Review Article

Application of Quality by Design and its Parameters for Pharmaceutical Products

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ABSTRACT

The application of quality by design (QbD) in pharmaceutical product development is now a thrust area for the regulatory authorities and the pharmaceutical industry. International Conference on Harmonization and United States Food and Drug Administration (USFDA) emphasized the principles and applications of QbD in pharmaceutical development in their guidance for the industry. The key elements of QbD viz., target product quality profile, critical quality attributes, risk assessments, design space, control strategy, product lifecycle management, and continual improvement are discussed to understand the performance of dosage forms within design space. Design of experiments, risk assessment tools, and process analytical technology are also discussed for their role in QbD. This review underlines the importance of QbD in inculcating science-based approach in pharmaceutical product development.

Keywords: Design of experiments, design space, process analytical technology, risk assessment, Quality by Design (QbD), Critical Quality Attribute (CQA), Quality Target Product Profile (QTPP), Failure Mode Effects Analysis (FMEA), Failure Mode, Effects and Criticality Analysis (FMECA), Fault Tree Analysis (FTA), Hazard Analysis and Critical Control Points (HACCP).

INTRODUCTION

The annex of International Conference on Harmonization (ICH), ICH Q8 (R2) guidance,[1,2] describes the principles of quality by design (QbD). This guidance further clarifies the key concepts mentioned in the parent guidance ICH Q8[3]. It defines quality as "the suitability of either a drug substance or drug product for its intended use." ICH Q8 (R2) defines QbD as "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." The concept and application of the principles of QbD has been an emerging topic in the pharmaceutical industry.[4] In QbD, the product quality is assured by understanding and controlling formulation and manufacturing variables. Thus, the consistent product quality results from the design, control of formulation, and the manufacturing process. This article focuses on the application of QbD for pharmaceutical product development. Application of QbD approach in pharmaceutical product development can lead to robust formulations and high success rate in regulatory approvals. QbD involves the use of multivariate statistics and design of experiments technique[5]. QbD involves a thorough understanding of the relationship of product performance with product attribute and process[6, 7]. Traditionally, formulations are manufactured to meet quality control tests outlined in product specifications. If the product is deemed fit for commercial purpose, then it should meet quality control tests. In case of a batch failing to comply with these tests, it is reprocessed or rejected which opens doors for regulatory questions and obvious cost burden. The application of QbD in pharmaceutical product development is systematic, involving multivariate experiments utilizing process analytical technology (PAT) and

other tests to identify critical quality attributes (CQAs) based on risk assessments (RAs). The QbD begins with predefined objectives and requires an understanding how formulation and process variables influence product quality[8]. Though end product testing can confirm product quality, it cannot be a part of a process consistency or process control[9]. **Figure 01** depicts an overall QbD system where RA and risk control for the product and process are involved.

The important components of product development by QbD are target product profile (TPP), target product quality profile (TPQP), design and development of product, developing the manufacturing process, identifying the CQA, assessment and management of the risks involved in the process, establishment of design space, and defining a control strategy for a product to stay within the design space. Control strategy is the knowledge driven from the relationship between formulation and manufacturing process variables that must be controlled in manufacturing a product of consistent quality. Product lifecycle management further adds to the knowledge base, helps in continuous product monitoring and improvement. **Figure 02** shows a schematic representation of how various ICH guidelines dealing with pharmaceutical quality can influence and result in a desired product quality.

KEY CHARACTERISTICS OF QbD[10-11]

- A tool for focused & efficient drug development
- Dynamic and systematic process
- Relies on the concept that Quality can be built in as a continuum
- It is applicable to Drug Product and Drug Substance development (chemicals / biologics)
- It is applicable to analytical methods
- Can implemented partially or totally
- Can be used at any time in the life cycle of the Drug
- Always encouraged by Regulators.

