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Review Article

Quality by Design- New approach to product development.

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ABSTRACT
Quality by design (QbD) is a new approach to product development that could increase product efficiencies, provide regulatory relief and flexibility, and offer important business benefits throughout the product life cycle. Quality by design (QbD) is a part of the modern advance to pharmaceutical quality. QbD is a quality in all pharmaceutical products. Under this concepts of be throughout design and growth of product. During design and development of a product in QbD, this need to desire product performance profile [Target product profile (TPP), Target Product Quality Profile (TPQP)] and identify critical quality attributed (CQA). It's also gives the comparison between product quality by end product testing and product quality by Quality by design. The application of quality by design (QbD) in pharmaceutical product development for the regulatory authorities and the pharmaceutical industry. International Conference on Harmonization and United State Food and Drug administration (USFDA) emphasized the principles and application of QbD in pharmaceutical development in their guidance for the industry. The plan of pharmaceutical development is to design a quality products and its manufacturing process always deliver the future performance of product. The base of Quality by Design is ICH Guidelines Q8 for pharmaceutical for development, Q9 quality risk management, Q10 for pharmaceutical quality systems. The main objectives of QbD is to the quality products, for the product and process characteristics important to desired performance must be resulting from a combination of prior knowledge and new estimation during the development of product. Quality by Design helps to reduce product variability and failures which help in achieving high quality pharmaceutical products.

KEYWORDS
Quality by design, Quality target product profile, Critical quality attributes, Design space, implementation of QbD, Quality risk management.

1. INTRODUCTION

1.1. Quality [1, 3]

In Quality by Design, Quality is the important word. Quality is critical to sale, cost control, productivity, risk management and compliance. So quality is "standard or suitability for intended use." This term include such as attributes as the identity, potency and purity.

1.2. Quality by Design

Quality by design (QbD) is an important and widely used technique in the pharmaceutical industry [1,4]. QbD was first described by Joseph M. Juran, and applies heavily, particularly in the automotive industry [1,2]. Quality by Design is defined as "a systematic approach to pharmaceutical development with predefined objectives". Quality by Design is a systematic approach to pharmaceutical product development and requires a thorough understanding of the critical factors affecting product's quality [5]. It demands an understanding of product and process controls. International Conference on harmonization (ICH) Q8 guideline was published in may 2006 for pharmaceutical product development, and has been complemented by the ICH Q9 on Quality risk Management and ICH Q10 for a Pharmaceutical Quality System.

Critical Quality Attribute (CQA) is a physical, chemical, biological, or microbiological property that should be within an appropriate limit to ensure the desired product quality [6,11]. A design space is determined at a lab scale and is scale and equipment dependent. This need to be appropriately justified when using as a commercial scale [12].

Quality by Design (QbD) include identifying and defining the target product profile (TPP), risk assessment, and identifying the Quality Control Attributes (CQA) of the product which must controlled to meet the quality of product[7]. It also includes developing a control strategy for the manufacturing process controls and further monitoring the process to ensure product quality[8,9].

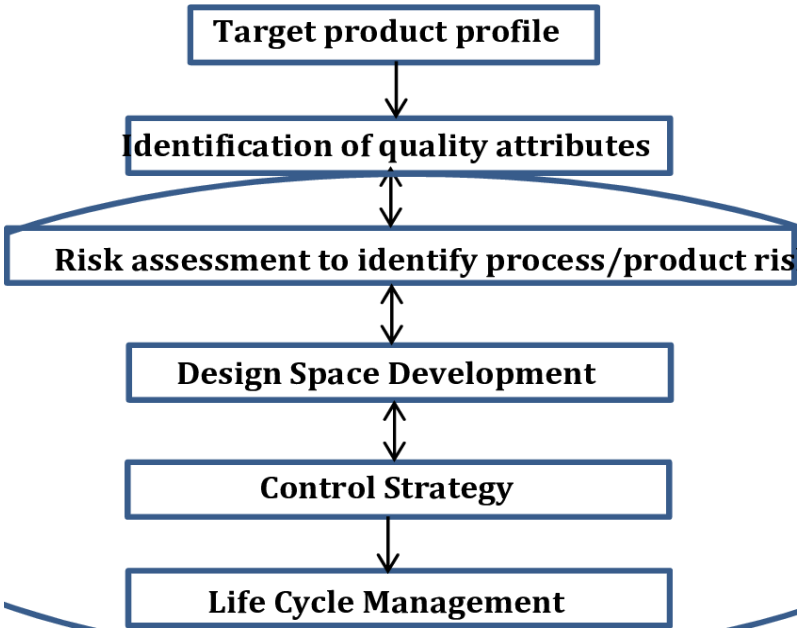

Fig. 1. Steps in Quality by Design.

