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A Review Article On Quality By Design

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Abstract
Pharmaceutical has vast areas of formulation and development which design different formulations that uses for different disease conditions and its treatment. Each product develop in the pharmaceutical has to pass the standard at prescribed in the monographs. QbD play an important role in drug product development that is very important because it ensure the stability, safety and quality of the product. The product quality should be best so that it as per the patient compliance. QbD ensure all the safety procedure in the industries that make the stable and good quality and validate the procedure. It also helps in the design of product and its procedures. It controls all the manufacturing process and understanding that develop the best quality product. It modern approach in the pharmaceuticals which aim to develop and design a quality product using its manufacturing process that intended to deliver constantly and shows good performance.
Keywords: Disease condition, Design, Monographs, Pharmaceuticals, Quality by Design

1.0. Introduction

Quality by Design plays a vital role in the holistic approach in the development of different dosage forms that ensure the quality of the pharmaceuticals. This approach helps to increase the efficiencies, flexibility and provide the regulatory relief to the drug development that offers the business benefits to the product throughout the life cycle. This concept should be embraced by the pharmaceuticals industries because of improving the robustness of the manufacturing process and facilities that help in the continuous improvement of the shape and size of the product that enhance the quality and productivity. Before the introduction of this concept, it is mediatory to accept that quality of the product should be designed and built during the manufacturing process.[1]

QbD fundamentally meant that building a quality product not testing it. This is a good business & science project because of complete product and process understanding. The comprision before without this approach, QbD posses the greater opportunities for developing and designing the

efficient and flexible system that increased the efficiency of product, reduce the cost, minimum chances of project rejections and less waste product will produced. This approach solves all the problems that were related with the quality in the pharmaceuticals product as the poor designed, safety, efficacy and quality. Thus due to which its clear that by analyzing the product the quality could not be improved. It ensured the consistent incorporated risk management and information.[2]

"Quality by Design" is a method of conveying a good scientific understanding of the essential process steps & aspects that aid in product quality, design, and control testing on the basis of scientific limits during development stage, using knowledge gained from the product's life cycle to work on continuous environmental improvement. QbD is a term used to describe the pharmaceutical development process for the formulation development and manufacturing process in order to maintain the product quality standards.[3]

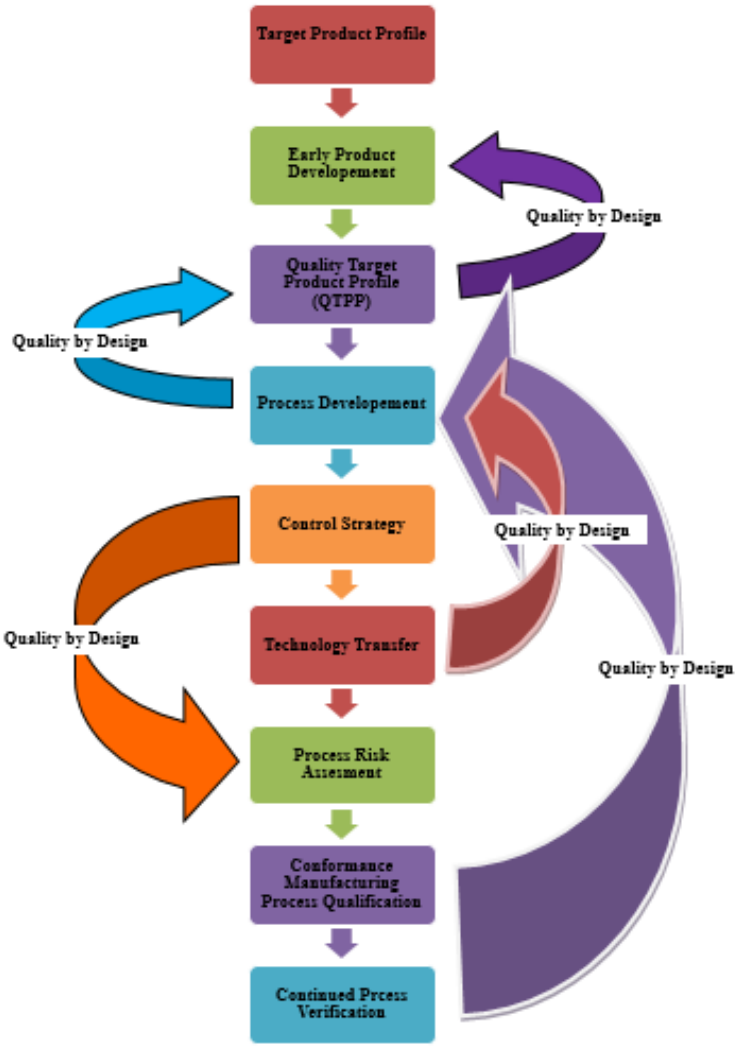
1.1. Continuous Improvement of Hallmark of QbD

Figure (i) Graphical representations of QbD process

1.2. Significance

• The QbD enhance the identifying ability of the root cause that fails the manufacturing process, manufacturing environment as to give the development activities, efficiency of manufacturing was to increased, it also have an objective to enhance the root cause, post approval change management to provide return of investment by of batches.[4]

• Its increase the development capacity, speed and design of formulation and transfer the resource to the upstream protective mode from the downstream corrective mode.



