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Quality Assurance

QbD: Key to Quality Pharmaceuticals

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Review Article

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Abstract: This article describes the concept of pharmaceutical Quality by Design (QbD) and how it can be used to ensure pharmaceutical quality. QbD is a significant part of the present-day approach to improving pharmaceutical quality. It can be described as a novel approach to development of any product which may increase efficiencies, offer regulatory relief and pliability, and also provide business advantages throughout the product lifecycle. In the present review, basics of QbD along with its regulatory needs are discussed. For the detailed explanation of how QbD ensures the drug product quality, several documents from ICH such as ICH Q8, i.e. Pharmaceutical development; ICH Q9, i.e. Quality Risk Management; ICH Q10, i.e. Pharmaceutical Quality Systems and FDA's Process Analytical Technology (PAT) were referred. By using QbD, formulation and manufacturing variables can be appropriately understood and controlled.

Keywords: Quality by design, Target product profile, and Critical quality attributes, control strategy, design space, Design of experiments.

INTRODUCTION

"Quality could be planned and most of the quality deficit arises in the way process is planned and developed" as said by Joseph Moses Juran defines QbD in the best way. QbD is a modern and a holistic approach toward drug development. Although this concept is new in the pharma industry, it is tried and tested and has been extensively applied [20]. Acc to ICH Q8 guideline, QbD is explained 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 [9]."

Advantages of QbD

- The scale-up, validation and commercialisation are made transparent, rational and predictable
- It is efficient and cost saving for any pharmaceutical industry.
- Potential compliance actions, costly penalties, and drug recalls are minimized or eliminated.
- Several opportunities for continual improvement are offered.
- A higher level of drug product quality is assured.
- The efficiency of pharmaceutical manufacturing processes is increased thereby reducing the manufacturing costs, and product rejects.
- Post-approval manufacturing changes and regulatory processes are streamlined.
- Continuous improvement is facilitated, and CMC supplement is reduced.
- The quality of CMC is enhanced and the CMC review time is reduced.
- Innovation for unmet medical needs is facilitated.
- More focused post-approval CGMP inspections
- Enhanced opportunities for first cycle approval.
- More efficient regulatory oversight is provided.

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Traditional vs. QbD approach

When compared to traditional, QbD is more advanced for pharmaceutical development. It can be shown by comparing various aspects which are used for developing a product. It is explained in the table below.

Through this table, we get to know that by applying QbD to existing product development, we can reduce the chances of failure by multiple folds and also improve the product quality [23].

Table-1: Comparing various aspects for traditional and QbD approach

Aspects	Traditional	QbD approach
Pharmaceutical Development	Empirical	Systematic, multivariate experiments
Manufacturing Process	Fixed	Adjustable within Design Space
Process Control	Offline analysis wide or slow response	PAT utilized for feedback and provide to Real- time
Product Specification	Based on batch data	Based on desired product performance
Control Strategy	Mainly by intermediate Product and end product testing	Risk- based, Controlled shifted upstream, real-time release
Lifecycle management	Post-approval Changes needed	Continual improvement enable within Design Space

ENABLERS OF QUALITY BY DESIGN

QbD has two primary enablers which help in its implementation and proper development of a pharmaceutical product. They are knowledge management and Quality Risk management. Knowledge management is well described under ICH Q 10, i.e. Pharmaceutical Quality Systems whereas ICH Q9 is the guideline for Quality Risk management. They both play an essential role in achieving product realization, establishing and maintaining control and continual improvement. A brief explanation of these two and their importance is well described in following sections [1].

ICH Q9 (Quality Risk Management)

QRM is the pivotal enabler for the developing and applying QbD. In the development stage, it helps in enabling resources to be explicitly focused on the critical areas that may affect the process and final product. It provides

It is a tool that offers an approach to identify, scientifically evaluate, and control the potential threat to quality. It also eases continual development in the product and process performance during the complete product lifecycle [3].

ICH Q10 (Knowledge Management)

Knowledge management for both products and processes is necessary. It must be managed through all stages of development and also through the commercialization of the product, including its discontinuation.

Examples of prior knowledge include the knowledge about drug substances and products which was obtained from early development work, of physicochemical and functional properties of materials and components used, from published scientific literature, and from experience of a manufacturer of related dosage forms and products etc [4].

