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Quality by Design (Qbd) -Ensuring Quality of Product

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ABSTRACT

Quality by design is a standout amongst the most techniques which go about as a piece of current methodology to pharmaceutical industry. This paper gives thought regarding the Pharmaceutical Quality by Design (Qbd) and depicts utilization of Quality by design to guarantee quality of pharmaceuticals. The idea advances industry's understanding of the product and manufacturing process with product development, fundamentally constructing quality in, not testing it. It incorporates the Quality Target product profile ,critical quality attributes and key parts of Quality by Design .It likewise gives examination between product quality by end testing and product Quality by Quality by Design. The establishment of Quality by Design is ICH Guidelines. It is focused around ICH Guideline Q8 for pharmaceutical development, Q9 for quality risk management, Q10 for pharmaceutical quality system. It additionally gives application of Quality by Design in pharmaceutical development and manufacturing of pharmaceuticals.

Keywords: Quality by design(QbD), Target product quality, Design space, Critical quality attributes.

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INTRODUCTION

Joseph Juran, characterized the term Quality in two ways , the result from his first definition is; " Product characteristic must meet the customers's demands ",while the second definition is , "Product must be free from insufficiencies". Both the two meaning of joseph juran has real effect on expense of item (1). Universal Conference on Hormonization (ICH) created the Q8 R2guideline for pharmaceutical development utilizing risk based approach i.e. Quality by Design (Qbd) (2).Since January 2013 ,Food and Drug Administration requesting that generic manufacturers must implement the Qbd paradigmn into their Abbreviated New Drug Application (ANDA),Module 3 Quality 3.2.p.2 Pharmaceutical Development. The aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product. The information and knowledge gained from pharmaceutical development studies and manufacturing experience provides scientific understanding to support the establishment of the design space, specifications and manufacturing controls. Information from pharmaceutical development studies can be 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. Design space is proposed by the applicant and is subject to regulatory assessment and approval. Working within the design space is not considered to be a change and would normally initiate a regulatory post approval changes.

