DOI: 10.15415/jptrm.2014.22015

Panoramic View on Quality by Design

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Received: Oct 20, 2014| Revised: Nov 23, 2014| Accepted: Nov 25, 2014

Published online: November 30, 2014

Abstract: Quality by design (QbD) is an essential tool in pharmaceutical environment for having product/process/method impregnated with quality. Now, QbD is the greatest solution to construct quality in all pharmaceutical products, while in the same time making it as a part of system is also a key challenge for Industry. For understanding of QbD, it is very much essential to understand the desire product performance profile [Target product Profile (TPP), Target Product Quality Profile (TPQP)] and identify critical quality attributed (CQA). Basically, for meeting the product attributes, the product formulation and process can be designed on the basis of these stated parameters. Nonetheless, this helps in recognizing the effect of raw materials, critical material attributes (CMA), critical process parameters (CPP) on the CQAs and identification and control sources of variability. The in and out understanding for QbD in generic pharmaceutical industry is really vital, because now and then FDA is taking firm stand to make mandatory "deadline" for inclusion of QbD. Therefore, an attempt has been made to highlight quality by design for generic drugs and its implications to pharmaceutical industry.

Keywords: Quality by Design (QbD), Target Product Profile (TPP), Target Product Quality Profile (TPQP), Critical Quality Attributes (CQA), Critical Material Attributes (CMA), Critical Process Parameter (CPP).

1. INTRODUCTION

Quality by design (QbD) is nothing but architecting a formulations and manufacturing processes which should ensure preplanned product specifications. Quality by Design (QbD) is a holistic way towards drug development. It has provided the solution to assist both industry and regulatory

Journal of Pharmaceutical Technology, Research and Management
Volume 2, No. 2,
November 2014
pp. 217–231

bodies to move towards a more scientific and proactive approach. This concept appreciates the approach to build quality in, but not testing it (Woodcock, 2004; Asmasiddiqua *et al,* 2013). Quality by Design is a systematic scientific approach to improvement and design of products and methods illustrated and facilitated through the organisations of the design space (Lionberger, *et al*, 2008). Woodcock defined QbD had also been a high quality drug product as a product free of contamination and repeatedly delivering the therapeutic benefit assured in the label to the consumer (Nasr, 2006; Yu, 2006).

ICH Q8 defines quality as *"The correctness of a drug product for its anticipated use. This term includes aspects such as the identity, purity, and strength"*. A most widely used definition of quality is *"Relishing the customers by fulfilling their needs and expectations"* which may consists of appearance, supply, maintainability, performance, consistency, cost effectiveness and total customer satisfaction (Gawade, *et al.*, 2013; Roy, 2012). It is important that quality needs to be built in by design. To achieve a high level of quality, there is the necessity of Quality by Design (Gawade, *et al*., 2013). This manuscript provides an opportunity to know what exactly Quality by Design means, its advantages, application, requirement, and implementation and different key steps of QbD. This manuscript provides advantages, requirement, and implementation of QbD for providing a clearer knowledge and scenic view for abbreviated new drug applications (ANDAs). The objective is to study Quality by Design concept and there advantages & application, the implications of QbD & area of implication, to study different key steps of QbD as well.

2. HISTORY

This idea was first outlined by well-known quality expert Joseph M. Juran. In the late 1990, FDA's internal discussion began and in the year 2002 the concept paper on 21st century Good Manufacturing Practice was published (Trivedi, 2011). With assistance of several biopharmaceutical companies, pilot programs were started to explore QbD application and understandings (Roy, 2012). EMA and FDA launched a pilot program with an objective of parallel assessment of certain qualities/CMC section like development, design space and actual time release testing by both agencies which are relevant to Quality by Design (QbD) in March 2011 (Bhatt and Rane, 2011; US Food and Drug Administration, pharmaceutical cGMPs for the 21st century: A risk based approach, 2002). The pilot program aimed at ensuring consistent implementation of ICH Q8, Q9, Q10, Q11 guidelines between EU and US in the assessment process and to facilitate sharing of regulatory decisions on new regulatory concepts. Hence, regulatory bodies across the globe are showing appreciable interest for QbD (Purohit and Shah, 2013, Patel *et al*, 2013).