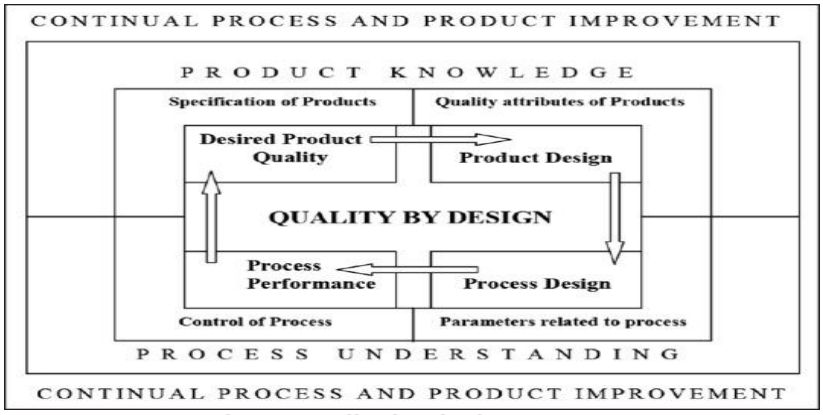

Fig. 1: Quality by design system

Fig. 2: Pharmaceutical quality systems for quality by design

BENEFITS OF QbD[12-14]

- Eliminate batch failures
- Minimize deviations and costly investigations
- Avoid regulatory compliance problems
- Empowerment of technical staff
- Efficient, agile, flexible system
- Increase manufacturing efficiency, reduce costs and project rejections and waste
- Build scientific knowledge base for all products
- Better interact with industry on science issues
- Ensure consistent information
- Incorporate risk management
- Reduce end-product testing
- Speed-up release decision

KEY ELEMENTS OF QbD

ICH Q8: Pharmaceutical Development discusses the various elements of quality by design. These in combination with the enablers form the fundamental basis for the QbD approach to development. Figure 1 provides a pictorial representation of the typical elements of QbD.

It involves the following key elements during pharmaceutical development

1. Define the Quality Target Product Profile
2. Identify the Quality Attributes
3. Perform a Risk (Assessment) Analysis
4. Determine the Critical Quality Attributes and Critical Process Parameters
5. Determine the Design Space
6. Identify a Control Strategy

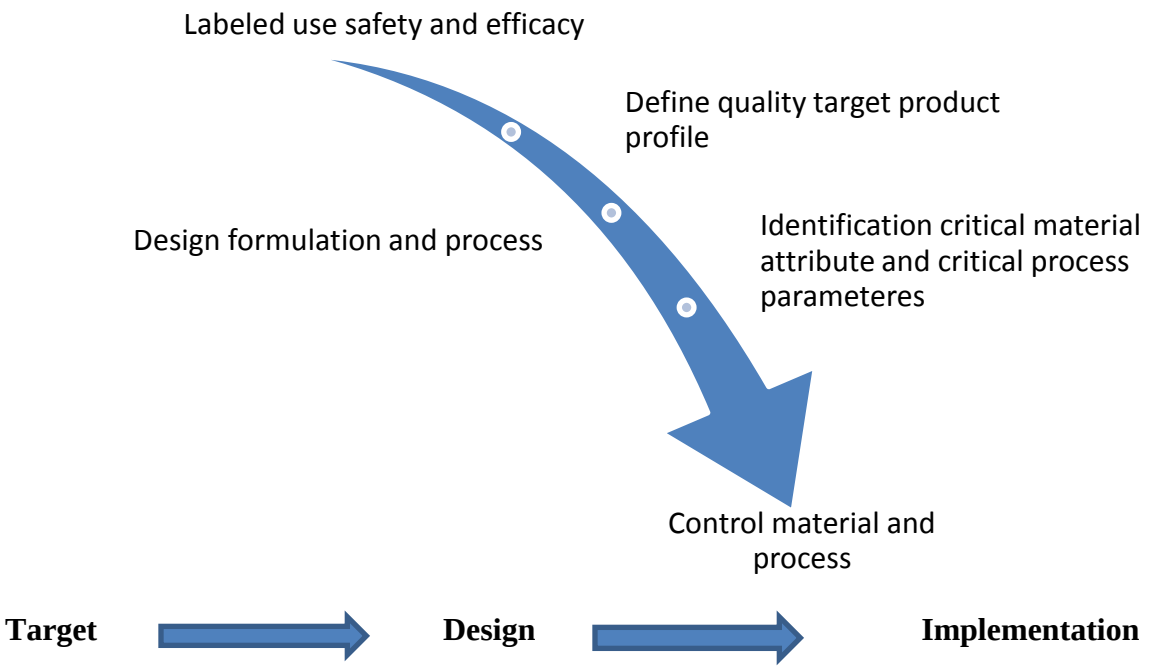

Fig. 3: Overview of QbD.