Pharmaceutical quality assessment system

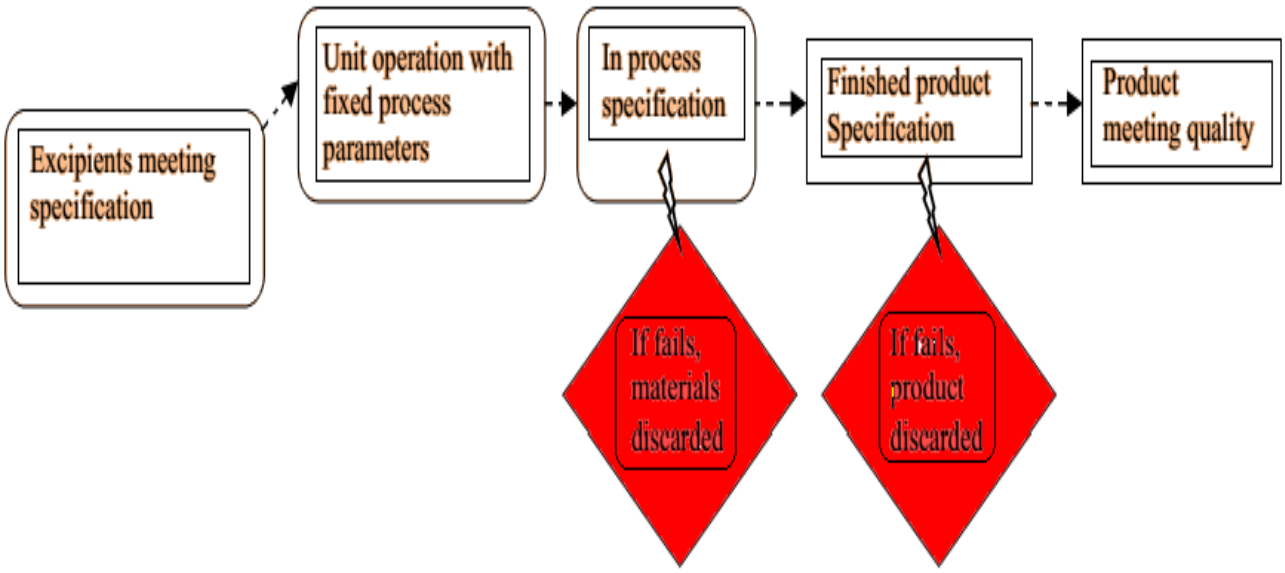

Figure 1: A Simplified Quality Control diagram using QbT

Traditionally, pharmaceutical quality was characterized as the product meeting the pre-specified quality traits and regulatory specification. There is no connection between the product quality attributes and clinical performance. In quality by testing (QbT) crude materials, in process and finished product are observed by testing. Figure.1 demonstrates an simplified quality control diagram under the quality by testing (QbT) regulatory structure for generic drug. Finished products are tested for quality by surveying whether they meet the manufacturers proposed or FDA approved specifications. If not, they are disscarded and large root cause for failure are not caught on. The stringent specification has brought about recalls and drug shortage[2].

Quality by design leverages lesions from experience

Past experience is significant to the gathering of institutionalized knowledge. At the point when outlining methodologies that can adapt to variability, we need to look at historical production data to learn from mistakes and successes. The FDA's Janet Woodcock has as often as possible expressed that QbD is derived from a blend of former information, experimental evaluation, and a cause-and-effect model that links critical process parameters and critical quality attributes . Achieving the goal of manufacturing process excellence through QbD requires us to begin the work in process development. It's natural to think of the flow of data and information in the forward direction from process development into manufacturing, but data and information also needs to flow backward from manufacturing into process development. By utilizing information and data from current business courses of action to aid with future process development for new products, we leverage that we have effectively made and experience we have officially picked up. To do this, on interest information access and investigational examination are needed for fruitful joint effort between the process development and manufacturing teams. This permits us to design and build additional risk reduction and ruggedness into the next process so that it can better handle variability. The FDA's Process Analytical Technology (PAT) rule, shows the value of continuous learning that comes from analyzing process data when coupled with systems that support the acquisition of knowledge from those data, saying: "Constant adapting through information accumulation and examination over the lifecycle of an item is important. These information can help defending suggestions for post-approval changes. Approaches and information technology systems that support knowledge acquisition from such databases are valuable for the manufacturers and can also facilitate scientific communication with the agency"[3-4]. Figure 2 represents the key steps that are taken for implementation of QbD for a pharmaceutical product. The steps are in arrangement with the proposals in the ICH direction Q8 and ICH direction Q8 Annex records[9].

Identifying target product quality

Target Product Quality Profile (TPQP) will be a device for setting the key foundation for drug development "planning with the end in mind." More as of late a stretched utilization of the TPP being developed planning, clinical and commercial, regulatory agency interactions, and risk management has begun to develop. The target profile is a rundown of the drug development program depicted in the context of prescribing information goals. The TPP can assume a focal part in the drug discovery and development process, for example, effective optimization of a drug candidate, decision making within an organization, design of clinical research strategies, and constructive communication with regulatory authorities. TPP is at present basically communicated in clinical terms, for example, clinical pharmacology, indications and usage, contraindications, warnings, precautions, adverse reactions, drug abuse and dependence, over dosage, so on. Accordingly, it is sorted out as per key segments in the product's label. TPP therefore links drug development activities to specific statements intended for inclusion in the drug's label. Target Product Quality Profile (TPQP) is a term that is a common augmentation of TPP for product quality. It is the quality character that the drug product should have so as to reproducibly deliver the therapeutic benefit promised in the label. The TPQP guides formulation scientists to establish formulation strategies and keep the formulation effort focused and efficient. TPQP is identified with personality, measure, measurement structure, virtue, soundness .The TPQP of a generic drug can be readily determined from the reference listed drugs (RLD). Along with other available data from the scientific literature and potentially the pharmacopeia, the TPQP can be utilized to characterize product specifications to some degree even before the product is produced. Predefined, high quality product specifications make the product and process design and development more objective and efficient. FDA published a recent guidance defining a Target Product Profile (TPP): "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. Normally, the accumulated lab, nonclinical and clinical experience within particular product quality trait, is the key in making these risk evaluations. Such learning may likewise incorporate important information from similar molecules and information from literature references. Taken together, this data gives a basis to relating the CQA to safety and efficacy. The conclusion of the risk evaluation would be a list of CQAs ranked in order of importance. Use of robust risk assessment methods for identification of CQAs is novel to the QbD paradigm.