Sr. No.	Aspects	Before QbD	After QbD
1.	Pharmaceutical Development	Empirical	Systematic and multivariate experiments
2.	Process Control	In the process testing, manual analysis wide and reduced response	PAT is used for the feedback & forwarding of feed at real time
3.	Manufacturing Process	Fixed	Adjustable with the design space
4.	Control Strategy	The intermediate and final product was tested	Risk based parameters, real time release
5.	Life Cycle Management	Reactive to time problems and out of specifications	Continual improvement
6.	Product Specifications	For the quality control	Overall for the control strategy and based on the products

DESIGN

The product designed in different manner to acquire the patient compliance and requirement performance that consistently meet the quality product attribute, process parameters and starting raw materials on the quality product is understood; process variability of the critical sources can

be identified and controlled. The process was previously reviewed and adjusted to ensure a constant level of quality throughout time.[5]

As per the **ICH Q8 (R1)** According to the **FDA PAT Guideline,** the system for design, analyze and controlling the manufacturing through timely measurement of critical quality and performance the new in-process materials and processes with a goal that ensure the safety of the final product.[6]

BENEFITS OF QUALITY BY DESIGN

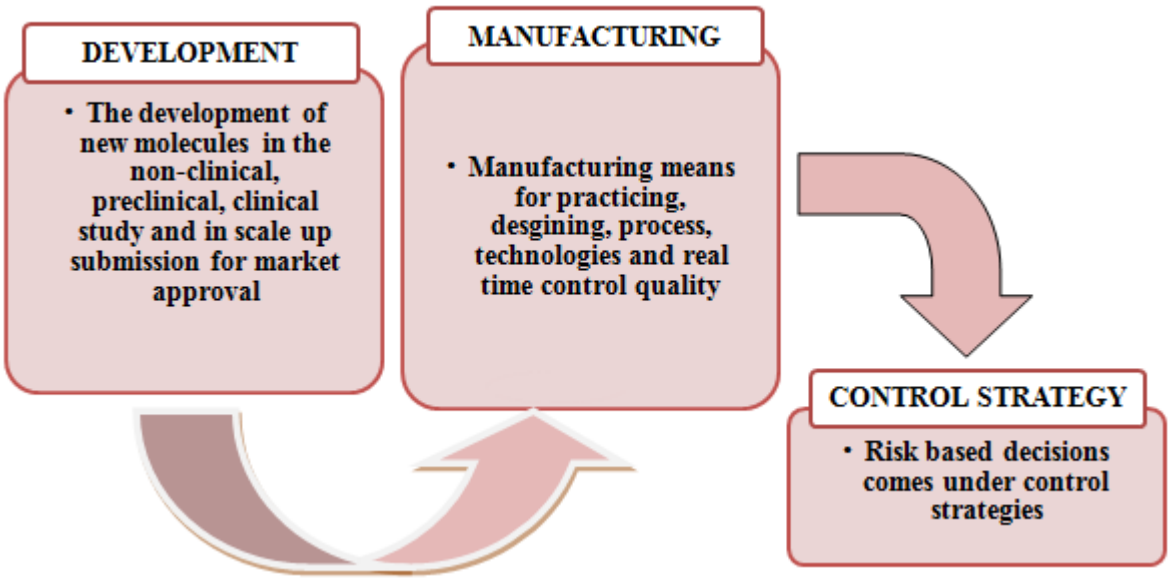
Benefits for industries [7]

- QbD focused on the collaboration between the research and manufacturing.
- It is advance process of understanding for the efficiency and effectiveness.
- It ensures the better design with fewer problems.
- It reduces the number of manufacturing supplements.
- All for new technology implantations.
- Reduce the difficulties during review of reduced deficiencies.
- Provide the continuous improvements.
- Provides the level of assurance of the product quality.
- Having less validation burdens.
- It avoids the problems that caused in the regulatory compliance.
- It also helps in minimizing the deviations and avoids costly investigation as well.
- Help in empowering the technical staff.

Benefits for FDA [8]

- Help in enhancing the scientific based review.
- Also provides the good consistency.
- Helps in the addresses the higher risks.
- Reduce the post approval regulatory submissions.
- Improves the information in regulatory submission.
- Provides the flexibilities in decision making.

STEPS INVOLVED IN QUALITY BY DESIGN [9]



ELEMENTS OF PHARMACEUTICAL QUALITY BY DESIGN

An applicant approaches the QbD for identifying the characteristic of the product development to critical quality on the behalf of patient compliance and converts them into the drug product critical quality attributes (CQAs), this help in developing the good relationships between the formulation, manufacturing process and CQAs for the delivery of good quality products to the patient.[10]

QbD has following elements which are discussed below –

- A QTPP is used in identifying the different CQAs of the pharmaceutical products.
- It helps in the product designing that includes the identification of CMAs.
- Product design consists of identification of the critical process parameters (CPPs) and help in the linking of scale up principle with CMAs and CPPs with the CQAs.[11]
- The control strategies involved in the specification of all the APIs and excipients that are used in the drug product that help in the controlling all the process and steps that involved in the manufacturing process.[12]
- It increased the capability of the process and continues the improvement.