3. ADVANTAGES OF QbD

The QbD concept has numerous advantages. Some of the advantages of QbD are tabulated in Table 1 (Nasr, 2006; Winkle, 2007; Tang, 2013; Somma, 2013).

Basically research has underlined many challenges that may occur in the implementation of QbD. These featured challenges specify several areas that FDA may consider in order to speed up the QbD adoption.

Table 1: Advantages of QbD

• It offers an advanced level of assurance of drug product quality.
• It offers cost savings and efficiency for the pharmaceutical industry.
• It increases the transparency of the sponsor understands the control strategy for the drug product to attain approval and ultimately commercialization.
• It makes the scale-up, validation and commercialization transparent, rational and predictable.
• It eases innovation for unmet medical needs.
• It increases efficiency of pharmaceutical manufacturing processes and reduces manufacturing costs and product rejects.
• It minimizes or eliminates potential compliance actions, costly penalties, and drug recalls.
• It offers opportunities for continual improvement.
• It provides more efficiency for regulatory oversight.
• It updates post approval manufacturing changes and regulatory processes.
• It more focused post approval cGMP inspections.
• It enhances opportunities for first cycle approval.
• It assists continuous improvement and reduces the Computer (CMC) supplement.
• It enhances the quality of CMC and reduces the CMC review time.
• Improves information in regulatory submissions.
• Regulatory flexibility.
• Improves interaction with FDA –deal on a science level in its place of on a process level.
• Reduce Product Variability.

Implementation of QbD by regulatory bodies

The actions that FDA takes becomes extra noticeable when applied to the subdivisions *viz.* type of drug and adoption level. Options that the VS FDA should consider to ensure QbD implementation are depicted as follows:

4. FDA POLICY OPTIONS

- ***Define and codify Incentives***: Although the FDA may have faith in that there are benefits to advance defining and codifying incentives, from conversations with industry, it is clear many companies see this as a powerful way to incentivize QbD adoption.
- ***Tangible guidance for QbD execution***: Companies, especially in early stages of adoption, have identified confusion around what QbD means and how to actually execute as a huge challenge.
- ***Mandate:*** Some drug areas, for e.g. several areas inside the generics industry (e.g., controlled and modified release drugs), have had many safety matters. For drugs such as these, where there is a public health risk due to absence of procedure understanding, mandating QbD is a reasonable option.

4.1. Internal FDA change management

1. Consistency of review process (scientific knowledge and quality): The desire for a regular review process and well skilled reviewers is common throughout industry. The FDA is aware of this need and has been working to train and educate reviewers to prepare them to handle QbD applications.

2. Harmonizing QbD approach: There is a need to harmonize QbD practices and requirements through FDA including OPS and associated functions e.g. compliance and inspectors. The current state where decisions around QbD are sometimes called into question or even reversed when areas subsequent to operations (OPS) review are involved has the chance of eroding or even stopping the momentum around QbD adoption in industry.

4.2. External change management

- ***Change in communication method:*** Industry almost universally asked for more frequent, "*no risk*" dialogs with the FDA. The companies who participated in the pilot programs felt they have been benefited from the increased, and often less formal communications.
- ***Creating more buy-in (disseminating case):*** Industry has made a clear call for real, tangible examples of what the FDA has actually approved or rejected and why. However, there are legal obstacles for the FDA in disclosing this information.

- ***Improving international harmonization***: There are questions around whether or not the FDA is responsible for addressing international harmonization of QbD acceptance. This is an area worth at least examining as the FDA is currently one of the biggest proponents of QbD and the lack of international harmonization is one of the biggest challenges raised by companies.
- ***Utilization of third party model:*** As a means of catalyzing and standardizing QbD within industry. There is a call for more substantial direction from and interaction with the FDA.