QUALITY TARGET PRODUCT PROFILE (QTTP)

According to ICH Q8 (R2), QTTP is "Prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product". Basically it is a tool for setting the strategy for drug development. Recently QTTP is widely used in development planning, clinical and commercial decision making, regulatory agency interactions, and risk management.

It is the quality characteristics that the drug product should possess in order to reproducibly deliver the therapeutic benefit promised in the label. The QTTP guides formulation scientists to establish formulation strategies and keep the formulation effort focused and efficient. QTPP is related to identity, assay, dosage form, purity, stability in the label. For example, a typical QTPP of an immediate release solid oral dosage form would include

- Tablet Characteristics
- Identity
- Assay and Uniformity
- Purity/Impurity
- Stability, and
- Dissolution

It is important to acknowledge that QTPP should only include patient relevant product performance elements. For example, tablet density or hardness may be included as a specification for process monitoring but may not be included in QTPP. Also, if particle size is critical to the dissolution of a solid oral product, then the QTPP should include dissolution but not particle size[15-16].

RELATIONSHIP BETWEEN RISK AND CRITICALITY[27]

Risk includes severity of harm, probability of occurrence, and detectability, and therefore the level of risk can change as a result of risk management.

Quality Attribute criticality is primarily based upon severity of harm and does not change as a result of risk management.

Process Parameter criticality is linked to the parameter's effect on any critical quality attribute. It is based on the probability of occurrence and detectability and therefore can change as a result of risk management.

CRITICAL QUALITY ATTRIBUTES (CQAS)

Once QTPP has been identified, the next step is to identify the relevant CQAs. A CQA is defined 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". CQAs are generally associated with raw materials (drug substance, excipients), intermediates (in-process materials), and drug product. Drug product CQAs are the properties that are important for product performance, that is, the desired quality, safety, and efficacy (**Figure.04**).

This indicates that CQAs are subsets of QTPP that has a potential to be altered by the change in formulation or process variables[16-17]. For example, QTPP may include additional quality attributes of the drug product such as strength and dosage form, which are not the part of CQA as it will not change during drug development process. However, QTTP attributes such as assay, content uniformity, dissolution, and permeation flux will also be a part of CQA as they may be altered by formulation or process variables. For example, the CQAs of drug substance and drug product are enlisted in **Table 1**.

Identification of CQAs is done through risk assessment as per the ICH guidance Q9. 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 knowledge may also include relevant data from similar molecules and data from literature references. Taken together, this information provides a rationale for relating the CQA to product safety and efficacy[18].