1.3. Objectives of QbD

1. The main objectives of QbD is to the quality products, for the product and process characteristics important to desired performance must be resulting from a combination of prior knowledge and new estimation during the development of product.
2. From this knowledge and data process measurement and desired attributes may be constructed [28].
3. Ensures the combination of product and process knowledge gained during development.

1.4. Advantages of QbD

1. It provides a higher level of assurance of drug product quality.
2. Avoid regulatory compliance problems.
3. Increases manufacturing efficiency to reduce costs and the project rejections and waste.
4. It makes the scale-up, validation and commercialization transparent, rational and predictable.
5. It minimizes or eliminates potential compliance actions, costly penalties and drug recalls.
6. Reduce end-product testing
7. Eliminates batch failure
8. Allows for continuous improvement in products and manufacturing process.

1.5. Elements of QbD

1.5.1. Quality Target Product Profile (QTPP)

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. The drug profile or target product which ensure desired quality, safety and efficacy [9,13,29].

Target product profile should include,

a) Dosage form
b) Assay and Uniformity
c) Dosage strength
d) Purity/impurity
e) Dissolution
f) Stability

QTPP is widely used in development planning, clinical and commercial decision making, regulatory agency interactions and risk management. For example, tablet density or hardness

It may include as a specification for a process monitoring but may not be include in QTPP. Also, if particle size is critical to dissolution of a solid oral product, then the QTPP should include dissolution but not particle size [14,15].

Table 1. Quality Target Product profile (QTPP) Safety and Efficacy Requirements Critical Quality Attributes (CQA).

Tablet	**Characteristics**	**Translation into QTPP**
Dose	30 mg	Identity, Assay and Uniformity

Subjective Properties	No off-taste, uniform color and suitable of global market	Appearance, elegance, size, unit integrity
Patient Stability- Chemical purity	Impurities below ICH	Acceptable hydrolysis levels at release
Patient Efficacy- Particle Size Distribution (PSD)	PSD does not impact bio performance	Acceptable API PSD Dissolution
Chemical and Drug product Stability – 2 yr shelf life	Degradates below ICH and no change in bio performance over expiry period	Hydrolysis degradation and dissolution changes controlled by packaging

A CQA is defined as "a physical, chemical, biological or microbiological property or characteristic that should be within a appropriate limit, range or distribution to ensure the desired product quality"[16].

CQA's are subset of QTPP that has an altered by the change in formulation or process variables. Thus QTPP guides the selection of CQA specification range.

Example of more than 80% dissolution within 30 minutes and disintegration time of the tablet within 15 minutes are CQA's for above mentioned QTPP of IR tablet dosage form of a drug X.

CQAs are generally associated with raw materials (drug substance, excipients), intermediates (in-process material) and drug product. Drug product CQAs are the properties that are important for product performance, that is, the desired quality, safety, and efficacy.

Table 2. Typical CQAs for drug substance and drug products.

For Drug Substance (Chemical)	**For Drug product (Tablet)**
Appearance	Appearance
Particle size	Identification
Morphic form	Hardness
Water content	Uniformity of dosage
Residual solvent	Physical form
Organic impurities	Dissolution
Heavy metal	Degradation products
Inorganic impurities	Water content
Assay, Reduce on ignition	Assay

