ABSTRACT
Quality by Design is the modern approach for quality of pharmaceuticals. Quality means customer satisfaction in terms of services, product and process. QbD is best key to build a Quality in pharmaceutical products. This paper discusses pharmaceutical Quality by Design (QbD) as a way to generate high quality pharmaceuticals. Details about Quality by Design are given in addition to a list of components and tools of Quality by Design. It is based on the ICH Guidelines Q8 for Pharmaceutical development, Q9 for Quality risk management, Q10 for Pharmaceutical Quality system. Quality by Design (QbD) and describes use of Quality by Design to ensure quality of pharmaceutical analysis. Under this concepts of be throughout design and growth of products, it is important to identify desire product performance report Target Product Profile (TPP), Quality Target Product Profile (QTPP), and identify Critical Quality Attributes (CQA). QbD (Quality by Design) was one of design experiment approved by the FDA to maintain the quality of drug product before reaching to market.

KEYWORDS: CQA, CS, DS, DoE, QbD, QRM.

INTRODUCTION
Quality by design (QbD) is concept first developed by the quality pioneer Dr. Joseph, M.Juran. Dr. Juran believed that quality should design into a product band that most quality crises and problem related to the way in which a product was designed in the first place. The aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product. It is important to recognize that quality cannot be tested into product i.e quality should be built in by design. QbD tools will minimize the hazard by increasing the outputs and quality. USFDA has
released specific QbD guidance for immediate and extended release drug products as well as biotechnological products. Implementation of QbD helps to develop rugged and robust (strong) method that helps to go with ICH therefore for that reason pharmaceutical industries are adopting the conception of QbD.[3]

**BENEFITS OF QbD**[^4][^5][^6][^7]
- QbD is good business.
- Helps in rate reduction of batch failure.
- Minimize errors and costly investigation.
- Avoid regulatory compliance problems.
- QbD is good science.
- Better development decision.
- Empowerment of technical staff.

**OPPORTUNITIES**[^8]
The following are the opportunities for generic drug and new drug development that will be arise by implementing the QbD approach
- Opportunities for industry and regulators to jointly achieve a more comprehensive understanding of what is meant by design space;
- Opportunities for discussion on how design space can be established and submitted for both new and existing products;
- Understanding of how quality risk management can be used to develop a design space;
- Identification of scientific expectations that need to be fulfilled for the successful implementation of regulatory flexibility;
- QbD provides opportunities for facilitating continuous improvement throughout the product life cycle and contributes a better understanding of scientific and risk based regulatory submission and reviews, thereby maintain high quality.

**BENEFITSTO INDUSTRY**[^9]
- Ensure better design of product with fewer problems in manufacturing.
- Reduce number of producing supplements required for post market changes rely on process and risk understanding.
- Allow for implementation of latest technology to enhance manufacturing without regulatory scrutiny.
- Allows for possible reduction in overall cost of producing less waste.
• Improves interaction with FDA deal on a science level rather than on a process level.

**ROLES OF QbD**\[^{10}\]

• QbD ensures that the designing of the product is made in a way to fulfill the needs of the patients and requirements for better performance.
• Additionally, when QbD is implemented, the process is designed to continuously meet the product’s essential quality criteria.
• Understanding the impact of process variables and starting raw materials on product quality is made easier with application of QbD.
• Critical source of the process variability are controlled and identified by means of suitable control strategies.
• QbD ensures the continuous monitoring of the process and also it has to be updated constantly in order to maintain consistent quality over time.

**STEPS INVOLVED IN QUALITY BY DESIGN APPROACH**\[^{11}\]

1] **Developed of new molecular entity**
  - Preclinical study
  - Non-clinical study
  - Clinical study
  - Scale up
  - Submission for market approval

2] **Manufacturing**
  - Design space
  - Process Analytical Technological
  - Real time quality control

3] **Control Strategy**
  - Risk based decision
  - Continuous improvement
  - Product performance
TRADITIONAL APPROACH AND ENHANCE QbD APPROACH\textsuperscript{[12]}

<table>
<thead>
<tr>
<th>ASPECTS</th>
<th>CURRENT</th>
<th>QbD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmaceutical Development</td>
<td>Empirical, Random, Focus optimization</td>
<td>Modifiable within the design area and overseen by the organization’s quality system</td>
</tr>
<tr>
<td>Manufacturing process</td>
<td>Fixed</td>
<td>Adjustable within design space, managed by company’s quality system</td>
</tr>
<tr>
<td>Process Control</td>
<td>Some in process testing</td>
<td>PAT was used, and the process was tracked and examined.</td>
</tr>
<tr>
<td>Product Specification</td>
<td>Batch data is primary source of quality control</td>
<td>The intended performance of the product dictates the entire quality control plan.</td>
</tr>
<tr>
<td>Control</td>
<td>Through examination and testing</td>
<td>Risk-based control strategy, real time release possible.</td>
</tr>
</tbody>
</table>