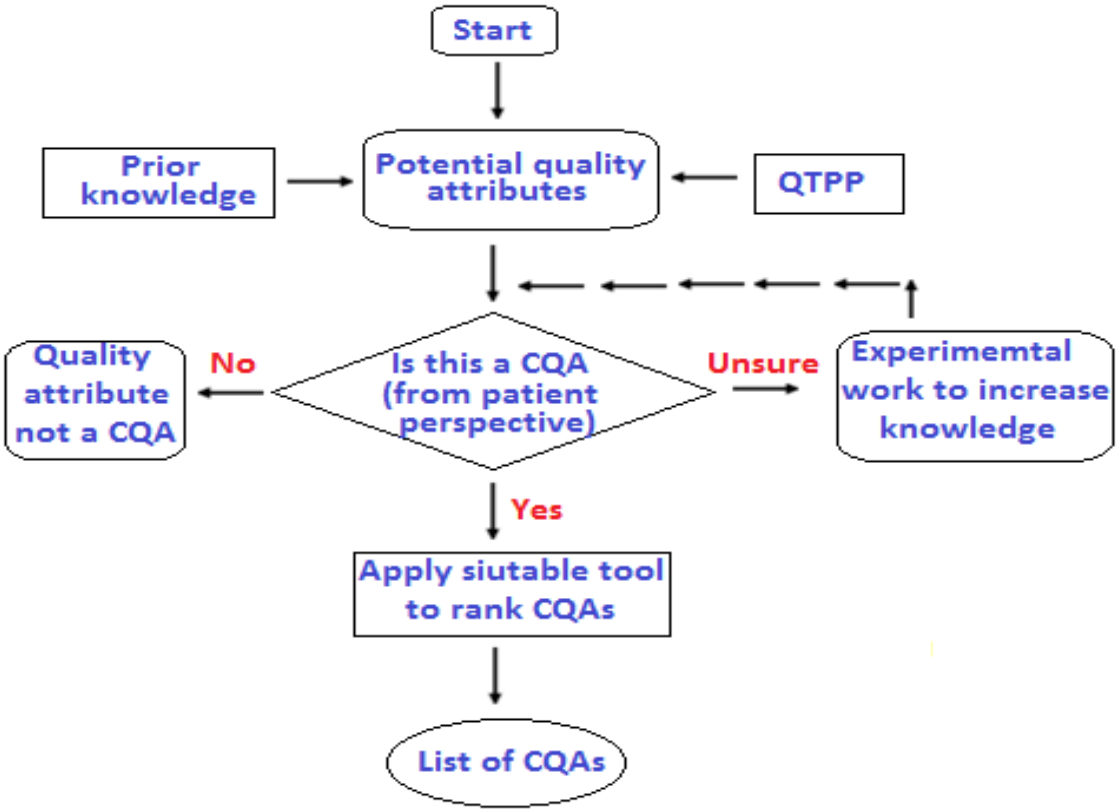

Fig. 4: Decision Tree to Decide CQAs

Table 1: Typical CQAs for drug substance and drug products

For Product Substance (Chemical)	For Drug Product (Tablet)
• Appearance • Particle size • Morphic forms • Water content • Residual solvents • Organic impurities • Inorganic impurities • Heavy metals • Residue on ignition • Assay	• Appearance • Identification • Hardness • Uniformity of dosage • Physical form • Dissolution • Degradation products • Water content • Assay • Microbiological limits

The FDA defines a Risk Management as, a strategic safety program designed to decrease product risk by using one or more interventions or tools. It is systematic process for the assessment, control, communication and review of risks to the quality of the drug product across the product lifecycle[19]. Overview of a typical quality risk management process is given in **Figure 05.**

The ICH Q9 guideline: Quality Risk Management provides a structure to initiate and follow a risk management process. The relevant tools of QRM are as follows:

QUALITY RISK MANAGEMENT PROCESS

Fig. 5: Overview of a typical quality risk management process (as per ICH Q9: Quality Risk Management)

A.FAILURE MODE EFFECTS ANALYSIS (FMEA)

FMEA is one of the most commonly used risk-assessment tools in the pharmaceutical industry. It is a systematic and proactive method to identify and mitigate the possible failure in the process. Failure modes represent any errors or defects in a process, material, design, or equipment. Once failure modes are established, FMEA tool evaluates the effect of these failures and prioritizes them accordingly. This tool is further advanced with studying criticality of the consequences and providing clear indication of situation.

B.FAILURE MODE, EFFECTS AND CRITICALITY ANALYSIS (FMECA)

It is the extension of earlier said FMEA tool. Extending FEMA to incorporate an investigation of the degree of severity of consequences, their probabilities of occurrence and their detect-ability is Failure mode, effects and criticality analysis. In FMECA, each failure mode of the product is identified and then evaluated for criticality. This criticality is then translated into a risk, and if this level of risk is not acceptable, corrective action must be taken. This can be utilized for failure and risk associated with manufacturing processes. The tool can also be used to establish and optimize maintenance plans for repairable systems and/or contribute to control plans and other quality assurance procedures.