Identifying critical quality attributes

Once TPP has been recognized, the following step is to recognize the relevant CQAs. A CQA has been characterized as "a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality"[8]. Identification of CQAs is carried out through risk evaluation according to the ICH direction Q9 **(Figure 2)**. 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. Such information might likewise incorporate significant information from similoar molecules and information from literature references. Taken together, this data gives a reason to relating the CQA to item safety and efficacy. The conclusion of the risk assessment would be a list of CQAs ranked in order of importance. Use of robust risk assessment methods for identification of CQAs is novel to the QbD paradigm.

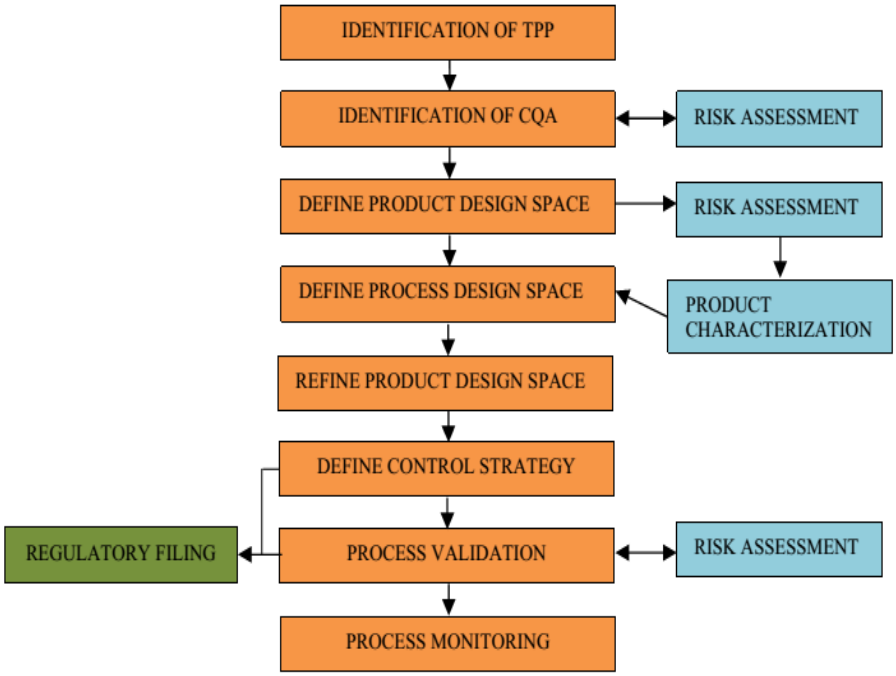

Figure 2 : "Key steps in implementation of QbD for pharmaceutical product"

Design product and defining product design space

After CQAs for an product have been recognized, the following step is to define the product design and design space (that is, specifications for in-process, drug substance and drug product attributes). These specifications are established based on several sources of information that link the attributes to the safety and efficacy of the product, including, but not limited to, the Published literature on other similar products, Process capability with respect to the variability observed in the manufactured lots, Design space, Clinical and nonclinical studies with similar platform products.

The distinction between the actual experience in the clinic and the specifications set for the product would depend on our level of understanding of the impact that the CQA under consideration can have on the safety and efficacy of the product. In QbD, an improved understanding of the linkages between the CQA and safety and efficacy of the product is required. QbD has brought a realization of the importance of the analytical, nonclinical and animal studies in establishing these linkages and has led to the creation of novel approaches. In order to design and develop a robust generic product that has the desirable TPQP, a product development scientist must give serious consideration to the biopharmaceutical properties of the drug substance. These biopharmaceutical properties include physical, chemical, and biological properties[9].