REGULATORY ACTIVITIES

QbD activities within FDA

In 2005, USFDA made it compulsory for participating firms that they must submit their Chemistry manufacturing control (CMC) information which demonstrates QbD application when applying for New Drug Application. In 2006, Merck & Co.'s Januvia became the first product approved based upon such an application. In QbD, accurate understanding of the process is necessary for which a goal or objective is defined before starting the process. Like ICH, FDA also gave guidelines for Process Analytical Technology (PAT), the framework for Innovative Pharmaceutical Development Manufacturing and Quality Assurance, stating the importance of quality of pharmaceuticals. FDA views QbD as a "systematic approach to product and process design and development[11]."

In 2011, FDA released Process Validation Guidelines which states that the industries benefits from the knowledge gained, and improve continually throughout the process lifecycle by changing to ensure that root causes are corrected[1].

In a nutshell,

- By designing efficient manufacturing processes, product quality and performance can be assured.
- Specifications of both product and processes are based on the understanding of how process factors affect product performance.
- To ensure product quality and performance, risk-based regulatory approaches are developed.
- To accommodate the real-time scientific knowledge, regulatory policies and measures are modified.
- Quality assurance is a continuous process.

ICH Activities

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) was developed by Europe, Japan, US to bring together the regulatory authorities of these three nations. The underlying principles of QbD i.e.risk assessment, lifecycle approach, science and risk-based product development and method design are described in quality guidelines of ICH which are ICH Q8, i.e. Pharmaceutical development; ICH Q9, i.e. Quality Risk Mangement; ICH Q10, i.e. Pharmaceutical Quality Systems. Steering committee developed by ICH discusses the progress of its effort by meeting twice in a

year. It ensures that quality risk management and knowledge management are being used to make lifecycle changes that maintain product quality and process control[17].

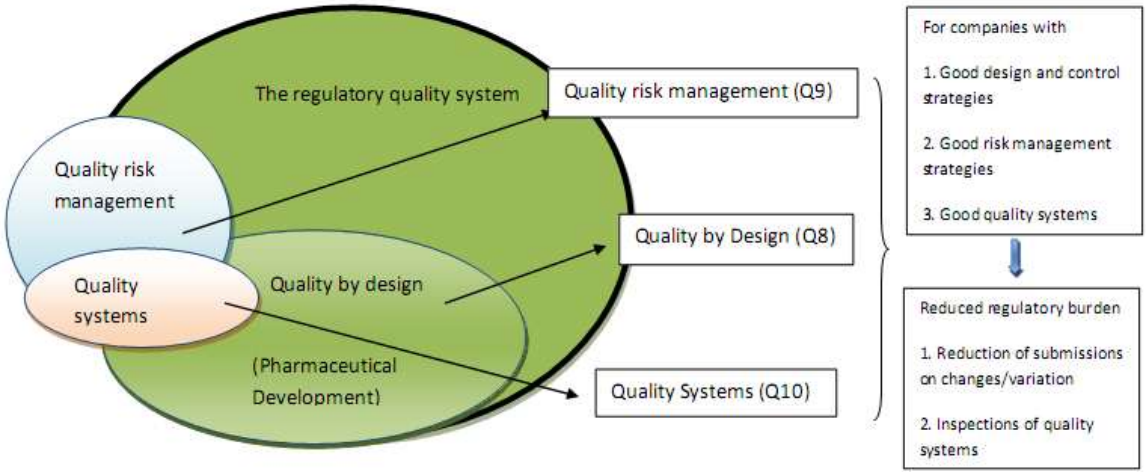

Fig-1: Vision of ICH for the future pharmaceutical quality system [23]

ELEMENTS OF QbD

ICH Q8 (R2)

Guidelines for pharmaceutical development, i.e. Q8 (R2) describes various elements of quality by design. When combined with enablers, they form the basis for the developmental approach to QbD. Figure 2 provides a pictorial representation of the typical elements of QbD [9].

