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A Review on Pharmaceutical Quality by Design (QbD)

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Abstract

Quality by design (QbD) is an essential part of the modern advance to pharmaceutical quality. Quality has been given an importance by all regulatory body for pharmaceutical products. Quality means customer satisfaction in terms of service, products, and process.QbD is best key to build a quality in all pharmaceutical products. This paper gives idea about the Pharmaceutical Quality by Design (QbD) and describes use of Quality by Design to ensure quality of Pharmaceutical Analysis. Under this concepts of be throughout design and growth of product, it is important to identify desire product performance report Target product profile (TPP), Quality Target product profile (QTPP) and identify critical quality attributes (CQA). To recognize the impact of raw material critical material attributes (CAM), critical process parameters (CPP) on the CQAs and identification and control sources of changeability. USFDA launched a pilot programme in 2005 to permit participating firms a prospect to submit chemistry, manufacturing, and controls (CMC) of NDA information representing application of QbD. QbD has its perspectives to contribute the drug design, development, and manufacture of high-quality drug products. In the present review basic consideration of the QbD approach, its historical background, and regulatory needs arediscussed. In detail explanation of elements of QbD i.e. method intent, design of experiment, and risk assessment is given. The foundation of Quality by Design is ICH Guidelines. It is based on the ICH Guidelines Q8 for pharmaceutical development, Q9 for quality risk management, Q10 for pharmaceutical quality systems. It also gives application of Quality by Design in pharmaceutical development and manufacturing of pharmaceuticals.

Keywords: Quality, Pharmaceuticals, Quality by Design, Analysis, Risks.

Introduction

Quality: In Quality by Design, Quality is important word. So Quality is "standard or suitability for intended use." This term includes such attribute of the identity, potency, and purity. 'Quality in manufacturing is a measure of Excellence or a state of being free from defects, deficiencies, and significant variation.' "Good pharmaceutical quality represents an acceptably low risk of failing to achieve the desired clinical attributes." ICH Q8 defines quality as "The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength, and purity. "ICH Q8 guideline states that Quality by Design is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management."

Quality by Design: A lot of approaches to the development of pharmaceutical products and their subsequent manufacture have been advocated by the US FDA and the International Council Harmonization (ICH). This approach has been mounted 'Quality by Design' (QbD) and it defined as- "A systematic approach to development that begins with predefined objective and emphasizes product and process understanding and process control, based sound science and quality risk management"

QbD is not a new concept for the world. The concept was formulated by J.M. Juran, an American Engineer, in the early 1970s through his famous book "Juran on Quality by Design", which was later adopted by several technology-driven areas like, telecommunication, automobile, and aviation industries engaged in the development of high- quality products and services. The concept was later adopted by health-care industries, and especially utilized by medical device manufacturers in the 1990s. QbD into the pharmaceutical industry entered quite late in 2004, when USFDA took initiative for improving the standards of pharmaceutical manufacturing [5]. Based on the heels of Juran's philosophy and culture of quality, pharmaceutical QbD also relies on development of drug product(s) and process (es) using systematic approaches and rational scientific principles for achieving target quality in the end product.8 With QbD around, the predefined objectives of the target quality enable zero quality defects and avoid quality crisis. Many scientists consider quality as a matter of conscious intent and meaningful execution of the operations involved in the manufacturing of the drug products. QbD also facilitates improvement in quality by thoughtful planning and meaningful execution. Hence, QbD is also called quality

by planning, but not by chance. Use of sound scientific principles and quality risk management (QRM) are the two key enablers of QbD philosophy, which provides enhanced products and process understanding on the target drug products. Based on these principles, QbD delivers enormous benefits manufacturing and business benefits. Additional merits of the QbD approach in drug product development include reduced consumer generic scepticism, faster product launch, and enormous regulatory flexibility [5].

QbD doesn't essentially mean less analytical testing, rather it means that proper analysis at the right time, and is based on science and risk assessment. Implementation of QbD helps to develop rugged and robust (strong) method that helps to go with ICH therefore for that reason pharmaceutical industries are adopting the conception of QbD. Factors that have an effect on the robustness are considered for development of analytical method in QbD environment. This approach facilitates continuous improvement in method. Parallel opportunities of the applying of QbD to

analytical technique as that of manufacturing process are available in literature. It put forth approach like target profile, Critical quality attributes (CQA), design space, risk assessment are applicable to analytical method also.