Process design and defining process design space

Procedure and it product design and development can't be differentiated since formulation cannot become a product without a process. process design is the starting phase of process development where outline of commercial manufacturing processes is identified including the intended scale of manufacturing. This incorporate all the factors that need to be considered for the design of the process, including facility, equipment, and material transfer and manufacturing variables [16]. Critical process parameters (CPP) are process inputs that have a direct and significant influence on critical quality attributes when they are varied within regular operation range. Process robustness is defined as the ability of a process to demonstrate acceptable quality and performance and tolerate variability in inputs at the same time [18]. To demonstrate the reproducibility and consistency of a process, process capability should be studied. Process capability is a statistical measure of the inherent process variability for a given characteristics. Design of Experiment (DOE) is structured and organized method to determine the relationship among factors that influence outputs of a process. The overall approach toward process characterization involves three key steps. First, risk analysis is performed to identify parameters for process characterization. Second, studies are designed using design of experiments (DOE), such that the data are amenable for use in understanding and defining the design space. And third, the studies are executed and the results analyzed to determine the importance of the parameters as well as their role in establishing design space. Failure mode and effects analysis (FMEA) is commonly used to assess the potential degree of risk for every operating parameter in a systematic manner and to prioritize the activities, such as experiments, necessary to understand the impact of these parameters on overall process performance[19]. A group comprising of delegates from process development, manufacturing and other relevant deciplines performs an appraisal to focus on severity, occurrence and detection. The seriousness score measures the seriousness of a specific failure and is based on an estimate of the

severity of the potential failure effect at a local or process level and the potential failure effect at end product use or patient level. Occurrence and detection scores are based on an excursion (manufacturing deviation) outside the operating range that results in the identified failure. Although the occurrence score measures how frequently the failure might occur, the detection score indicates the probability of timely detection and correction of the excursion or the probability of detection before end product use. All three scores are multiplied to provide a risk priority number (RPN) and the RPN scores are then ranked to identify the parameters with a high enough risk to merit process characterization. Despite the fact that FMEA and DOE are not new ideas for the development of manufacturing processes, linking the establishment of design space to the relevant CQA is novel. For instance, a granulation step that has an immediate effect on a few CQAs and an immediate bearing on whether the last drug product meets particulars would be expected to undergo a more thorough process characterization and examination of a larger process design space. In contrast, a non-functional coating step that is robust and has no direct influence on any CQA may require relatively limited process characterization.

Defining 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"[20]. The control system in the Qbd standard is secured by means of risk assessment that considers the criticality of the CQA and process capacity (Figure.2). The control procedure can incorporate the accompanying components: procedural controls, in process controls, lot release testing, process monitoring, characterization testing, comparability testing and stability testing. It is worth noting that the use of risk assessment in creating the control strategy is unique to the QbD approach.

Process validation

An improved understanding of the manufacturing procedure and a stretched process design space should give more manufacturing flexibility during process validation[21, 22]. Since the designs space "guarantes quality" of the drug product, these limits should also provide the basis of the validation acceptance criteria. The constrains that secure the satisfactory variability in item quality and process performance qualities would likewise serve as the procedure approval acknowledgement criteria. When the procedure outline space has been made, process validation becomes an exercise to demonstrate (i) that the process will deliver a product of acceptable quality if operated within the design space and (ii) that the small and/or pilot scale systems used to establish the design space accurately model the performance of the manufacturing scale

process. Thus, in the QbD paradigm, unanticipated manufacturing excursions that remain within the process design space should not affect the success of the validation exercise.

Regulatory filings

After the process design space has been made and validated, the regulatory documenting would incorporate the acceptable ranges for all key and critical working parameters that characterize the process design space in addition to a more restricted operating space typically described for drug products. The documenting would likewise incorporate validation exercise and plan for process monitoring (Figure.2). In the QbD paradigm, the filing could also include protocols (e.g., comparability protocols or expanded change protocols) that would allow future flexibility in process changes with respect to pre-approved criteria that have been agreed upon between the applicant and the agency.