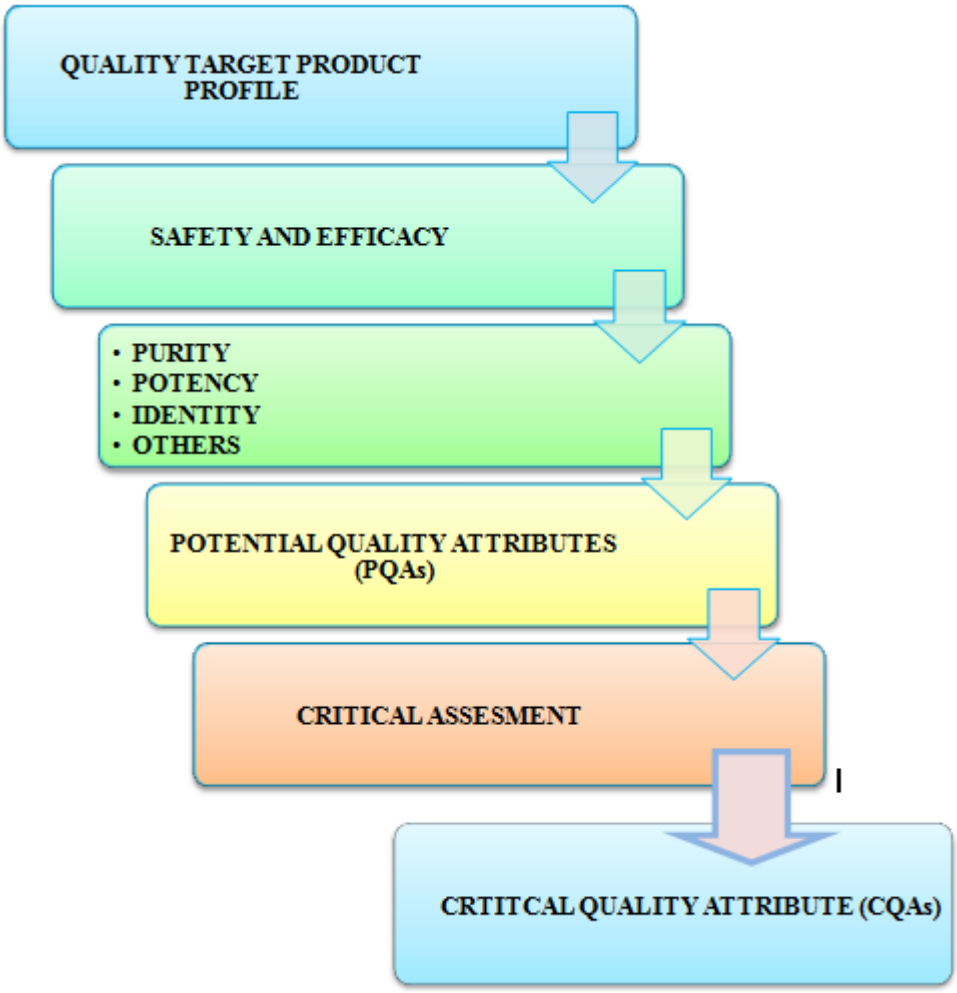
Quality Target Product Profile (QTPP) [13]

QTPP is the tool that is applied for the development of the strategies for the product development. The term explain itself clearly that **planning with the end in mind** which is the natural extension for the quality product.

According to the FDA, "the TPP provide the information about the drug development program and gives the accurate statement to the drug at the time of development. This was developed according to key section in labelling and development activities of the drug for specific intended concept to inclusion in drug labelling." [14]

QTPP is a prospective summary of the drug product that consist the quality characteristic that ideally achieved to ensure the desired quality of the product in the account of safety and efficacy of the product. In new drug development the QTPP evolve and refined the product as development process progresses. It is a quantitative and qualitative description of the design goals strategies prior to the knowledge and process experience or availability of equipment and facilities can affect the QTPP.[15] It involve in identification of different aspects of the critical quality attributes that include the purity, potency, pharmacokinetic profile, shelf life and the sensory properties of the formulated drug products. Design of the developed drug product based on the QTPP form.

- Dosage strength
- Dosage forms
- Route of administrations
- Container and closure system
- Pharmacokinetics
- Drug product quality criteria



QTPP that identifies the CQAs of the drug products [16]

QTPP deals with the quality characteristic of the pharmaceutical product that used to ensure the achievement of desired quality, safety and efficacy of the product. In order to develop the effective and safe product, here are the following parameters of QTPP that include –

- Intended to use in different areas such as clinical studies, route of administration, dosage form and delivery systems.[17]
- Strength of the dose
- Container and closure system
- The pharmacokinetic characteristics and aerodynamic characters of the dosage forms also affected by the change in the rate of dissolution of the drug moiety.
- The drug product quality criteria are appropriate for the intended marketed products.

The next step in the product development is the identification of the CQAs which conclude the quality attribute of the product that includes physical properties such as shape, colour, odour, score configuration, friability, degradation products, drug release or dissolution studies, assay, residual solvents, content uniformity, moisture content and microbial limits.[18]

Critical Quality Attributes (CQAs) [19, 20]

According to **ICH Q8 (R2) –** It is the appropriate range or limit or distribution of the physical, chemical, biological and microbiological characteristic or properties to ensure the quality of desired products. It usually the combined with API, excipients, in-process materials and the drug

products for example the solid oral dosage form are typically that aspects which affect the purity, release, strength and stability of the drug product whereas the sterility and clarity of the parenteral products as well. It also includes other properties like bulk density and particle size distribution that also affect the drug product quality.[20]

ICH Q9 stated the potential drug substance that used in CQA that guides the process of formulation and development. The exclusion and inclusion cab be performed for the known drug samples that increase the method of process used for preparation and development enlisted in the list of potential CQAs.[21]

Using quality risk management, the pharma product may be prioritised using the list of possible CQAs for the evaluation that will come after. The appropriate CQAs can access the extent for identifying the iterative process of quality risk management and experimentation through which the variation might have an influence on the quality of the drug product. A good quality attributes management system and appropriates formulation process; design and development are used to achieve all target attributes using these target elements.[22]

There certain point on which the CQAs depends mostly are discussed below –

- It depends upon the capability analytical methodology.
- This method should be used to determine the degree of variability of the products.
- The variability of the analytical methods directly depends upon the inherent variability of the products.[23]
- Instruments, operators and samples are the quantitative discernment between the different source of variability.
- Product attribute is the most important function of the formulation process and its parameters that used to studied in the design of experiments (DOE).[24]

Product Design and Understanding [25]

From the decades, the main objective of the QbD was to focus on the process design, understanding and controlling the quality as they are discussed in the ICH Q8 (R2). These points are the most important aspects of the QbD that helps in order to design the product which meets as per the desired criteria that fulfil the patient needs through the clinical studies and maintains the optimized therapeutic activity throughout its shelf life that was determined by the stability studies.[26] The main objective of the product design was to develop and formulate the optimized product that delivers the desired QTPP over the shelf life of the product. Product design has the key elements which are discussed below –

- Characterization of the drug using the biological, physical and chemical parameters.
- Selection and identifications of the excipients having different grade and types.
- Interactions studies between the drug product and excipients.
- Identifications and optimization of the CMAs of drug and excipients.

