships are more easily praised than practiced and should be viewed as a something needs constant attention over its lifetime. Viewed as a continuing process requires a common language, common method of working together; both needed for the development of trust, an essential ingredient of a healthy partnership[9,10].

Figure 2: QbD is a continuing process.

QbD can also help create the approach and common language needed for developing the relationships required for successful outsourcing[4]. QbD is a disciplined and systematic approach for effectively creating and communicating the process understanding needed to develop, launch and operate compliant processes[6]. A holistic approach to QbD with a focus on how the needed process understanding is developed to enable effective process development, transfer, improvement and control. Improved communication and collaboration is developed as a natural by-product of using QbD. Quality by Design enables both sponsors and CMOs to increase competitiveness[6,7,9].

Technology transfer is also critical to successful Sponsor-CMO relationships. QbD can help here as well. The price paid by the Pharma Company to the CMO is a function of the risks involved including: technology transfer will be done rapidly and smoothly, manufacturing will be stable and capable. Risk is a function of process understanding - Ability to: predict process performance and move technical information between the parties. An effective strategy is to use QbD to build quality into critical processes thereby increasing process understanding and reducing risk. Some critical processes include: product and process design, technology transfer, manufacturing and process control and quality assurance and control[11,12].

QbD provides an in-built quality assurance for tech transfer, speedy process and reduced costs. Overall QbD is benefit at all level and for all level (figure 3). It also help in defining roles at all levels enhances communication and identifies the needed skills. Also included are structures for tech transfer at the tech transfer program level and individual tech transfer project level and the needed tech transfer management systems such as project selection and sequencing, management review, communication and recognition and reward, measurement system evaluation and the creation of the needed process understanding[13,14].

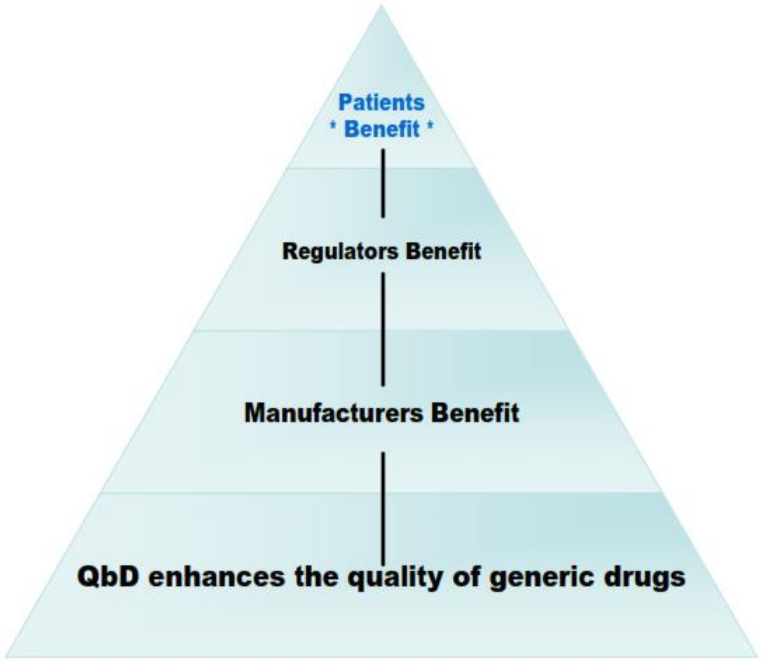

Figure 3: Benefits of implementing QbD

QbD: More than just a design

QbD must also be done effectively for the approach to deliver the promised benefits. An impression that one might get from reading the literature is that QbD is synomous with design of experiments (DOE). That all you need to do to implement QbD is to use DOE. Nothing could be further from the truth. DOE is an important tool of QbD but QbD has many more important building blocks such as process control, process robustness, failure modes assessment, etc.[4,6]

When developing models used to create the design space it is important to have a plan and strategy to guide the experimentation as summarized in Figure 4. This approach which was developed at DuPont in the 1960s and was used as an integral part of their QbD work speeding up the experimentation process, thereby increasing the probability the right data are collected at the right time[15].

Another important consideration is that the models used to develop the design space be confirmed before used to construct the design space (short-term validation). It is also critical that an ongoing process of model verification (long-term verification) be done as the manufacturing process operates. Such a process should be an integral part of the "Continued Process Verification" system that is an integral part of Stage 3 of the FDA's new process validation guidance.

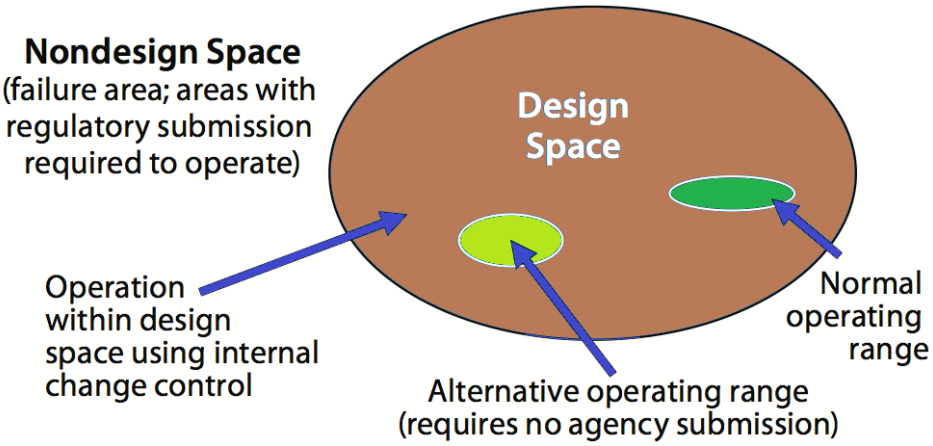

Figure 4: Positioning of design space and operating space.

Pharmaceutical equivalence and the bioequivalence are the two parameters which are adopted to ensure the quality of generic products being filed for ANDA. FDA had given emphasis that this approach is used only for those formulations which are simple in design i.e. solutions and immediate release dosage forms, but for the complex delivery systems like transdermal delivery system, modified release dosage forms such paradigm is utilized which ensure the quality of generic products[16-18].

At International Forum Process Analytical Chemistry (IFPAC) meeting, held in Baltimore (US), FDA CMC Reviewer/ QbD Liasion in the office of Generic Drugs, it was emphasized to implement QbD elements while filing ANDA for the pharmaceutical [1,2,5]. It was revealed that a steady increase in the inclusion of the elements of QbD in ANDA filling. Table 1 portrays the growing share of QbD element in ANDA filled.

Table 1: QbD in ANDA filings

Month/ Year	% ANDAs filled (with QbD element)
June 2012	**24.6**
July 2012	**25.5**
August 2012	**53.3**
October 2012	**62.5**
January 2013	**82.9**

CONCLUSION

Literature reports has shown that QbD is an effective method for developing new products and processes, enabling effective technology transfer, and the optimization and improvement of existing processes. QbD enables the development of process understanding that is fundamental to tech transfer, creation of design space and sustaining performance, process control and improvement systems and very important, the reduction of risk. QbD also provides a common language and methodology for working together - creating win-win partnerships

resulting in the promised regulatory flexibility, improved process performance and compliance and enhanced bottom-line results for all parties involved.

The implementation of QbD would also improve the quality of Chemistry, manufacturing, and controls information to be submitted in drug approvals. Above all it would surely enhance the assurance of quality in pharmaceuticals in the world market.

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