5. AREAS OF QbD IMPLEMENTATION

5.1. Clinical Trials

Quality-by-Design (QbD), an idea that has been successful applied in the manufacturing, emphasizes building quality into a process from the starting. Applied in clinical development, this approach would prospectively examine the objectives of a trial and define critical factors (key data and trial processes such as randomization) critical to meet there objectives. Understanding what data and processes required for successful trial is essential to subsequently identifying and managing important and likely risks to trial quality (http//www.ich.org, 2005). These risks would then be managed through tailoring trial design, implementation, and sensible, risk-based oversight. Focusing on critical aspects of a trial could also substantially reduce the burden of clinical trial conduct by relieving sponsors of a perceived obligation to mitigate every potential risk occur by a trial, especially for those activities that minimally affect data quality and human subject protection. However, the current models for clinical trial design, implementation and oversight may have become outmoded and unsustainable in a global, complex clinical trial environment (How to apply QbD principles in clinical trials?, 2013; Workshops on QbD and quality risk management in clinical trials, 2013, http://ctti-clinicaltrials.org).

5.2. Validation

During the past few years, regulatory agencies have placed an increased emphasis on pharmaceutical process understanding. The US Food and Drug Administration's (Pharmaceutical cGMPs for the 21st Century)—A Risk Based Approach describes how combining a focus on process understanding with a structured risk-assessment process can help develop control strategies that enhance process robustness (FDA CDER draft guidance for industry,

(2010). Similar concepts are also discussed in ICH Q8 (Pharmaceutical Development) and International Conference on Harmonization (ICH) Q9 (Quality Risk Management) (http//www.ich.org, 2005 and 2006). Collectively, these principles are described as "quality by design" (QbD).

QbD for process includes patient requirements followed by process design & development then risk assessment & process design space definition and finally control strategy. QbD for analytical methods includes method performance requirements followed by method development then risk assessment & analytical method design space definition and finally analytical method control strategy. QbD for analytical methods method performance requirements and analytical method control strategy are correlated with control strategy of QbD for process. The whole process followed continuous improvement (Subrahmanyam, 2006; The application of quality by design to analytical methods, 2013, http://www.pharmtech.com/).

6. DESIGN GOALS OF QbD

The advantages of QbD principles to pharmaceutical development and manufacturing have been rang the bell recently. The key steps of QbD in pharm industry include – identification of TPP and CQA, defining the product & process design space followed by refinement of product design space. Further, the control strategies and process validation to be done before regulatory filling. The risk assessment should be done while identifying CQA, define the product design space & during the process validation. The product should also be characterized at the time of defining process design space (Subrahmanyam, 2006).

6.1 Target Product Profile (TPP)

Means prospective and dynamic summary of the quality feature of a drug product that achieved to assured that the desired quality, and thus the drug product safety and efficacy realized (Gawade *et al.*, 2013). A recent guidance defining a Target Product Profile (TPP) issued by FDA is the statement of the overall intent of the drug design program, and information about the drug at a particular time in development given by TPP (Lionberger *et.al.*, 2008).

This includes dosage form and route of administration, dosage form strength(s), therapeutic moiety release or delivery and pharmacokinetic characteristics (e.g., dissolution and aerodynamic performance) appropriate to the drug product dosage form being developed and drug product-quality criteria (e.g., sterility and purity) appropriate for the intended marketed product (Asmasiddiqua *et al.*, 2013; Trivedi, 2011; Roy, 2012).The TPP guides formulation scientists to establish formulation strategies and keep formulation efforts focused and efficient. TPP is related to identity, assay, dosage form, purity,

stability in the label (Lionberger *et al.*, 2008). The TPP provides a statement of the overall intent of the drug development program, and gives information about the drug at a particular time in development. Generally, the main point in the drug labeling and element of drug design activities to definite concepts intended for insertion in the drug labeling the TPP is organized according to this. TPP forms the basis for product design in the ways Dosage form; Route of administration; Strength, maximum and minimum; Release/delivery of the drug; Pharmacological characteristic; Drug product quality criteria and Pharmaceutical elegance (Purohit and Shah, 2013; Patel *et al.*, 2013).