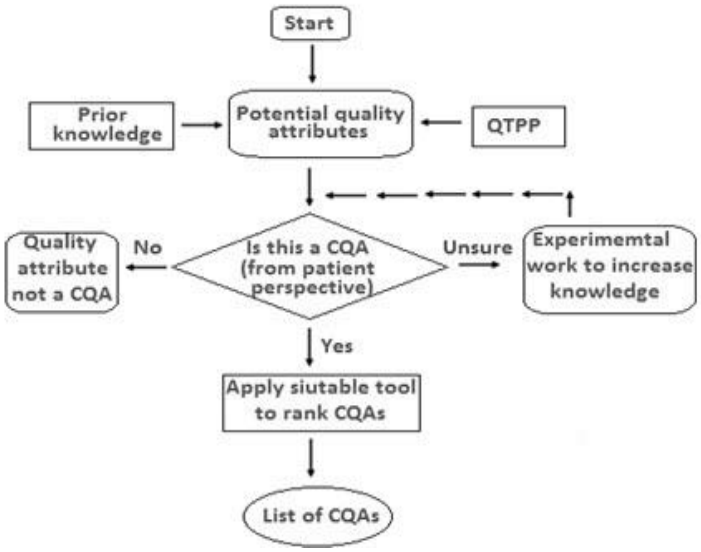

Fig. 2. Critical Quality Attributes

1.6. Quality Risk Assessment Method (QRM)

Risk assessment is the linkage between material attributes and process parameters. It is performed during the product cycle. To identify the critical material attributes and critical process parameters.

The FDA defined a Risk Management as, a strategic safety program to decrease product risk by using one or more intervention or tools. It is systematic process for the assessment, control, communication and review of risk to the drug product quality across the product lifecycle [17].

1.6.1. Material Attributes

A material attributes can be an excipients raw material, drug substance, reagent, solvent, packaging and labeling materials. A material attributes can be quantified and typically fixed but sometimes can be changed during further processing [10].

E.g. Impurity profile, specific volume, porosity, sterility.

1.6.2. Process Parameter

Process parameter variability has an impact on a critical quality attribute and therefore should be controlled to ensure the process produce the desired quality. (ICHQ8) process parameters can be measured and controlled [10, 30].

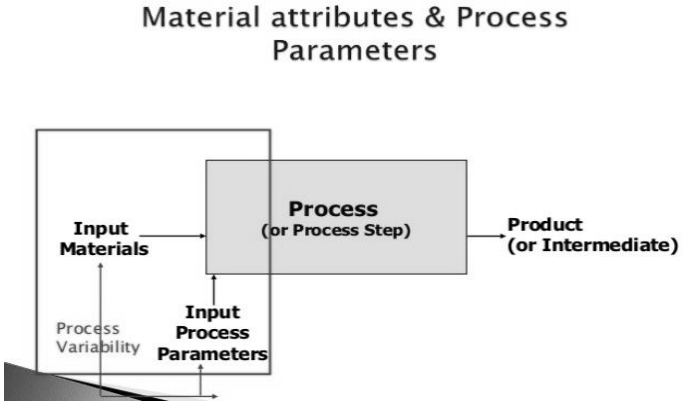

Fig. 3. Material attributes and Process Parameters.

1.6.3. Quality Risk Assessment

1. It is systematic process for the assessment, control, communication and review of quality risks.
2. The evaluation of the risk to quality should be based on scientific knowledge and it provides safety to the patients.
3. It should be Applies over the product lifecycle, development, manufacturing and distribution.

There are various method for determination of risk are as follows:

1) Failure mode effects analysis (FMAL)
2) Fault tree analysis (FTA)
3) Hazard analysis and critical control point (HACCP)