C.FAULT TREE ANALYSIS (FTA)

This tool assumes failure of the functionality of a product or process. The results are represented pictorially in the form of a tree of fault modes. This can be used to investigate complaints or deviation in order to fully understand their root cause and ensure that intended improvement will resolve the issues and not cause any other different problem.

D.HAZARD ANALYSIS AND CRITICAL CONTROL POINTS (HACCP)

HACCP provides detailed documentation to show process or product understanding through identifying parameters to control and monitor. The definition of hazard includes both safety and quality concern in a process or product. It involves hazard analysis, determining critical control point, establishing critical limit, establishing a system to monitor critical control point and establishing a record keeping system. This might be used to identify and manage risk associated with physical, chemical and biological hazards.

The output of a risk assessment may be a combination of quantitative and qualitative estimation of risk. As part of FMEA, a risk score or **Risk Priority Number (RPN)** may be assigned to the deviation or to the stage of the process that is affected; this helps to categorize the deviation. RPN is calculated by multiplying Probability (**P**), Detectability **(D)** and Severity **(S),** which are individually categorized and scored. Rating scales usually range from 1 to 5.

RPN = probability score × severity score × detectability score

Where, the score was defined prior to the risk analysis stage. A RPN of < 40 was considered a low risk; a RPN of 40–99 was identified as an intermediate risk; and a RPN of ≥ 100 was defined as a high risk[16, 19].

DETERMINATION OF CRITICAL PROCESS PARAMETERS

A critical process parameter (CPP) is any measurable input (input material attribute or operating parameter) or output (process state variable or output material attribute) of a process step that must be controlled to achieve the desired product quality and process consistency. A parameter is critical when a realistic change in that parameter can cause the product to fail to meet the QTPP. Thus, whether a parameter is critical or not depends on how large of a change one is willing to consider. Thus the first step in classifying parameters is to define the range of interest which we call the potential operating space (POS). The POS is the region between the maximum and minimum value of interest for each process parameter. Criteria for identifying critical and non-critical parameters are that a parameter is non-critical when there is no trend to failure within the POS and there is no evidence of interactions within the proven acceptable range (PAR), which is the range of experimental observations that lead to acceptable quality[20,21]. The different CCPs during tablet manufacturing along with CQAs are given in **Table 2**.

Table 2: Different critical process parameters with potential quality attributes during tableting

S. No	Operations during tableting	Critical Process Parameters	Potential Quality Attributes
1	Wet granulation	Mixing time Impeller speed Binder fluid addition rate & time Method of binder addition Temperature	Blend uniformity Granule size & distribution Moisture content
2	Drying	Drying time Inlet air flow Exhaust air temperature & flow	Bulk/tapped density Moisture content Granules strength & uniformity
3	Milling	Milling speed Screen size Feeding rate	Flow properties Particle size distribution Bulk/tapped density
4	Mixing	Mixer type Mixing time Order of addition	Blend Uniformity
5	Compression	Pre compression force Main compression force Dwell time Hopper design Punch penetration depth Roller type Auger screw rate Ejection force	Weight variation Hardness Friability Content uniformity Assay Dissolution Disintegration
6	Coating	Inlet air flow Time Temperature Spray pattern & rate	Thickness Hardness % of weight gain Appearance

DESIGN SPACE

ICH Q8 (R2) defines design space as "the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. 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 post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval."

Design space may be constructed for a single unit operation, multiple unit operations, or for the entire process. Though according to FDA guideline, defining design space is optional since the product and process understanding can be established without a formal design space, nevertheless, such approach can assist to better understanding and attain overall control of a system.

The Design Space is linked to criticality through the results of risk assessment, which determines the associated CQAs and CPPs. It describes the multivariate functional relationships between CQAs and the CPPs that impact them, and should include their linkage to or across unit operations. Such relationships are arrived at by iterative application of risk assessment and experimental design, modeling, as well as the use of literature and prior experience.