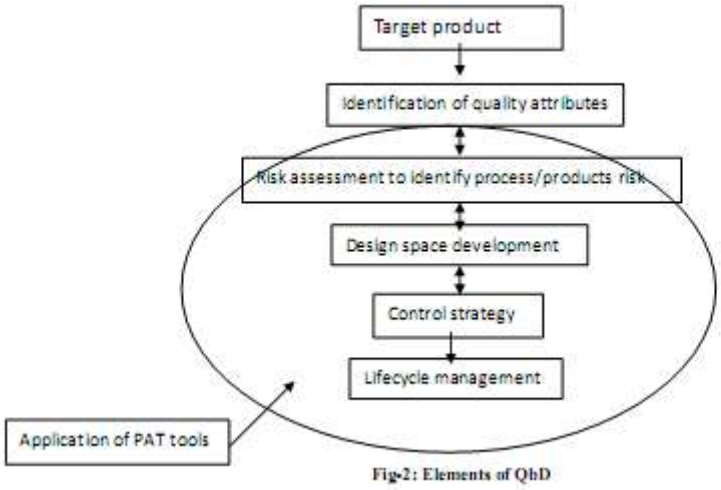

Fig-2: Elements of QbD

Following are the elements of QbD:

- Quality Target Product Profile
- Identify Critical Quality Attributes
- Risk Assessment
- Design Space
- Control Strategy
- Product Lifecycle and Continual Improvement

Quality Target Product Profile

The FDA has published a guidance defining the Target Product Profile (TPP), that focuses on the consumer (patient) and the desired product label. The QTPP is a subset of the TPP and is more oriented towards the chemistry, manufacturing and controls (CMC) aspects of development.

The quality target product profile forms the premise of style for the event of the merchandise. issues for the standard target product profile may include:

• Meant use in clinical setting, route of administration, dose type, delivery systems;
• dose strength(s);
• instrumentality closure system;
•therapeutic moiety unleash or delivery and attributes poignant pharmacokinetic characteristics (e.g., dissolution, mechanics performance) acceptable to the drug product dose type being developed;
• drug product quality criteria (e.g., sterility, purity, stability and drug release) acceptable for the meant marketed product.

Identification of Critical Quality Attributes

In pharmaceutical development, product and process design and development plays an important role. While designing a product and process, it is may be important to focus on the clinical performance, manufacturability, and global acceptability of the drug product. In the QbD paradigm, it is imperative that the manufacturing process is capable of accommodating typical variability in the inputs, resulting in a product that always meets the requirements of the QTPP.

Critical Quality Attributes (CQA)

A CQA is 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 the drug substance, excipients, intermediates (in-process materials) and drug product.

Quality Risk Assessment: Linking Material Attributes and Process Parameters to Drug Product CQAs

Risk assessment is a precious science-based method employed in quality risk management (see ICH Q9) which will aid in identifying material attributes and process parameters which have a potential effect on product CQAs. Risk assessment is often performed early in the pharmaceutical development process and can be repeated if extra information becomes available and more knowledge is obtained.

Critical Process Parameter (CPP)

A process parameter whose inconsistency has an impact on a critical quality attribute and therefore should be supervised or checked to ensure that the process produces the required quality

Critical Material Attributes (CMA)

A CMA is a physical, chemical, biological, or microbiological property or characteristic that ought to be within a suitable limit, range, or distribution to confirm the required drug substance, excipients or in process materials' quality [8].

Risk management methodology

- Tools for parameter screening: Examples are Ishikawa diagram, What if analysis, HAZOP (Hazard Operability) Analysis.
- Tools for risk ranking: Examples are Failure Mode and Effect Analysis (FMEA)/Failure Mode Effects and Criticality Analysis (FMECA), Pareto Analysis, Relative Ranking.
- Experimental tools for process understanding: Statistically designed experiments (DoE), Mechanistic models etc.

Design of experiment

The design of experiment (DOE) begins with 'Screening' of the process variables to decide which parameters are important for the result (excipients type, disintegration time, percentage etc.). Then comes 'Optimization' in which finest setting for the major variables are determined. In this step, use of 'mixture designs' are done in which mixture compositions are changed, and then they are explored for changes which may affect the properties of the mixture[16].

Use of DOE

DOE is used to determine the causes of variation in the response, the find conditions under which the optimal (maximum or minimum) response is achieved, to compare responses at different levels of controlled variables & to develop a model for predicting response.

Key steps for DOEs

- Obtaining good results from a DOE involves those seven steps.
- Set objective
- Select process variables
- Select an experimental design
- Execute the design
- Check that the data are consistent with the experimental assumptions.
- Analyze and interpret the results.

Design Space

In the design, the relationship can be described between the process inputs i.e. material attributes and process parameters, and the critical quality attributes.