A typical pharmaceutical manufacturing process consists of a number of unit tasks that interact to produce the required product quality. To complete unit operations, batch or continuous production techniques might be employed. Mixing, milling, granulating, drying, compressing, and coating are a few examples of discrete unit processes that include physical or chemical changes. A process is often considered to be well-understood when all important sources of variability have been identified and explained, variability has been controlled by the process, and product quality attributes can be accurately and reliably predicted.[27]

Process parameters are factors that affect a process step or unit operation, such as the input operating parameters (such as speed and flow rate) or process state variables (such as

temperature and pressure).[28] Establishing process understanding involves taking the following steps, which are quite similar to those for establishing product understanding:

- The performance of the process should be affected by all known process parameters, therefore identify them all.
- Determine possibly high-risk parameters using risk assessment and scientific knowledge.
- Establish limits or values for these potentially hazardous variables.
- Develop and execute tests, integrating DoE as necessary.
- Assess the scalability of the experimental data and use first-principles models to estimate the significance of a process parameter. Connect CMAs and CPPs to CQAs wherever possible.[29]
- Develop a plan for keeping everything in check. For important parameters, define acceptable ranges. The range examined for parameters that are not crucial is the acceptable range. When more than one process parameter or material feature is involved, these declared allowed ranges are known as the "process design space."[30]

Critical Material Attributes (CMA) [31]

- Identification of important medicinal product quality attributes It's crucial to analyse the relationship between drug substances and drug products.
- The drug substance's intended quality was determined by taking into account its use in drug products as well as knowledge of its physiochemical, biological, and microbiological properties and characteristics that could influence the development of the drug product, such as the drug substance's solubility, which influences the dosage form choice.[32]
- The rationale for selecting the excipients' kind, grades, and amounts. Understanding which material attributes contribute the most to the excipient's functioning is critical to success.
- Critical quality aspects such as solubility resolution rate, chemical and physical stability, and manufacturability will be influenced by the choice of the correct salt solid form particle size, shape, and degree of aggregation (bonding index flow filterability).[33]

Critical Process Parameters (CPP) [34, 35, 36]

A significant process parameter, according to the ICHQ 8(R2), is variability, which has an influence on a critical quality characteristic and should be monitored or controlled to guarantee the process achieved the appropriate quality. It is in charge of ensuring that the CQAs are met, as well as identifying possible CPPS through risk assessment.[34]

Categories of Parameters [35]

- **Unclassified parameters** are the unknown criticalities. In this parameter there is need of the additional data that used to classify the unclassified parameters that are critical or non-critical.

- **Critical parameters** is critical at the time when the change in the product that cause failure to achieve the QTPP.

- **Non-critical parameters** observed in the potential of the operating space and no any change caused do to interaction that don't fails the QTPP and established the suitable range.

When CPPs are altered with regular operation range, they have a direct and considerable impact on CQAs. The type of equipment and its settings, as well as the working circumstances of the equipment and the surrounding environment, such as moisture temperature, should all be taken into account. Process capacity should be investigated to demonstrate a process's repeatability and

consistency. A statistical evaluation of the inherent process variability of a certain attribute is called process capacity. The most often used formula for process capability is six sigma. A given attribute's tolerance value is divided by its process capability to get the process capability index.[36]

ICHQ10 specifies that the condition of control must be maintained. A mechanism for assessing the effectiveness and quality of processes should be developed and put into place by pharmaceutical companies. To create a control plan, the process performance and quality monitoring system should incorporate quality risk management.[37]

Six Sigma & QbD [38, 39, 40]

Motorola coined the phrase Six Sigma in the 1980s, and it refers to the use of a component-based technique to reduce variability in production and optimise processes. Six sigma has focused on continuous improvement of an existing process, using the DMAIC technique (D-Define, M-Measure, A Analyze, I-Improve, C-Control). In the pharmaceutical sector, technologies such as Design of Experiments (DoE) and Control Charts are employed at various phases throughout the product lifecycle. Early Six Sigma practitioners developed an extra set of tools and practises known as Design for Six Sigma as a result of their recognition of the costs associated with bad product design (DFSS).[38]

PMADV (D-Define, M-Measure, A-Analyze) is the approach used by DFSS. D-Design, V Verify is used to design new processes and is also used when there is no process or when an existing process has been developed using DMAIC but still does not meet the acceptable level.

DFSS also provides the tools and a systematic method for efficiently generating new processes, reducing the work, time, and costs associated with designing and eventually manufacturing the new product on a continuous basis. The primary assumption of DFSS is that in order to successfully develop the requisite goals, it is necessary to first understand the process and product, in order to identify and manage crucial material and process factors.[39]

For instance, QbD is a methodical approach to development that emphasises product and process understanding, process control built on solid science, and risk management in the pharmaceutical industry. QbD starts with specified goals. The DFSS technique is well-suited to the QbD framework of generating reliable products with thorough process knowledge.[40]

The DFSS and QbD share a philosophy based on the idea that applying systematic and structured aspects to product development will increase the amount of process knowledge gained by the

development team, allowing them to make better decisions and increasing the likelihood of developing a quality product that will perform as intended.[41]

Table.1. Correlation between DFSS & QbD [42]

DFSS	QbD
Define – Purpose of project and requirements of costumers	**QTPP** – To define the purpose of project and requirements of costumers
Measure – Agree in customer specifications to fulfil the needs	**CQAs** – Agree in customer specifications to fulfil the needs
Analyze – Processes, products, methods to meet the specifications	**Materials Attributes** – Processes, products and methods to meet specifications
Design – Processes, products and methods to meet specifications	**Design Space** – Processes, products and methods to meet specifications
Verify – Processes, products and methods to meet specifications	**Control Strategy** – Processes, products and methods to meet specifications

Control Strategy [43]

Control strategy defined as the set of plan of controls that are derived from the current product and understanding process that assure the performance of the process and good quality product. It requires ensuring that the materials and process are within the limit range that also help in avoiding the defect and maintains the desired quality. It is the quality by design process which is established by assessment of the risk that takes in the consideration of CQAs and capability of process. It includes different elements that help in ensuring the quality of the product such as input material, process controls and monitoring, design space to final product specification.