Methods for determining design space included: one-variable-at-a-time experiments, statistically designed experiments, and modeling approaches. Methods for presenting design space included graphs (surface-response curves and contour plots), linear combination of parameter ranges, equations, and models. Alternatively, the design space can be explained mathematically through equations describing relationships between parameters for successful operation[22-23].

DESIGN OF EXPERIMENTS (DoE)[27]

The factors to be studied in a DoE could come from the risk assessment exercise or prior knowledge. Inclusion of a full statistical evaluation of the DoEs performed at early development stages (e.g., screening) is not expected. A summary table of the factors and ranges studied and the conclusions reached will be helpful. For DoEs involving single- or multiple-unit operations that are used to establish CPPs and/or to define a Design Space (DS), the inclusion of the following information in the submission will greatly facilitate assessment by the regulators:

- Rationale for selection of DoE variables (including ranges) that would be chosen by risk assessment (e.g., consideration of the potential interactions with other variables).
- Any evidence of variability in raw materials (e.g., drug substance and/or excipients) that would have an impact on predictions made from DoE studies.
- Listing of the parameters that would be kept constant during the DoEs and their respective values, including comments on the impact of scale on these parameters.
- Type of experimental design used and a justification of its appropriateness, including the power of the design.
- Factors under study and their ranges can be presented in a tabular format. Submitters should indicate if the factors are expected to be scale-dependent.
- Reference to the type of analytical methods (e.g., HPLC, NIR) used for the evaluation of the data and their suitability for their intended use (e.g., specificity, detection limit).
- Results and statistical analysis of DoE data showing the statistical significance of the factors and their interactions, including predictions made from DoE studies relevant to scale and equipment differences.

CONTROL STRATEGY

ICH Q10 defines a control strategy as "a planned set of controls derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in process controls, finished product specifications and the associated methods and frequency of monitoring and control." A control strategy normally include input material controls, process controls and monitoring, design space around individual or multiple unit operations, and/or final product specifications used to ensure consistent quality [24, 25]. The finished drug products are tested for quality by assessing if they meet specifications. In addition, manufacturers are

usually expected to conduct extensive in process tests, such as blend uniformity or tablet hardness.

A QbD based control strategy for blending process is shown in **Figure 06**. Pharmaceutical quality is assured by understanding and controlling formulation and manufacturing variables to assure the quality of the finished product. The end product testing only confirms the quality of the product.