Selection of Variables

The risk assessment and process development experiments may cause an understanding of the linkage and result of material attributes and process parameters on product quality attributes, and also help in finding the variables along with their ranges within which desired quality of the product can be achieved. These material attributes and process parameters are then chosen to be included in the design space. An explanation should be given in the application of the process parameters and material attributes which are considered for the design space, justification for including them and their effect on product quality. Sometimes providing the rationale for why some parameters were excluded is also helpful. Information gained from studies must be described in the submission.

Describing a Design Space in a Submission

A design space can be explained concerning ranges of process parameters and material attributes, or via more complex mathematical relationships. It can be described as a time-dependent function (e.g., pressure, temperature, etc.), or as a fusion of variables like elements of a multivariate model. If the design space is meant to cover multiple operation scales, scaling factors may also be considered. Analysis of past data may also

lead to the establishment of a design space. It is assumed that if one operates within the design space, it will result in a product with the defined quality, regardless of how a design space is developed.

Unit Operation Design Space(s)

The applicant can select to create a single design space for multiple operations or to develop separate design spaces for one or more unit operations. While an independent design space for each operation is easy to create, design space that covers the whole process can provide more pliability. For example, in case of a drug product which is subjected to degradation before lyophilisation, design space to control the degradation can be created for each unit operation or applied over all unit operations.

Relationship of Design Space to Scale and Equipment

When explaining a design space, the applicant must evaluate the type of functional flexibility required. It may be developed at any scale. The applicant must justify the pertinence of a design space established at small or pilot scale to the planned production scale and describe the prominent risks in the scale-up operation. If it is applicable for the multiple operational scales, it ought to be explained in terms of relevant scale-independent parameters. For example, if a product is described as a shear sensitive during mixing, the design space might include shear rate instead of agitation rate. Dimensionless models or numbers for scaling may be enclosed as a part of design space.

Design Space versus Proven Acceptable Ranges

A combination of proven acceptable ranges does not constitute a design space. However, proven acceptable ranges based on univariate experimentation can provide useful knowledge about the process.

Design Space and Edge of Failure

It can be used to estimate the edge of failure for material attributes or process parameters, exceeding which the desired quality attributes can't be met. Still, it is not essential parts of demonstrating a design space to determine the edge of failure or exhibit failure mode.

Control Strategy

A control strategy is intended to make sure that a product of desired quality will be produced consistently.

It may include, however not restricted to the following:

- A supervising program (e.g., full product testing at regular intervals) for validating multivariate prediction models;
- In-process or real-time release testing instead of end-product testing (e.g. control and measurement of CQAs during processing);
- Controls for unit operations that affect downstream processing or product quality (e.g., particle size distribution of the granulate on dissolution, the impact of drying on degradation);
- Specification(s) of products;
- Management of input material attributes (e.g. excipients, drug substance, and primary packaging materials) depending on an understanding of their effect on processability or product quality.

Product Lifecycle Management and Continual Improvement

Throughout the merchandise lifecycle, firms have opportunities to assess innovative approaches to boost product quality (see ICH Q10). Lifecycle approach varies from that of the traditional approach of method development.

According to USFDA, it contains continuous improvement of method performance, and the design space permits pliability for such development in the analytical method without which can be done without previous regulatory approval. Knowledge obtained from the data collected and risk assessment from DOE can be used as the storehouse of information to make even amendment whenever needed.

CONCLUSIONS

Quality by design is an essential part of the modern approach to pharmaceutical quality. This paper clarifies the use of QbD including:

- Emphasis on the importance of the Target Product Quality Profile in articulating a quantitative performance target for QbD.
- Identification of critical material attributes that offer a mechanistic link of the finished product quality to the manufacturing process.
- An explanation that critical process parameters are working parameters and must be fused with critical material attributes to outline the relation between unit operation outputs and inputs.
- A definition of non-critical, unclassified, and critical that provides a way to classify process parameters and in-process material attributes
- The role of the control strategy as the mechanism for incremental implementation of QbD elements into practice.
- An efficient path to a design space through the identification of non-interacting process variables and their exclusion from formal experimental designs.

ABBREVIATIONS

- QbD: Quality by Design
- ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
- PAT: Process Analytical Technique
- CMC: Chemistry Manufacturing and Controls
- cGMP: Current Good Manufacturing Practices

- QRM: Quality Risk Management
- FDA: Food and Drug Administration
- QTPP: Quality Target Product Profile
- CQA: Critical Quality Attributes
- CPP: Critical Process Parameters
- CMA: Critical Material Attributes
- DoE: Design of Experiments

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