Process monitoring, life cycle management and continuous improvement

After approval, CQAs would be checked to guarantee that the process is performing inside the defined acceptable variability that served as the premise for the recorded process design space. The essential advantage of an extended process design space would be a more adaptable approach by regulatory agencies. In the Qbd paradigm, process changes inside the design space won't oblige audit or support[24]. Therefore, process improvements during the product life cycle with regard to process consistency and throughput could take place with fewer post approval submissions. In addition to regulatory flexibility, the enhanced understanding of the manufacturing process would allow more informed risk assessment as per ICH Q9 regarding the affects of process changes and manufacturing deviations (excursions) on product quality[23]. As manufacturing background develops and opportunities for process change are distinguished, the working space could be modified inside the design space without the requirement for post-approval submission. Over the lifetime of a product, process changes may be required to be made and may require process characterization, validation and filing of the changes to the approved process design space (Figure-2). The quality system needs to provide adequate oversight during QbD implementation to changes that will not go through regulatory approval[21]. Robustness of the quality framework would need to be showed as for the accompanying four components: process performance/product quality monitoring; preventative/ corrective action, change management and management review of process performance and product quality.

Implementing quality by design

Quality by Design (QbD) is obviously prepared to help an association solve the perpetual difficulties of drug advancement and manufacturing. The availability of any association for Qbd

starts with an understanding of QbD basics, advantages, and barriers to usage, followed by a status evaluation that can guarantee that one has the right attitude, needs, and resources adjusted for an effective execution. As long prior as 2004, Janet Woodcock, chief of FDA's Center for Drug Evaluation and Research, expressed that the essential standards of Qbd are practically oppositely contradicted to made industry practices. By expanding scientific understanding of products and process, Qbd makes risk based compliance possible. Its objective is not to kill variability in methods yet to create a process that can suit the scope of adequate variability for keeping up product quality. Beginning from a Target Product Profile (TPP) focused around Critical-to-Quality Attributes (CQA) (Figure.2), one can then utilize appropriate analytical methods and instruments to comprehend Design Space, defined by ICH Q8 as "the multidimensional blend and connection of information variables (e.g., material properties) and methodology parameters that have been showed to give confirmation of value. "Such methods and tools include high-end statistics like multivariate analysis, modelling tools, and design of experiments (DoE). They are used to help understand the most critical process parameters (CPPs) and map out the Design Space so that one can create an in-control operating space, preferably near the center of the Design Space where the most process robustness will be found. And with a demonstrable, scientific understanding of Design Space, process can be continuously improved without additional regulatory review. Robust, scientifically understood processes that allow for variation without compromising quality generate operating improvements that translate into business benefits, including: Faster time to market and reliable supply, Fewer lost batches, Fewer manufacturing deviations, Reduced out-of-specification results, reducing rework, Reduced compliance exposure and increased regulatory flexibility with fewer remediation and the ability to make process changes without re filing. These operating successes also help reinforce a “right-first-time” culture, where quality means continuously creating more value, not simply correcting problems. These reservations are not entirely misplaced. Implementing QbD does require a significant cultural shift, as well as organizational re-training and learning. Like most transformations, QbD requires time, effort, and commitment, particularly from senior management. That said, benefits emerge relatively early in implementation in weeks to a few months and QbD’s ability to lower costs, reduce waste, and eliminate non-value-added activities associated with noncompliance rapidly outweighs the cost of adoption. The key is to begin with a QbD readiness assessment that can tell you what practices and resources you need to put in place to ensure rapid, sustainable, and successful implementation. Readiness assessment for QbD falls into three major areas: strategy, organization and culture, and operations. Depending on the specific circumstances of the company and the operation, the value