Through its not adopted by all pharmaceutical industries it's future perspective as a result of it's become necessary by regulatory bodies. Voluntary adoption of this concept by industries is feasible attributable to its varied advantages and easy compliance regulatory authority. Pharmaceutical research and manufactures of America (PhRMA), Analytical Technical group (ATG) and European Federation of Pharmaceutical Industries and Association (EFPIA) provide clear ideas regarding parallel implementation of QbD to analytical method [3]. QbD is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control based on sound science and quality risk management (ICH Q8(R)) QbD means designing and developing formulations and manufacturing processes to ensure predefined product quality. Thus, QbD requires an Understanding and controlling formulation and manufacturing process variables influence product quality. Relevant documents from the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), ICH Q8, Pharmaceutical Development, along with ICH Q9, Quality Risk Management, and ICH Q10, Pharmaceutical Quality Systems, indicate on an abstract level how quality by design acts to ensure drug product quality [6].

Historical background

In 2007 FDA received an 5000 supplements, it was actually a striking raise in the number of manufacturing supplements to applications of New Drug Applications (NDAs), Biological License Applications (BLAs) and Abbreviated New Drug Applications (ANDA's). FDA recognized that there is an increase in lapse of NDA or ANDA submissions by the firms, large number of a supplemental application for every manufacturing change were received. In both original applications and supplements the data mainly focused was on chemistry. And the least attention was given on other important aspects of the manufacturing, such as engineering, product development. Eventually, the FDA acknowledged that more and more controls were required for drug manufacturing processes for efficient drug product and no doubt for better regulatory decision making. It resulted in more stringent regulatory upbringing. To solve this issue in 2002, the FDA implemented changes through the Pharmaceutical cGMP (good manufacturing practice) for the 21st Century. Expectations were mentioned in Process Analytical Technology (PAT) which is a system for designing, analysing, and controlling manufacturing processes based on understanding science and factors which affect the quality of final product. In 2005 here came the time to implement QbD for more systematic approach and USFDA asked some firms to submit their CMC in QbD format. Question base review (QbR) forms the platform of QbD principle. Recent interview by with Lawrence Yu Deputy Director, Science and Chemistry, FDA indicates warning that 2013 is deadline for generics to implement QbD. Quality has been given an importance by all regulatory bodies for pharmaceutical products. Quality means customer satisfaction in terms of service, product, and process. Many of these quality related activities reflect need for companies to excel in global competition. Customer demands the perfection in quality, reliability, low cost and timely performance. Customer satisfaction can be achieved by two ways i.e. features and free from deficiencies in goods. The features like performance, trustworthiness, robustness, ease of use, and serviceability have to built in the product and such product should be free from deficiencies [15]. In March 2004, the FDA launched The Critical Path Initiative (CPI) to address the steep decline in the number of innovative pharmaceutical products submitted for approval. The national strategy was to modernize the pharmaceutical sciences through which FDA-regulated products are developed, evaluated, manufactured and used [9]. This prompted to the publishing of a guideline to aid manufacturers implementing modern quality systems and risk management approaches to meet the requirements of the Agency"s current thinking for cGMP regulations.

The impetus is to have quality in-built. Quality by design, in conjunction with a quality system, provides a sound framework for the transfer of product knowledge and process understanding from drug development to the commercial manufacturing processes and for post-development changes and optimization [10]. Good manufacturing practices for the 21st century have been continually evolving as the ICH quality initiatives have been adopted. The move from empirical assessment based on performance to the concept of "building quality in" based on critical attributes has gained traction as new guidance documents have been published.

Principle of QbD

- Risk and knowledge based decisions
- Systematic approaches process development
- Continuous Improvement
- This leads to "capable" processes.

Basic considerations of QbD As far as the pharmaceutical industry is concerned, safety of the

patient and providing a quality product have been given prime importance; and to achieve this target, QbD assists the industry by thorough understanding of the process which is the ultimate goal of QbD. Advantages of QbD can be summarized as,

- Patient safety and product efficacy are focused.
- Scientific understanding of pharmaceutical process and methods is done.
- It involves product design and process development.
- Science based risk assessment is carried out.
- Critical quality attributes are identified and their effect on final quality of product isanalysed.
- It offers a robust method or process.
- Business benefits are also a driving force to adopt QbD. Method design concept helpsto avoid cost involved with post approval changes [21].