Target Product Quality Profile (TPQP) is a term that is a natural extension of TPP for product quality. It is the quality characteristics that the drug product should possess in order to reproducibly deliver the therapeutic benefit promised in the label (Gawade *et al.*, 2013). The target product quality profile (TPQP) is a quantifiable alternate for characteristic of clinical safety and efficacy this can be applied to design and optimize a formulation and manufacturing process (Lionberger *et al.*, 2008). The target product profile (TPP) has been defined as a "*prospective and self-motivated summary of the quality features of a drug product that preferably will be achieved to ensure that the preferred quality, and thus the safety and efficacy, of a drug product is realized*". This includes dosage form and route of administration, dosage form strength(s), therapeutic moiety release or delivery and pharmacokinetic characteristics (e.g., dissolution aerodynamic performance) appropriate to the drug product dosage form being developed and drug product-quality criteria (e.g., sterility and purity) appropriate for the intended marketed product . The concept of TPP in this form and its application is novel in the QbD paradigm (Roy, 2012). The TPQP is not treated as condition because it includes bioequivalence or stability test that are not applicable in batch to batch release.TPQP includes only the patient applicable product performance (Trivedi, 2011; Roy, 2012).

6.2 Critical Quality Attributes (CQA)

The ISPE PQLI explained critical quality attributes (CQAs) as physical, chemical, biological or microbiological attributes or features to assure product quality that are required to be guarded (directly or indirectly). ICH Q8 (R1) defines CQAs as physical, chemical, biological or microbiological properties or characteristics to ensure the desired product quality that should be within an appropriate limit, range, or distribution (Lionberger *et al.*, 2008; Trivedi, 2011). The ICH definition of CQA is: "*A CQA is a quality attribute (a physical, chemical, biological or microbiological property or characteristic) that must be controlled (directly or indirectly) to ensure the product meets its intended safety, efficacy, stability and performance*" identification of CQAs is

performed through risk assessment as per the ICH guidance Q9 (Parks, 2012). Prior product knowledge, such as the accumulated laboratory, nonclinical and clinical experience with a specific product-quality attribute, is the key in making these risk assessments (Asmasiddiqua *et al.*, 2013).

In addition to defining the requirements to design the product, the QTPP will help to identify critical quality attributes such as potency, purity, bioavailability or pharmacokinetic profile, shelf-life, and sensory properties (http//www.ich.org, 2005).

Critical quality attributes (CQA) contain parameters (Purohit and Shah, 2013; Workshops on QbD and quality risk management in clinical trials, 2013, http://ctti-clinicaltrials.org) such as appearance; particle size; morphic forms; water content; residual solvents; organic impurities; assay; inorganic impurities (heavy metals & residue on ignition) (Trivedi, 2011; Roy, 2012).

CQA is used to describe product performance as well as determinants of product performance both the aspects (Figure 1). Critical Process Parameter (CPP) The desired product quality and process consistency should be achieved by measurable input (input material attribute or operating parameter) or output (process state variable or output material attribute) of a process step has been explained by CPP (Trivedi, 2011). According to this system, there are four classes of parameters and attributes (Lionberger *et al.*, 2008; Patel *et al.*, (2013)].