1.7. The ICH Q9 guidelines

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

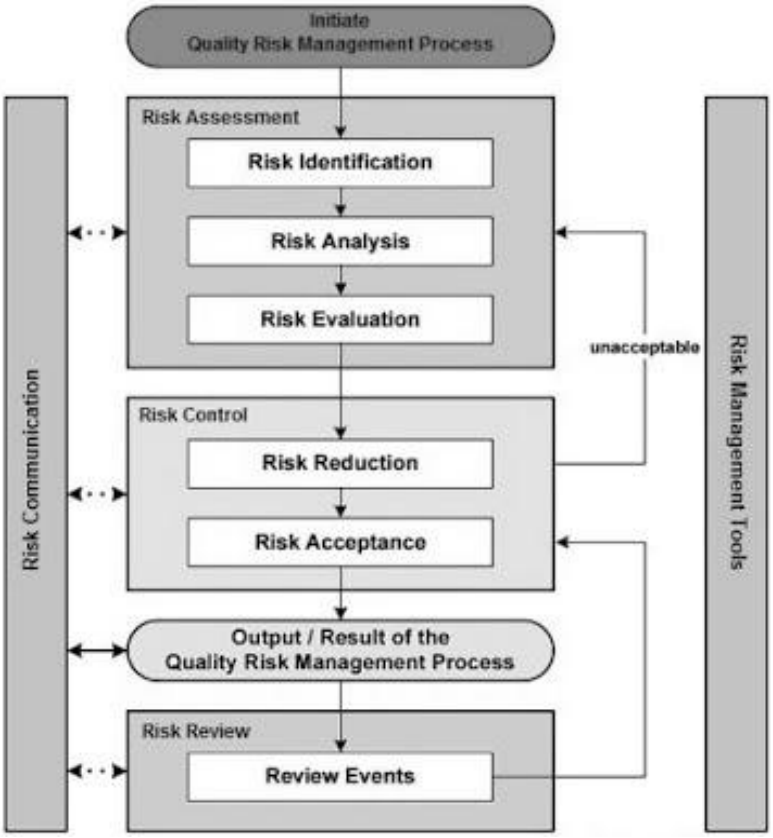

Fig. 4. Quality Risk Management Process.

1.9. Design Space [18]

A design space is defined as, "Multidimensional combination and interaction of input variables (e.g. material attributes and process parameters) that have been demonstrated to provide assurance of quality".

Design space is proposed by the applicant i.e. manufacturer and subject to regulatory assessment and approval. "Design Space" developed at lab or pilot scale can be proposed for commercial scale, but needs to be verified at production scale for scale dependant parameters.

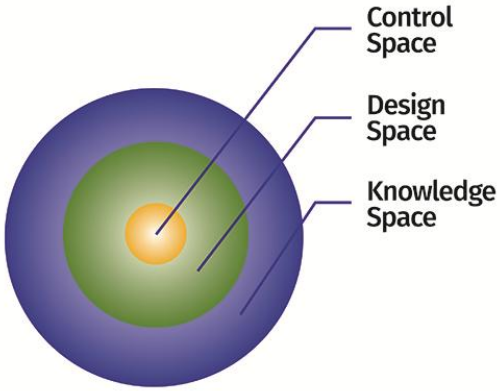

Fig. 5. Design Space.

Defining design space is optional to the manufacturer. But it assists to better understanding and a good control on system. Generally a factorial design is used as a design experiments and establishes design space.

1.10. Advantages

1. In the absence of interaction factorial design has maximum efficiency in estimating main factor that have impact on CQAs.
2. If interaction exists it is useful to identify the extent of interaction.
3. The factor effects is measured over varying levels; the conclusion drown applies to wide range of data.
4. It can be estimated all effects and interactions are independent of each other.

1.11. Control Strategy

ICH Q10 defined a control strategy as a "planned set of controls derived from current derived from current product and process understanding that assures process performance and product quality. The control can include that of the parameters and attributes related to drug substance and drug product material and components, facilities and equipment operating conditions, in process control, finished product specification 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 final product specification used to ensure that the consistent quality [19,20].

Control Strategy may include:[16, 21,22]

- Control of input material attributes (e.g., Drug substance, excipients and primary packaging materials) based on an understanding of their impact on process-ability or product quality.
- Product specification
- Procedural controls
- Facility controls, such as utilities, environmental system and operating conditions.
- Control for unit operations that have an impact on downstream or end-product quality (e.g. the impact of drying on degradation, particle size distribution of the granulate on dissolution)
- A monitoring Program for verifying multivariate prediction models.

The control strategy should establish the necessary to control based on patient requirement to be applied throughout the whole product lifecycle from product and process design through to final product, including.

Elements of a Control Strategy [23]:

- Procedural controls
- In-process controls
- Batch release testing
- Process monitoring
- Characterization testing
- Comparability testing
- Constancy testing

The control strategy in QbD standard is established via risk assessment that takes in to account the critically of the CQAs.

A QbD based control strategy for blending process is shown in fig. pharmaceutical quality is assured by understanding and controlling formulation and manufacturing variables to assure that the quality of the finished product. The end product testing only confirms the quality of the product [24].

According to this strategy the parameter to be controlled are ranked as high risk in the initial risk assessment. Based on during formulation development. Then the robustness of manufacturing process is confirmed by deliberately varying the process / formulation variables with in control space by conducting the experiments according to the appropriate DOE.