KEY ELEMENTS OF QbD\textsuperscript{[2,13]}

- Defining of Target Product Profile (TPP)
- Identify the quality Target Product Profile (QTPP)
- Determine the Critical Quality Attributes (CQA)
- Initiate Risk Assessment
- Design space
- Design and Implementation Control Strategy
- Product Life Cycle and continuous Improvement

STEPS IN QUALITY BY DESIGN\textsuperscript{[14]}

1. Quality Target Product Profile (QTPP)
2. Critical Quality Attributes (CQA)
3. Risk Assessment
4. Design Space
5. Control Strategy

TARGET QUALITY PRODUCT PROFILE

When discussing products, it may be logical to use TQPP as a follow-up to TPP. Comprehending and tracing data that cannot be accessed required the QTPP that is transferred from one generation to the next. This is accomplished by laying out the desired characteristics of drug product while also considering the products potential side effects and safety concerns, TQPP’s indefinite quantity type and purity include quantity, strength,
instrumentation closure system and identity.[15] QTTP is “Prospective summary of the quality characteristics of a drug product that ideally will be achieved to establish the desired quality, taken into account safety and efficacy of the drug product.”[16] The design of generics is based on QTPP, which is an essential element of a QbD approach. A quantitative substitute for an aspect is QTPP, which is the quality target product profile. Clinical safety and efficacy can be quantitatively measured using the quality target product profile (QTPP).[17]

A few things to think about adding to the QTPP are as follows[18]

- Dosage strength
- Drug product quality criteria (e.g.- Purity, Stability, Sterility and the release of drug suitable for the marketing of the intended products)
- Dosage form, delivery system(s), mode of administration, and intended use in a therapeutic environment.
- Therapeutic delivery or moiety release and attributes affecting the pharmacokinetics characteristics (e.g., aerodynamics and dissolution performance) a dosage form that is suitable for the drug product is being created.
- Container Closure System.

CRITICAL QUALITY ATTRIBUTES

“A CQA is a quality attributes (a physical, Chemical, biological or microbiological property or characteristics) that must be controlled (directly or indirectly) to ensure the product meets its intended safety, efficacy, stability and performance.”[10] Identifying the relevance of CQAs is the next step. A CQA is term used to describe physical, chemical, biological or microbiological attributes or features that a thing ought to have.[19] It is commonly assumed that this is characteristic of the finished product, but it is also possible to indicate it, checking the quality of an intermediate or raw material. While disintegration has been cited by many as a crucial quality trait, we believe that a different set of CMAs offers clear objectives for assessing a manufacturing process. Differentiating the properties of CMAs and multifaceted performance tests are part of movement away from QbT to QbD because independent CMAs are the best way to provide a mechanistic link of the product quality to the CPPs in the manufacturing process.[20]
QUALITY RISK MANAGEMENT\[^{[3]}\]

- Scientific knowledge should be the basis of risk assessment for quality and ensures the patient safety.
- Describe the methodical procedure for assessing, handling, addressing and reviewing the quality risk.
- Applies over the process of products lifecycle, development, manufacturing and distribution
- Method mentioned in ICH Q9 guidelines are as follow-
  - Failure Mode, Effect and Critically Analysis(EMECA)
  - Fault Tree Analysis (FTA)
  - Hazard Analysis and Critical Control Points(HACCP)
  - Hazard Operability Analysis(HAZOP)
  - Preliminary Hazard Analysis (PHA)
  - Risk Ranking and Filtering
  - Supporting Statistical Tools

DESIGN SPACE

“Design Space is the multidimensional and interaction of input variables (e.g. Material attributes) and process variable that have been shown to offer quality assurance.”\[^{[10]}\] Design space is a way to show the development of the understanding of a process and the advantages of creating a design space are obvious. However one of the challenges for effective use of design space is the cost of this formation.\[^{[13]}\] The design space is the established range of process parameters and formulation attributes that have been demonstrated to provide assurance of quality. It forms the linkage between development and manufacturing design.\[^{[14]}\] A design space is multidimensional union and interplay of input factors that have been shown to offer quality assurance. Design space describes the relation between the process input and critical quality attributes. Understanding the relationship and effects of the process parameters and material qualities on products and the limit within which consistent quality can be attained can be aided by risk assessment. Analysis of historical data can provide the basis for establishing a design space.\[^{[21]}\]

CONTROL STRATEGY

A design space 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.”[3] It is important that the set method performance as indented and consistently gives accurate result, for that purpose control of the method is required. A factor identified to have risk has to be controlled. More attention is given to the high risk factors system suitability, the risk assessment can also help identify a specific control strategy.[22] An all encompassing strategy for producing high quality goods includes raw material specification, method controls and final products testing. This method provides a wealth of information for both the substance and the method you’re researching PAT is excellent tool for this because it can be scaled back depending on the house’s style.[15]

Elements of an effective Strategy[15]
- Procedural Controls
- In process Controls
- Batch release Testing
- Method Observational Characterization testing
- Comparability testing
- Constancy testing

The risk management strategy of the QbD common place is based on the important of CQAS.