Here are the different elements of the control strategies that used in the development of the quality product are as follow –

- Procedural Control
- In-process Controls
- Batch Release Testing
- Process Monitoring
- Comparability Testing
- Constancy Testing

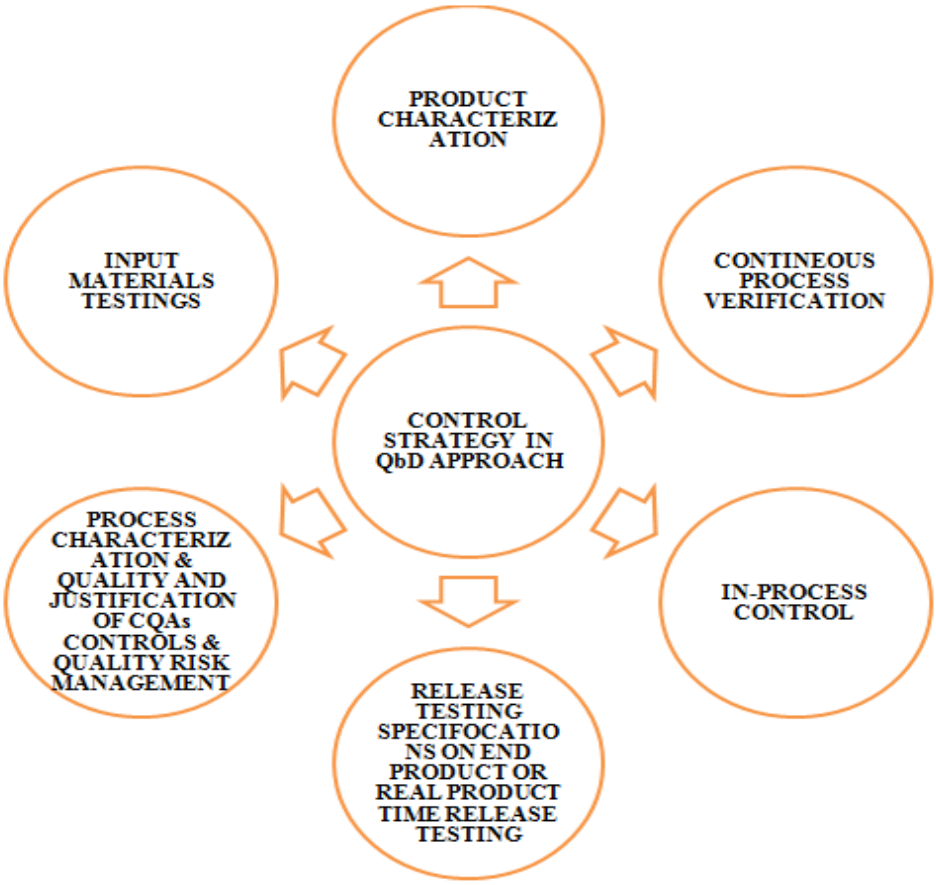


Figure.1. Representation of some examples of Control Strategy in advancement approach of the development (QBd) [44]

Product Life Cycle & Continuous Improvement [45, 46]

Process life cycle can increase product quality. Companies can examine current approaches to increase product quality, and process performance has been reviewed to ensure quality consistency. Periodic maintenance can be accomplished using the company's own internal quality system. The goal of a contemporary quality system is to prove efficiency by streamlining a process and minimising wasted efforts in manufacturing. QBD focuses on product quality as well as continual process improvement and variability reduction. The Quality System procedure is the backbone of continual improvement. It aids in the "identification and implementation of specific product quality improvements, process improvements, and variability improvements, therefore boosting the capacity to consistently meet quality requirements."

Drug substance and Excipients [47, 48, 49]

Testing is used to keep an eye on the quality of raw materials, such as those used to make medications and excipients. If they satisfy further criteria like USP for drug substance or excipients, as well as manufacturer-planned and FDA-approved parameters, they can be used in the creation of the product. The method of producing drug substances is also carefully inspected because it's not obvious if the standards alone will be sufficient to ensure quality. QbD examines the qualities that are essential to patient satisfaction, transforms them into qualities the medication product ought to possess, and identifies the significant process variables that may be changed to reliably produce a therapeutic product with desired properties. This is done by

establishing the relationship between product features and formulation and manufacturing process factors (such as excipient and medication component quality and process parameters).