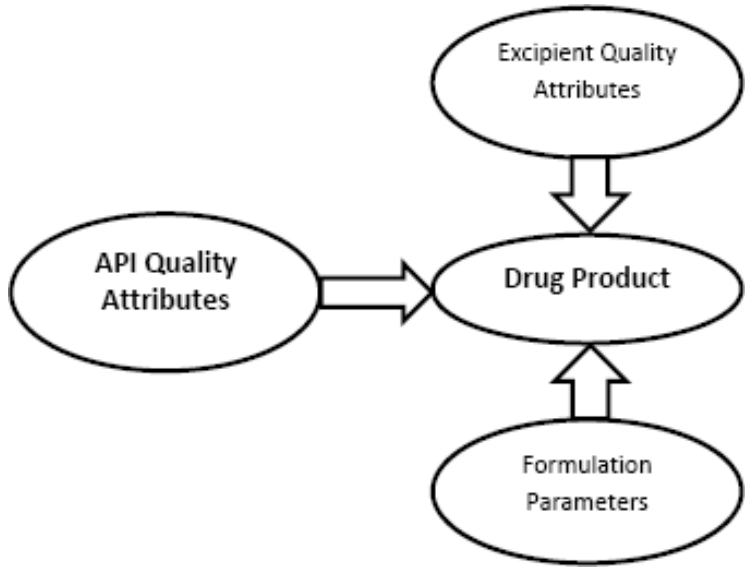

Figure 1: Significance of Quality Attributes

- Input material attributes
- Output material attributes
- Input operating parameters
- Output process state conditions.

Critical Process Parameter means when a practical change in that parameter can cause the product to failure to meet the TPQP. There, a parameter critical nature not depends on how large of a change one is willing to consider. In first step, the range of interest is defined in classifying parameters, which are potential operating space (POS). The region between the maximum and minimum value of interest is POS for each process parameter. This will also be considered as the extent of the sponsor's quality system with respect to these parameters (Lionberger *et al.*, 2008). The process parameters can be classified as Unclassified, Critical and Non-critical. The sensitivity/criticality of unclassified process parameters not established/unknown. The critical process parameters can cause product to fail to meet the TPQP whereas the known critical process parameters doesn't cause such failure in TPQP within the POS and there is no evidence of interaction with in the PAR (Patel *et al.*, 2013). The identification of critical and non-critical process parameters are mainly depends on the sensitivity of product characteristics to changes in the process parameters [Nosal, 2007); US Food and Drug Administration, guidance for industry- PAT, 2013).

6.3 Control Strategy

Control strategy is defined as "*a planned set of controls, derived from current product and process understanding that assures process performance and product quality*" (Food and Drug Administration final report on pharmaceutical cGMPs for the 21st Century, 2004, http://www.fda.gov; US Food and Drug Administration guidance for industry: Q10, 2010). Quality Control Strategy encompasses design Space, process controls and specifications. Particularly, the control strategy includes (Woodcock, 2004; Lionberger *et al.*, 2008):

- Control of raw material attributes (e.g., drug substance, excipients and primary packaging materials) based on an understanding of their impact on process-ability or product quality.
- Product specifications
- Procedural controls
- Facility controls such as utilities, environmental systems and operating conditions
- Controls for unit operations that have an impact on downstream processing or end-product quality (e.g. the impact of drying on degradation, particle size distribution of the granulate on dissolution)

- A monitoring program (e.g., full product testing at regular intervals) for verifying multivariate prediction models.

The Control Strategy should establish the necessary controls based on patient requirements to be applied throughout the whole product life cycle from product and process design through to final product, including API and Drug Product manufacture, packaging and distribution (Seely *et al*., 2014; FDA CDER draft guidance for industry, Q8, 2010).

6.4 Design Space

In the presence of interacting critical process parameters a design space is one approach to ensure product quality. The definition of design space is *"The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality"* (Lionberger *et al.*, 2008; FDA CDER draft guidance for industry, Q8, 2010).

Submission of a design space to FDA is a pathway obtaining the ability to operate within that design space without further regulatory approval. A design space is a way to represent the process understanding that has been established. The benefits of having a design space are clear; one challenge to the effective use of a design space is the cost of its establishment (Nasr, 2006; FDA CDER guidance for industry: PAT, 2013).