Product Life Cycle Management and Continual Improvement
Lifecycle approach differs from that of the traditional approach of method development. According to Elaine more field (Deputy director USFDA) it includes continuous improvement of method performance and the design space allows flexibility for continuous improvement in analytical method can be done without prior regulatory approval because of design space made earlier.[14] Continuous improvement is an essential in a modern quality system that aims at improving efficiency by optimizing a process and eliminating wasted efforts in production. These effects are primarily directed towards reducing variability in process and product quality characteristics.[23]

Tools Of Quality By Design – Design Of Experiments
Design of experiments- Historically, DoE has been an instrument that has contributed to improving product quality and reliability. Different industries are increasingly using DoE for their decision, whether for new product or process improvement. An experimental design, analysis and interpretation are part of study’s DoE. This type of applied studies is often used
to examine how changing the input variables (X’s) affects measuring the response variable (Y) in a system, process, or product.\cite{24}

**Benefits of Design Space**\cite{25}

- Experimental design involves manipulating the independent variables to observe the effect on the dependent variables. This makes it possible to determine a cause and effect relationship.
- As well as controlling the independent variables the experimenter attempts to eliminate unwanted extraneous variables.
- Control over extraneous variables is usually greater than in other research methods.
- Owing to stringent guidelines and directives, the tests can be repeated and their outcome “checked”. Replication is crucial at this point since it increase trust in the results when similar results are obtained.

**Commonly Used Types Of Design Of Experiment**

1) SCREENING DESIGN: In addition to determining which ingredient to include in follow up studies, these designs are used to quantify the gradient impact of individual components.\cite{24}

**a) TAGUCHI DESIGN**- Taguchi methods of design of experiments are used to optimize the process parameter in the casting process of the foundry. Results can be analyzed using ANOVA technique to know the percentage of contribution of each casting process parameters.\cite{26} In comparison with the traditional Design of Experiments (DoE) method Taguchi method standardizes experimental design by incorporating following unique features.

- **Defining quality**: For the Taguchi method, quality is quantified as being on target and with the lowest variance around the target.
- **Standardized experimental trials**: Taguchi developed a series of orthogonal arrays (OA) for experimental design, which were formulated to reduce the required numbers of trials through fractional factors analyses, instead of factor analyses as with DoE.
- **Robust design strategy**: For achieving a robust design that is closer to the target with minimum variance, uncontrolled “noise” factors need to be identified and included in the outer array design.
- **Formulation of quality loss**: By expressing the loss/gain in quality in a simple manner, the quality characteristics can be for a specific target value (nominal-is-best), high as possible (bigger-is-best) or low as possible (smaller-is-best).

- **Signal-to-Noise analysis**: To analyze the performance variance due to the noise factors, the Taguchi method employs the Signal-to-Noise (S/N) ratio transformation. This method consolidates multiple data points into a single value reflecting the amount of variance present for the specific quality characteristic selected.\textsuperscript{[27]}

**b) PLACKETT BURMAN DESIGN**- Plackett and Burman (PB) devised orthogonal arrays are useful for screening, which yields unbiased estimates of all main effects in the smallest possible design.\textsuperscript{[28]} It is a two-factorial (i.e.-1 and +1) design that locates significant variables for producing by screening “n” variables in “n+1” experiments. The main effect was calculated basically as difference between the mean measurement of each variable made at a high level (+1) and low level (-1).\textsuperscript{[29]} PB design screen a huge number of input factors and, at the same time, reduces the numbers of runs. They are therefore very useful when the aim is to identify factors or variables that can be fixed or eliminated in further investigation.\textsuperscript{[30,31]}

**2) FACTORIAL DESIGN**

With factorial designs, a predetermined matrix of factors is used to alter process parameters simultaneously and deliberately. They are distinguished from mixed designs by their ability to alter each aspect separately. Several factors can be used in a factorial experiment. An experiment with only one component is a simple comparative experiment. In this case we analyze the data by using t-test or an ANOVA.\textsuperscript{[24]} The term “Factorial Experimental Design” refers to the process of imposing modifications on the blend’s data production in order to achieve process control, including process monitoring and control aimed at identifying potential improvements in the process and formulation of research tests.\textsuperscript{[32]} Factorial Design (FD) is also known as experimental designs for the first degree models, are the most common technique. The simplest way to set up a design of experiments (DoE) is to take two or more variables (n) and test at different level.\textsuperscript{[33]}