Pharmaceutical Quality by Design

ICH Q8 defines quality as "The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength, and purity. "ICH Q8 guideline states that Quality by Design is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management". ICH Guidelines Q8 for Pharmaceutical Development, Q9 for Quality Risk Management, and Q10 for Quality systems are foundation of QbD "Product testing alone is not sufficient to assure that a process consistently produces a product with predetermined specifications. Adequate process design; knowledge and control of factors that produce, process variability and successful validation studies, in conjunction with product testing, provide assurance that the process will produce aproduct with the required quality characteristics"

Pharmaceutical Quality = f (Drug substance, excipients, manufacturing, and packaging)

Information from pharmaceutical development studies can be a basis for quality risk management. It is important to recognize that quality cannot be tested into products; i.e., quality should be built in by design. Changes in formulation and manufacturing processes during development and lifecycle management should be looked upon as opportunities to gain additional knowledge and further support establishment of the design space. Similarly, inclusion of relevant knowledge gained from experiments giving unexpected results can also be useful. Design space is proposed by the applicant and is subject to regulatory assessment and approval. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory postapproval change process. In all cases, the product should be designed to meet patients' needs and the intended product performance. Strategies for product development vary from company to company and from product to product. The approach can also vary and should be outlined in the submission. An applicant might choose either an empirical approach or a more systematic approach to product development, or a combination of both. A more systematic approach to development (also defined as quality by design) can include, for example, incorporation of prior knowledge, results of studies using design of experiments, use of quality risk management, and use of knowledge management (ICH Q10) throughout the lifecycle of the product. Such a systematic approach can enhance achieving the desired quality of the product and help the regulators to better understand a company's strategy.

Product and process understanding can be updated with the knowledge gained over the product lifecycle. [3, 15] The FDA imperative is outlined in its report "Pharmaceutical Quality for the 21st Century: A RiskBased Approach."(Pharmaceutical Quality for the 21st Century, 2007) In the past few years, the agency has implemented the concepts of QbD into its pre-market processes. The focus of this concept is that quality should be built into a product with an understanding of the product and process by which it is developed and manufactured along with a knowledge of the risks involved in manufacturing the product and how best to mitigate those risks. This is a successor to the "quality by QC" (or "quality after design") approach that the companies have taken up until the 1990s (Process Validation: General Principles and Practices. The QbD initiative, which originated from the Office of Biotechnology Products (OBP), attempts to provide guidance on pharmaceutical developmentto facilitate design of products and processes that, maximizes the product's efficacy andsafety profile while enhancing product manufacturability [20].

Objectives of Pharmaceutical Quality by Design

Pharmaceutical QbD is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and control based on sound science and quality risk management [2]. The goals of pharmaceutical QbD may include the following:

- To achieve meaningful product quality specifications those are based on clinicalperformance
- To increase process capability and reduce product variability and defects by enhancingproduct and process design, understanding, and control
- To increase product development and manufacturing efficiencies
- To enhance root cause analysis and post approval change management.

- The main objectives of QbD is to ensure the quality products, for that product & process characteristics important to desired performance must be resulting from a combinationof prior knowledge & new estimation during development.
- From this knowledge & data process measurement & desired attributes may be constructed.
- Experimental study would be viewed as positive performance testing of the model ability through Design space.
- Ensures combination of product & process knowledge gained during development

Under QbD, these goals can often be achieved by linking product quality to the desired clinical performance and then designing a robust formulation and manufacturing process to consistently deliver the desired product quality. Since the initiation of pharmaceutical QbD, the FDA has made significant progress in achieving the first objective: performance-based quality specifications. Some examples of FDA policies include tablet scoring and bead sizes in capsules labelled for sprinkle. The recent FDA discussions on the assayed potency limits for narrow therapeutic index drugs and physical attributes of generic drug products reflectthis trend. Nonetheless, it should be recognized that ICH documents did not explicitly acknowledge clinical performance-based specifications as a QbD goal, although this was recognized in a recent scientific paper (10). The second objective of pharmaceutical QbD is to increase process capability and reduce product variability that often leads to product defects, rejections, and recalls. Achieving this objective requires robustly designed product and process. In addition, an improved product and process understanding can facilitate the identification and control of factors influencing the drug product quality. After regulatory approval, effort should continue to improve the process to reduce product variability, defects,

rejections, and recalls. QbD uses a systematic approach to product design and development. As such, it enhances development capability, speed, and formulation design. Furthermore, it transfers resources from a downstream corrective mode to an upstream proactive mode. It enhances the manufacturer's ability to identify the root causes of manufacturing failures. Hence, increasing product development and manufacturing efficiencies is the third objective of pharmaceutical QbD. The final objective of QbD is to enhance root cause analysis and post approval change management. Without good product and process understanding, the abilityto efficiently scale-up and conduct root cause analysis is limited and requires the generation of additional data sets on the proposed larger scale. FDA's change guidance provide a framework for post approval changes. Recently, the FDA issued a guidance intended to reduce the regulatory filing requirements for specific low-risk chemistry, manufacturing, and control (CMC) post approval manufacturing changes [2,15].