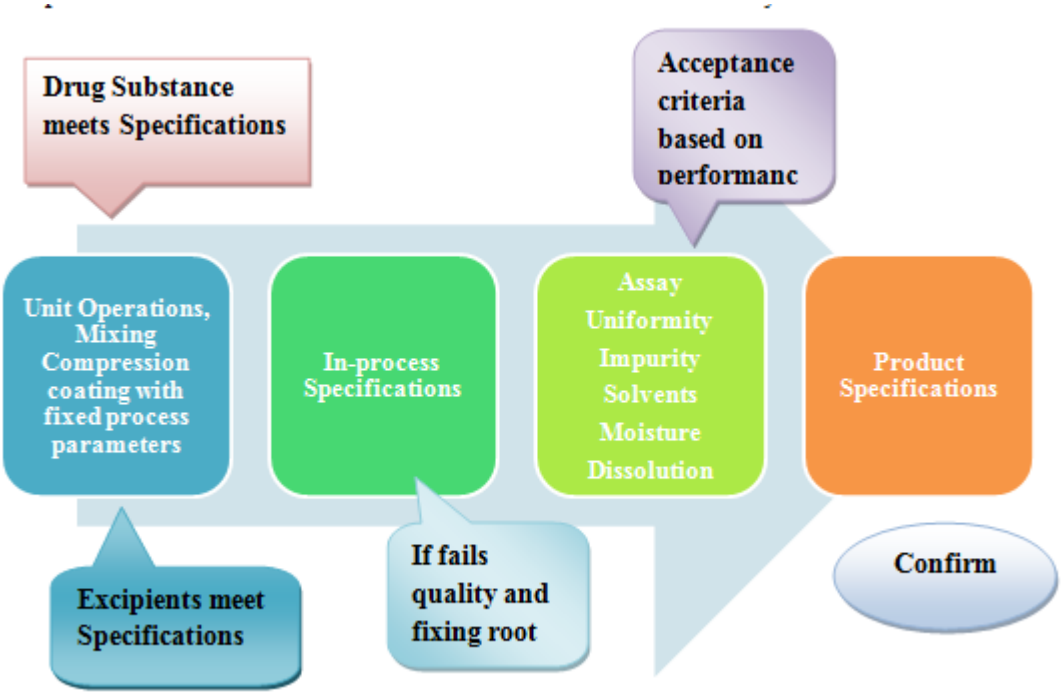


Figure.1. Diagrammatic representation of Quality Control using QbD [50]

Drug Substances [51, 52, 53]

The relationship between physicochemical and biological qualities, help in enhancing the product performance and manufacturing efficiency. The quality and physical qualities of beginning and source materials are critical in drug substance product development and manufacturing. The choice of beginning and source trials should be based on adherence to relevant principles as part of the manufacturing process development criteria. Solubility, for example, is one of the physicochemical and biological qualities that must be investigated. Size of the particles, crystal characteristics, biological activity, water content, and permeability are all factors to consider.

The Q11 paper explains how to link material characteristics and process parameters to drug-substance CQAS, how to apply Quality Risk Management to assist process parameter life cycle management, and how to offer a Design Space for a biotechnological product unit oration. ICH QUI also serves as a guide for drug substance makers when drafting a submission as part of the drug substance application process, regardless of whether they use a traditional or improved approach to design and development.

A Starting Material is a material with certain chemical characteristics and structure, and it is used as a "significant structural piece." A commercially accessible chemical is defined as one that is offered as a commodity in a pre-existing market. Chemicals created via bespoke syntheses were not regarded commercially available and should be justified when employed as Starting Materials, in addition to their intended usage as a Starting Material in the non-pharmaceutical sector.

Starting materials are classified as synthetic, semi-synthetic, and biotechnological/biological, according to the standard. The principles for synthetic drug substances include the knowledge that early in the manufacturing process, changes in material characteristics and operating circumstances have a lesser ability to affect drug substance quality. Regulatory authorities should

offer an adequate account of how impurities are created, how the bow process influences impurity formation, destiny, and purge, and if the control method is appropriate.