proposition for QbD could be based on any number of objectives and metrics. For example, could be built around reduction of regulatory workload, reduced quality costs through reduced or eliminated deviation investigations, or opportunities to apply Process Analytical Technology (PAT) to enable real-time testing and release. Operational assessment encompasses all of the technical and tactical elements that must be in place and integrated smoothly into a process in order to deliver the promised value. These elements could include everything from defining the target product profile (TPP) to virtually any process, technology or system in the operation. The list of such elements is long, but by keeping clear the distinctions between strategy, organization, and operations you can be sure that at any point in the assessment you are clear about what, precisely, you are assessing. This clarity is especially helpful when it comes to prioritizing each of the elements by importance, regardless of where each fits in the structure. Greater understanding and application of common risk management tools to pharmaceutical products: This is also critical because, as FDA and ICH documents have made clear, QbD is intended to enable a risk-based approach to quality which can be extended to the entire product life cycle. Failure Mode and Effects Analysis (FMEA) is a common risk analysis tool used for QbD. However, other risk assessment tools can be added to the QbD and total quality management toolbox to transform the organization's mindset and culture toward one of continuous improvement. Some of these risk assessment tools for use across the life cycle, in addition to FMEA, include Process Mapping, Hazard Analysis and Critical Control Points (HACCP), Hazard Operability Analysis (HAZOP), Fault Tree Analysis (FTA) and Cause and Effect Analysis (CEA). Quality Target Product Profile: The QTPP is indispensable for defining the critical to quality attributes (CQAs)—the desired outputs of the manufacturing process. It is equally important for mapping the Design Space—that, understands the relative impact of input variables (process steps, process parameters, and raw materials) on CQAs. As the organization's proficiency in risk assessment increases, the QTPP becomes more apparent. Statistical software resources: Also indispensable. Whether the company builds on its current software or acquires new software, the choice should be based on the ability of the package to perform multi-variate techniques. QbD success requires strong management commitment. Management should not only make its support of the initiative loud and clear but also actively sponsor the effort. As this company understood, implementation of QbD does result in additional work, new ways of working, and significant change. But as it also understood, QbD can be significantly less daunting if the organization understands clearly what is most important, where there are critical gaps, and what must be done to close them. Ultimately, companies that successfully adopt QbD are rewarded not only with the specific operational and business benefits

of the value proposition, but also with the creation of a culture of continuous improvement that keeps paying additional dividends.

CONCLUSION

The goal of a well-characterized method development effort is to develop a reliable method that can be demonstrated with a high degree of assurance to consistently produce data meeting predefined criteria when operated within defined boundaries. QbD can be applied to the development and evaluation of analytical methods. During method development, all potential factors (the inputs) and all critical analytical responses (the outputs) are studied to determine the relationships. Critical analytical factors are identified in an approach that parallels what is described for process development in ICH Q8 and Q9. The QbD process on an active partnership of analytical scientists at both the development and operational laboratories as methods are developed and as factors that lead to potential method failures are identified and controlled. A corporate knowledge repository is required throughout the process to ensure critical information is captured that can be reviewed and added to in the future such that lessons learned can be applied to the specific method under consideration and also to other similar methods being applied to other products. Such a repository (in line with concepts described in the draft ICH Q10) will enable continuous improvement and change control of the method to take place throughout its lifecycle. Rather than continuing to perform analytical technology transfer exercises and ICH validation, a QbD approach based on a risk-assessed change control procedure should be adopted. Each time a method is changed, a risk assessment should be performed. Where the change is identified as having a potential to take the method outside its known design space, a method evaluation and, if appropriate, an equivalency exercise should be performed to ensure method performance criteria are still met. This will allow for method improvements to be made via internal change control procedures, and even switches between different techniques (e.g., HPLC versus NIR) may become much easier to implement. A QbD approach for analytical methods that includes risk assessment, robustness testing, and ruggedness testing is much more rigorous than ICH validation requirements (Q2 (R1)). It also includes an assessment of method variability compared with the specification limits, which is one of the most important method attributes to test when deciding whether the method is fit for its purpose. The approach described herein suggests that ICH Q2 (R1), while adding some value, must be substantially rewritten to take account of the QbD risk-based approaches described in this article. This new QbD process offers the opportunity for much greater regulatory flexibility in the future. The method performance criteria could potentially be registered

instead of the method itself. The method used could be referred to as an example of how to attain the required method performance criteria. Any changes to this method would be covered by internal change control procedures.

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