The QbD Process

QbD is organized into five major activities, with multiple steps in each. As we have just noted, the design process has definite elements of linearity, but the specific tools applied ensure and facilitate collegial work in parallel. The five major activities are:

- Define
- Discover
- Design
- Develop
- Deliver

Define

The first step is to describe in general terms what the product is and what set of customers itis intended to serve. There may be multiple different target customers. The project charter includes not only this description of the product and target customers, but also the specific measured goals for the product. The specific goals adopted will depend on the product and itsrole in the enterprise strategy. These goals usually include:

- Market share
- Price point
- Margin
- Lead times
- Launch date
- Performance in terms of quality, cost, cycle time, or the like
- Customer loyalty

Discover

QbD requires the discipline to discover the exact needs of the customer – expressed in terms of the benefit that the customer is seeking. The needs must be specific and measurable so thatwe can design to them and measure our success in meeting them.

There are usually multiple customers – both internal and external – and some of them are hidden from our usual view of the business.

QbD incorporates robust science into the measurement and analysis of needs. In some cases this will be rather straightforward, but many cases will require the application of advanced survey and statistical techniques.

At this point, the project begins the completion of a series of planning worksheets thatdirectly tie:

- Customer to …
- Customer need to …

- Functional feature and goals to …
- Detailed design features and goals to …
- Process features and goals to …
- Control features and goals.

This systematic structure ensures that we meet all-important customer needs and that every feature in the design, production, and control of the delivery has a useful role and can be related unambiguously to the customers' needs.

Design

Once we know what the customer needs, we must design the product that will meet those needs better than competitors' and preceding products. Design, of course, encourages creativity and insight to meet needs in new and exciting ways that will appeal to the customer.

While it may seem contradictory to insist on structure to achieve creativity, that is exactly what is required. The proper structure encourages creativity and provides a safety net that allows the team to push the limits of creative ideas without running unnecessary risks.

QbD encourages multiple approaches to designing, including:

- Benchmarking
- Creative thinking techniques
- Competitive assessment
- Multiple alternative evaluation

The designs are solidly tied to reality through the application of …

- Market competitive analysis
- Deconstruction competitive analysis
- Salability analysis
- Multiple tools to assess failure modes and probability of failure
- Explicit trade-off analysis
- Design reviews at several stages
- Advanced techniques when needed, such as design of experiments, including non-linear response surfaces
- Value analysis to ensure that every dollar spent brings a return on the investment

Develop

Once the product is designed then the designers turn to the equally important job of developing the process for delivery. Process design is strongly rooted in a full understanding of the effects of variability and the need to measure and optimize process capability.

Finally, no design is complete without a rigorous control plan that will assure that the processwill continue to run free of defects indefinitely.

Deliver

The job is not done until the product is in production, meeting all the goals set out in the charter, and delighting the customers. Effective delivery relies on strong planning from transfer to operations, a scale-up strategy, and validation of the transfer.

Advantages of QbD [13, 15]

- It provides a higher 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 drugproduct to obtain approval and ultimately commercialize.
- It makes the scale-up, validation and commercialization transparent, rational andpredictable.
- It facilitates innovation for unmet medical needs.
- It increases efficiency of pharmaceutical manufacturing processes and reducesmanufacturing costs and product rejects.
- It minimizes or eliminates potential compliance actions, costly penalties, and drugrecalls.
- It offers opportunities for continual improvement.
- It provides more efficiency for regulatory oversight.
- It streamlines post approval manufacturing changes and regulatory processes.
- It more focused post approval CGMP inspections.
- It enhances opportunities for first cycle approval.
- It facilitates continuous improvement and reduces the CMC supplement.
- It enhances the quality of CMC and reduces the CMC review time.

- Patient safety and product efficacy are focused.
- Scientific understanding of pharmaceutical process and methods is done.
- It involves product design and process development. Science based risk assessment iscarried.
- Critical quality attributes are identified and their effect on final quality of product isanalysed.
- It offers robust method or process. Business benefits are also driving force to adoptQbD

QbD Terminology

The ICH Q8–Q11 documents have helped bring great clarity to terms and definitions. The pharmaceutical industry is complex and does not help itself when companies or individuals use different language to describe in essence the same thing. Indeed, there are exampleswhere the regulators have been concerned when there has been a lack of clarity. The following are some of the key terms on which QbD is founded:

- Quality target product profile (QTPP).
- Critical quality attributes (CQA).
- Critical process parameter (CPP).
- Critical materials attribute (CMA).
- Design space (DS).
- Control strategy (CS).
- Lifecycle.