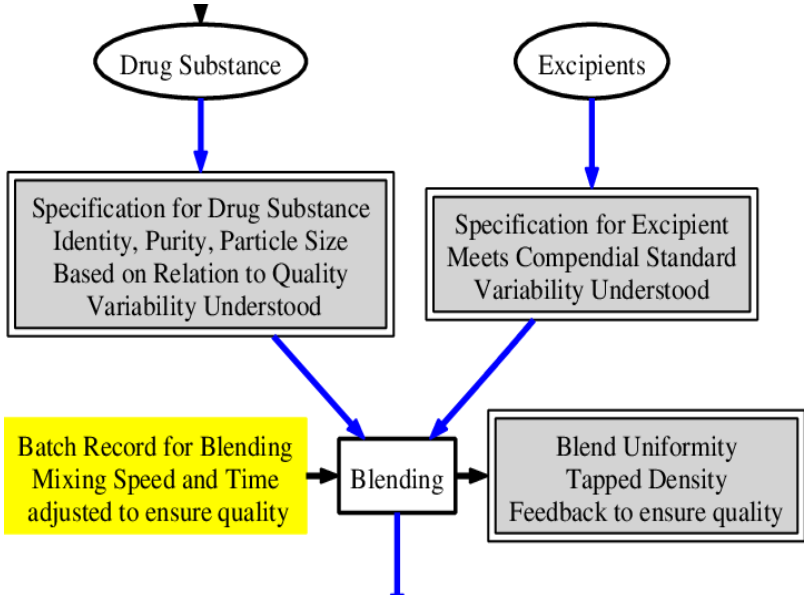

Fig. 6. Example of control strategy for QbD process.

1.12. Implementation of Quality by Design (QbD)

The principle of risk management- Implementation of quality by design is an essential part of pharmaceutical quality system. Implementation of QBD into ANDAs (Abbreviated New Drug applications) by manufacturers of generic products.

QBD is defined as "a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding based on science and quality risk management" [25, 26].

1. Risk assessment

Risk assessment is a processed used to identify and rank the parameters with potential to have an impact an product quality. Risk assessment consists of the identification of hazards and the analysis and evaluation of risk associated with exposure to those hazards.

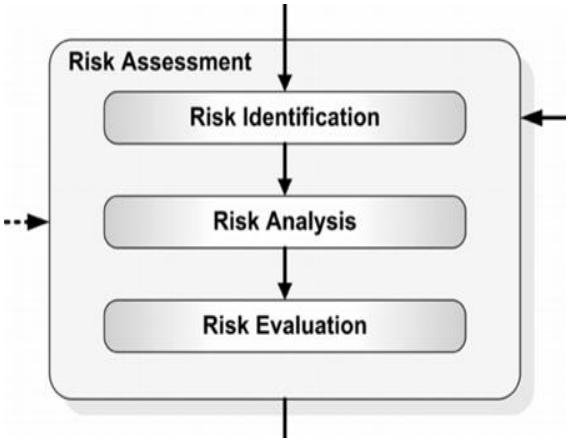

Fig. 7. Implementation of QBD.

2. Risk identification

It is based on the information available- Historical or through experience; hazards are identified.

3. Risk analysis

It is qualitative as well as quantitative process of estimation of probability of the risk associated with the identified hazards.

4. Risk evaluation

For effective risk evaluation robustness of data is important. Risk is expressed quantitatively or qualitatively as 'high', 'medium' or 'low'.

Table 3. Steps of initial risk assessment.

Step 1	**Step 2**	**Step 3**
Identify drug product CQA's	For each process step, identify intermediate CQA's that impact drug product CQA's.	Identify material attributes and process parameters that may impact the intermediate CQA's of the process step.

1.13. Challenges to Implement QBD[27]

1. Resistance to personnel to change.
2. Putting new concept.
3. Diversity of products.
4. Different regulatory processes (NDA, ANDA, BLA)
5. QBD increases the development cost significantly.

2. CONCLUSION

QbD is an important and widely used technique in pharmaceutical product development. While QbD is most effective when it is employed at product/process design level, it should also be accomplished in the manufacturing and quality assurance environment. The role of control strategy as the mechanism for completion of QbD element into practice. It is an efficient path to the design space through the identification of non interacting process variables. Implementing QbD concept in product development provide quality medicines to patients, production improvement to manufacturers with significantly reduced batch failures and drug regulatory bodies will have greater confidence in the robust quality of products. Quality by Design also having wide scope in biotechnological products such as vaccines, enzymes, monoclonal antibody etc not only in dosage forms. QbD acts as regulatory shifts, which facilitate manufacturing design and product approvals for vaccines and other products.

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