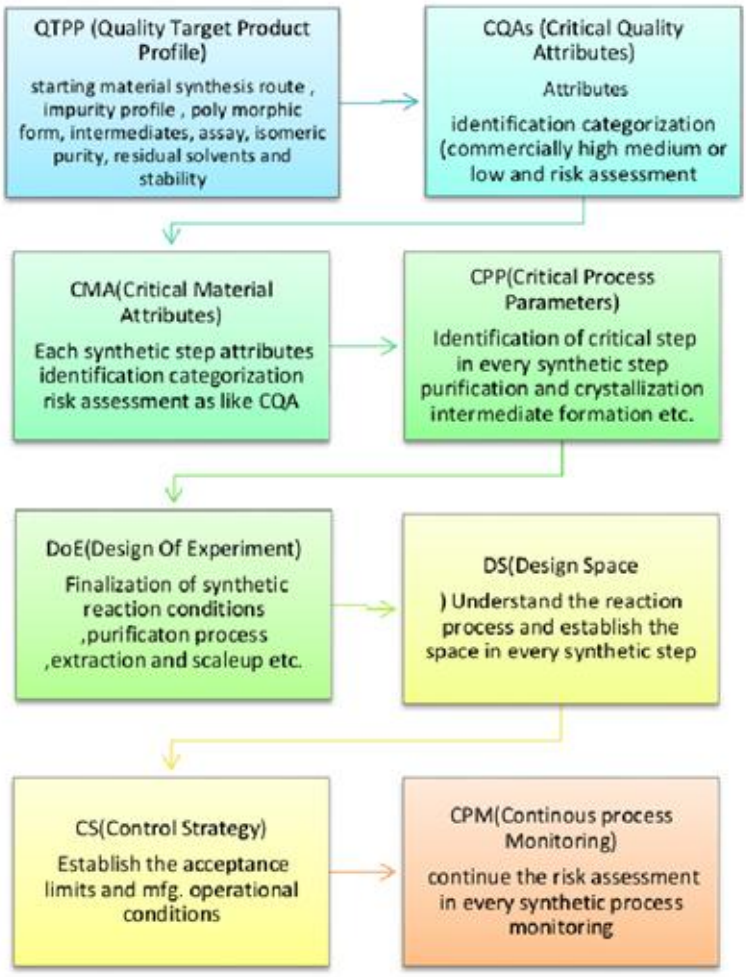


Figure.1. Drug substance synthesis in QbD approach

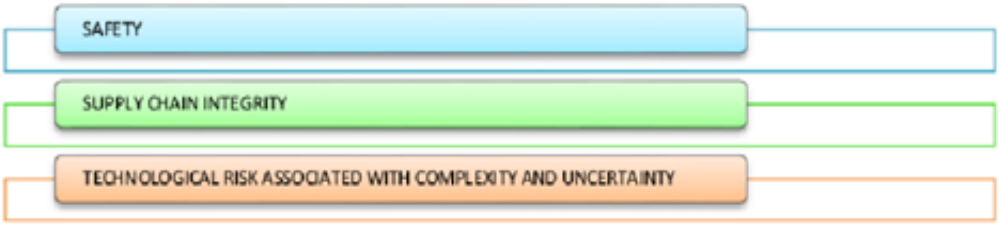
Excipients

Excipients are widely known to be a primary cause of variability. The purpose and utility of excipients determine the characterization and comprehension of their features. The knowledge and information on drug-excipient compatibility is useful for designing formulations and manufacturing procedures. These details may have come from both theoretical and experimental research. It is well understood that a mechanistic knowledge of degradation kinetics is more useful in forecasting stability than experimental data obtained under artificial stress settings.[52]

Stages involved in role of excipients in Quality by Design

Excipients must be established and approved by pharmaceutically affiliated producers and distributors to ensure the quality and safety of the completed product. Excipients were characterised as qualitative categories for the objectives and functions of an excipient in a medicinal product, and they served as the justification for their presence in the formulation.

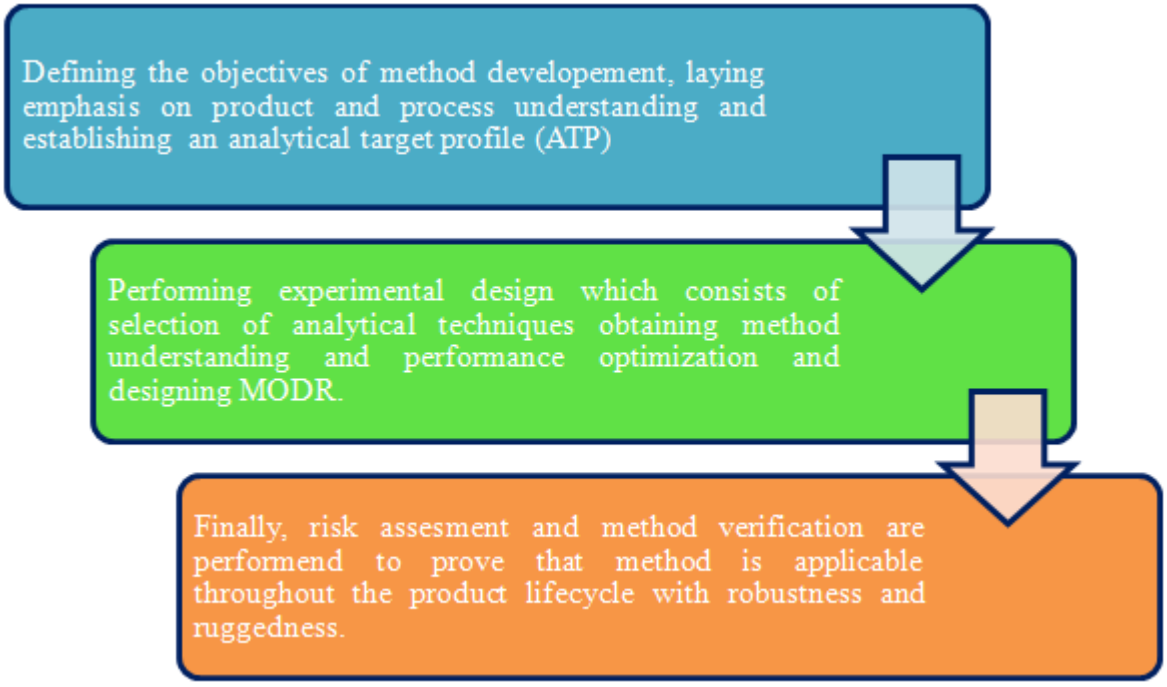
Sources of excipients related excipients risk management [44]



Analytical Quality by Design (AQbD) [49]

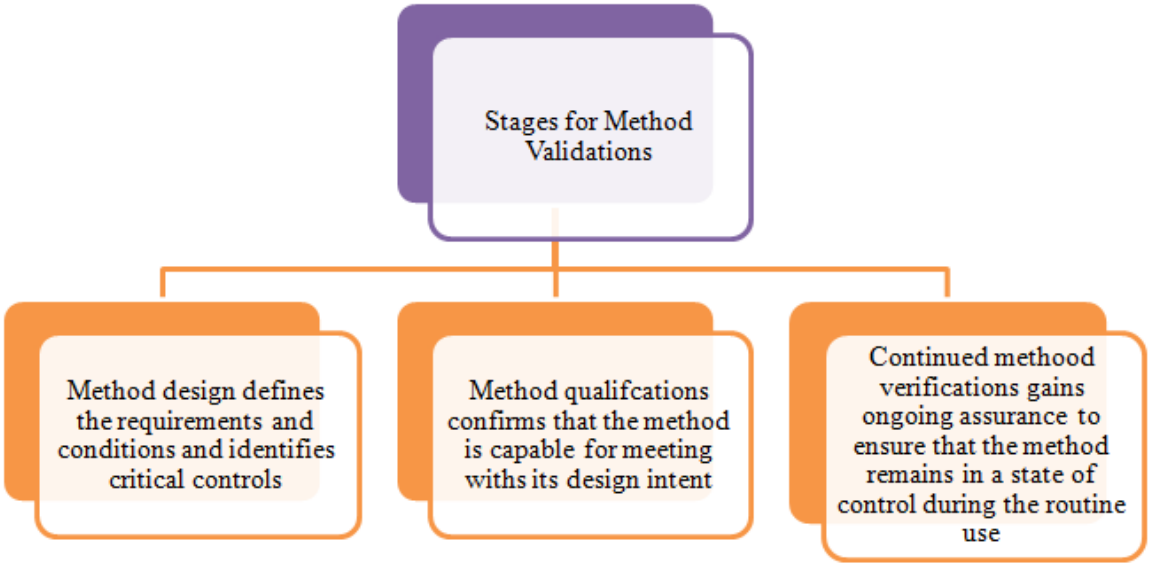
The goal of analytical Quality by Design (AQbD) is to build a robust approach that can be used throughout the life cycle of a drug product as well as on similar products using the same API. API, pharmacological contaminants, and biological metabolites may all be analysed using analytical QbD.