The various steps to design space are-

1. Identify the unclassified parameters then,
2. Applying design of experiments using the unclassified parameters with the other fixed unclassified parameters and
3. Selection of selected parameters.

6.5 Feedback Control and PAT

Application of PAT (ICH draft consensus guideline, 2010) may be part of a control strategy. ICH Q8(R) identifies one use of PAT as ensuring that the process remains within an established design space (US Food and Drug Administration guidance for industry: Q9, 2010). In a passive process, PAT tools provide continuous monitoring of CPP to demonstrate that a process is maintained in the design space. In process testing of CMA (Critical Material Attributes) can also be conducted online or in line with PAT tools. Both of these applications of PAT are more efficient ways to detect failures. In a more robust process, PAT can enable active control of CPP, and if there is variation in the environment or input materials the operating parameters can be adjusted to keep the CMA under control to ensure quality (Lionberger *et al.,* 2008).

A PAT system that combines continuous monitoring of CMA (instead of CPP) can potentially be combined with feedback control of process parameters to provide an alternative to design space based control strategies. A problem with design space is that it can limit flexibility. A design space is usually a specified space of process parameters that has been demonstrated to provide acceptable quality. There may be sets of process parameters that lead to acceptable quality but were not explored in the establishment of the design space. Thus, pursuit of a design space can be movement in the opposite direction from a flexible and robust manufacturing process. Direct assessment of product quality via PAT may support more flexibility and robustness than is represented by the design space (Lionberger *et al.*, 2008; US Food and Drug Administration guidance for industry: Q10, 2010).

6.6 Process Validation

Increased knowledge of the manufacturing method and an expanded process design space should provide more manufacturing adjustability during process validation. Because the process designs space "*assures quality*" of the drug product, these limits should also provide the basis of the validation acceptance criteria. The margin that demonstrated the acceptable variability in product-quality and process performance attributes would also serve as the process validation acceptance criteria (Seely *et al.*, 2014). The method design space has been created, process validation grown into an exercise to determine that

(i) The process will supply a product of satisfactory quality if operated between design spaces

(ii) The small and/or pilot scale systems used to set up the design space exact model the accomplishment of the manufacturing scale process. Therefore, in the QbD example, abrupt manufacturing excursions that remain between the process design spaces should not endanger the success of the validation exercise.

6.7 Regulatory Filings

The regulatory filing mainly include the acceptable limit for all main and detracting operating parameters that describe the process design space and to a more restricted operating space typically described for drug products after the process design space has been established and validated (US Food and Drug Administration guidance for industry: Q9, 2010). This filing would also involve the refined product design space, explanation of the control strategy, output of the validation exercise and strategies for process observing. The QbD example, in this the filing also include protocols (e.g., comparability protocols

or expanded change protocols) that would allow future suability in process changes with regard to pre-approved standards that have been consent upon within the applicant and the agency [Roy, 2012).

7. CONCLUSION

Quality by design is an essential part of the modern approach to pharmaceutical quality. Quality by Design (QbD) is unquestionably ready to help an organization solve the perennial challenges of drug development and manufacturing. The readiness of any organization for QbD begins with an understanding of QbD basics, benefits, and barriers to implementation, followed by a readiness assessment that can ensure that one has the right mindset, priorities, and resources aligned for a successful implementation. This paper highlights the use of QbD in ANDAs for drug filing structure by implementing a Question Based Review (QBR) structure. It's having the presence in drug development, process development, initial writing of labelling, in validation, in clinical trials and many more. Industries as well as regulators are making a move in geometric progress in bringing quality product by using QbD concept. Regulatory bodies across the globe are showing appreciable interest for QbD. Therefore, it can be concluded that the success of companies in the near future may be a directly impacted by-product of their ability to integrate the concepts of QbD. Nonetheless, Quality by Design (QbD) is geared up to help solve the challenges of drug development and manufacturing.

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