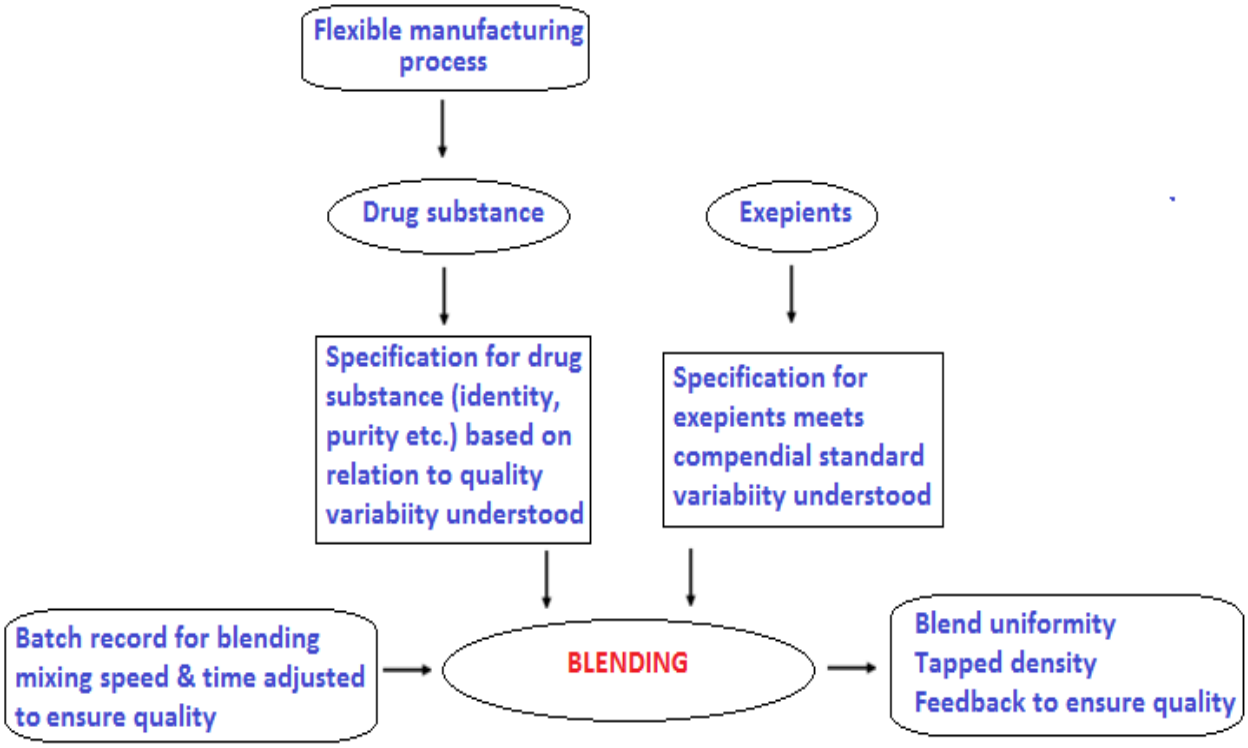

Fig. 6: Example of control strategy for QbD process

CHALLENGES

Though Quality by design is an essential part of the modern approach to pharmaceutical quality, but Lack of understanding regarding the pharmaceutical process is the cause and also the major limitation for QbD implementation. Pharmaceutical companies are traditionally tuned to care more about the end product, with little emphasis on the science-based understanding of the process involved. The majority of pharmaceutical companies feel that there is a need for a more easy guidance on how to actually implement QbD. Companies wanted clarification from FDA on QbD terminologies, acceptable methods, criteria to select and deselect critical quality attributes, standards by which to judge adequacy of controls, and criteria for analytical method substitution[25, 26]. 10 key challenges are the most problematic for QbD adoption. These challenges are evaluated by their relevancy against different drug types as well as different levels of adoption. The first four challenges occur within companies:

- Internal misalignment (Disconnect between cross functional areas, e.g., R&D and manufacturing or quality and regulatory)
- Lack of belief in business case i.e. there is a lot of uncertainty over timing of and investment requirements for QbD implementation.
- Lack of technology to execute (e.g., Difficulty managing data, limited understanding of Critical Quality Attribute (CQA) implications)
- Alignment with third parties (i.e., How to implement QbD with increasing reliance on suppliers and contract manufacturers?)

- The next six challenges are directly related to the regulatory authority:
- Inconsistency of treatment of QbD across regulatory authority
- Lack of tangible guidance for industry
- Regulators not prepared to handle QbD applications
- The way promised regulatory benefits are currently being shared does not inspire confidence
- Misalignment of international regulatory bodies
- Current interaction with companies is not conducive to QbD
- It is accepted that the challenges and concerns associated with the implementation of QbD can only be resolved if there is efficient communication between the industry and the regulatory bodies.

CONCLUSION

QbD is increasingly becoming an important and widely used technique in pharmaceutical product development. While QbD is most effective when it is employed at a product/process design level, it should also be accomplished in the manufacturing and quality assurance environments. Implementing QbD concept in product development provide quality medicines to patients, production improvements to Manufacturers with significantly reduced batch failures and drug regulatory bodies will have greater confidence in the robust quality of products. This approach allows the establishment of priorities and flexible boundaries in the process. As such QbD is becoming a promising scientific tool in quality assurance in pharmaceutical industry.

The changes in product and process can be managed better with QbD. Manufacturers can execute certain changes without filing prior approval supplements and can simply notify regulatory authority in annual reports. The economic and resource drain due to exhaustive validation requirements can significantly be minimized. The application of QbD principles can change the chemistry, manufacturing, and control regulatory process into a science and risk-based assessment.

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