**3) FULL FACTORIAL DESIGN**- A full factorial design (FFD) experiments is one whose design incorporates every potential combination of selected factors and levels.\textsuperscript{[34]} Factorial designs are widely applies in experiments that are taking into account several factors where it is necessary to study the interaction effect of factors on the response.\textsuperscript{[35]} The effect of factors
on response is examined under full factorial design experiments. The numbers of experiments geometrically increase with the increasing number of factors and levels. The two levels factorial design that includes $2^k$ experiments is the most preferred first order designs. Factorial experiments have advantages such as low cost and possibility to investigate the relation between factors.\[36\]

4) FRACTIONAL FACTORIAL DESIGN - FFED is systematic study of several factors in a process that may all be changed each time an experiment is performed. This differs from conventional experimentations, in which one factor is changed while all others are held fixed. FFED is most often employed for examining new process in order to optimize them.\[37\] For factors with just two levels apiece, even a full factorial can have a very large numbers of runs. To minimize the numbers of runs, it is possible to select the fraction of the whole factorial, such as the same as $2^k-p$ factorial designs. Fractional fractionation can cause confounding. Therefore, because the resolution measures how confused the resolution measure how confused the design is, it is a very important factors. The ease of use and high inductive power of factorial designs make them useful.\[24\]

5) RESPONSE SURFACE METHODOLOGY
Response surface methodology is statistical and mathematic technique for model construction, assessing the effect of several independent variables in order to reach the optimum values of variables to obtain desired product.\[38\] A set of experiments, referred to as Runs, that are used to evaluate the impact of changing input factors on output results.\[24\] By using the RSM approach in the optimization process, the laboratory test stage can be made more effective by reducing the amount of time needed to test all the factors related to the consumer’s evaluation. In addition, parameters estimation can identify the variables that are largely affecting the model which then helps researcher to focus on those particular variables that contribute to the product acceptance.\[39\]

a) CENTER COMPOSITE DESIGN – Response surface methodology comprised of several methods to design the experimental procedures and one of them is Central Composite Design (CCD). In addition, CCD is also able to evaluate a single variable or the accumulative effects of the factors to the response.\[39\]
For the purpose of optimization various research issues in the RSM category, CCD, which is suitable for fitting second order polynomial equations, has been explored a lot. A CCD has three groups of design points

- Two- level factorial or fractional factorial designs points($2^k$), consisting of possible combinations of +1 and -1 levels of factors;
- $2k$ axial points (sometimes called star points) fixed axially at a distance say alpha from the center to generate quadratic terms;
- The central point’s offers a reliable and independent estimation of experimental errors; these points represents replication terms.

b) **BOX BEHKEN DESIGN**

As a kind of multi level fractional factorial designs, Box Behenken can reproduce first and second order response surface. Three level full factorial designs are not much efficient than these, especially if there are many input variables. Design, known as the Box Behenken Designs that uses three levels for each element and fewer trials for each element that the core composite design. BBD is that it does not contain combinations for which all factors are simultaneously at their highest or lowest levels. Thus, these designs are useful in preventing studies carried out in harsh environments, where it may be possible for inadequate results to arise.

6) **MIXTURE DESIGN (MD)** – Different features of two or more components are combined, and the characteristics of the resulting products are noted in MDs. The responses are independent of physical state, depending only on the proportions of the ingredients present in the mixture.

a) **SIMPLE LATTICE**– In simple lattice the level of every component are defined by the ratios r/m (where m is the polynomial degree to be fitted and r goes from 0 to m) and the experimental points are the combinations of these levels.

b) **SIMPLE CENTROID** – In simplex-centroid design for q components mixture experiment consists of all possible subsets of these q components, which are present in equal amount. The entire centroid represents the one complete mixture blend that makes up the design. The conventional simplex centroid design has a total of (2q-1) design points.
CONCLUSION
QbD is progressively turning into a significant and broadly utilized method in pharmaceutical item improvement. Quality by Design (QbD) principle and appliances, play an important role in to make something easier to understand like higher level of process and create opportunities for investigation and developing control strategies in formulation and process development. A QbD approach for scientific methods that include risk assessment, robustness testing, and ruggedness testing is much more rigorous than ICH validation requirement (Q2 (R1)). The Quality by Design methodology evaluate the methods variability in relation to the specification limit, one of the most crucial method features to examine when determining if the method is appropriate for the task at hand.

REFERENCES


34. Jankovic, A., Chaudhary, G., & Goia, F. Designing the design of experiments (DOE)–An investigation on the influence of different factorial designs on the characterization of complex systems. *Energy and Buildings*, 2021; 250: 111298.