The process of Analytical Quality by Design [50]



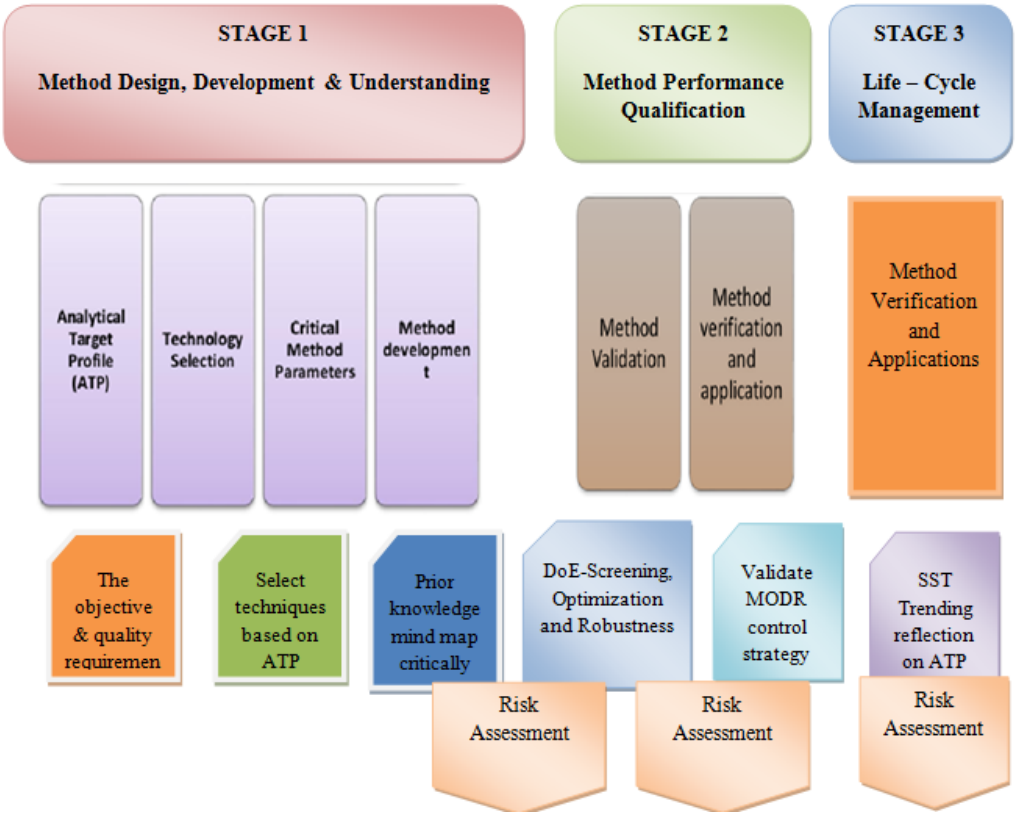
QbD in analytical method development and validations [45]

Analytical procedures are fully integrated into the QbD paradigm, and they play a critical role in the development of application techniques. The major goal is to specify the use of analytical methods, starting with validation and assessing their suitability.[52, 53] The three steps are depicted in the diagram below –



Steps involved in the AQbD

- Analytical Target Profile
- Technology Selection
- Critical Method Parameters
- Method Development
- Method Validations
- Method Verification & applications



Applications of ATP

Executive of QbD help to establish the best method technology to satisfy with the standard guidelines hence essential for the pharmaceuticals so that they easily accept the concepts of the QbD. Factors which enhance the robustness were always taken in the consideration for the development of analytical method of QbD.[53]

- Determination of impurities
- Simultaneous analysis of on API and its related Substances
- Multimolecular separations
- Natural product analysis
- Method optimization and applications to degradation kinetics

Conclusion

QbD plays vital role in the development of the good quality drug product which enhances the patient compliance. It procedure and method help in the ensuring the best techniques that can be useful for the product development. The main aim of the modern approach to develop and design the best quality drug product using its manufacturing process which will help in the constant release of the product and enhance its performance. The main goal on working on these modern approach to develop a well characterised method that reliable to demonstrate the high degree of assurance that meet with the predefined criteria when operated within defined boundaries. It also involved in the development and evaluation of different analytical methods that going to be used in the product development process.

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Abbreviations

Quality by Design **(QbD),** Food & Drug Association **(FDA),** Critical Quality Attributes **(CQAs),** Critical Process Parameters **(CPPs),** Critical Material Attributes **(CMAs),** Quality Target Product Profiles **(QTPP),** Potential Quality Attributes **(PQAs),** Design of Experiments **(DoE),** Critical Process Parameters **(CPP),** Define Measure Analyze Improve Control **(DMAIC),** Define Measure Analyze Design Verify **(DMADV),** Analytical Quality by Design **(AQbD),** Analytical Target Profiles **(ATP),** International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use **(ICH),** Process Analytical Technology **(PAT).**

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