



## Quality by Design(QbD): A Review

S. Savitha<sup>1\*</sup>, K. Devi<sup>2</sup>

<sup>1</sup> PG Student, Department of Pharmacy. Annamalai University, Chidambaram, Cuddalore, Tamilnadu 608002, India

<sup>2</sup> Assistant Professor, Department of Pharmacy. Annamalai University, Chidambaram, Cuddalore, Tamilnadu 608002, India

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### \*Address for Correspondence:

S. Savitha, PG Student, Department of Pharmacy. Annamalai University, Chidambaram, Cuddalore, Tamilnadu 608002, India

### Abstract

Quality by Design is the most recent quality-related trend in pharmaceutical manufacturing (QbD). This paper discusses Pharmaceutical Quality by Design (QbD) as a way to guarantee high-quality pharmaceuticals. Details about Quality by Design are given in addition to a list of its components. The quality parameters and attributes of each unit operation are unique. Pharmaceutical products can benefit from Quality by Design and the steps that can be taken to implement it. High-quality pharmaceuticals and their manufacturing processes form the core of pharmaceutical R&D. It is impossible to verify the quality of a product because this document includes a breakdown of the product's quality profile and the most important aspects of Quality by Design. Comparing the quality of various products can be done in two ways: through Quality by Design and end-product testing (QbD). Quality by Design is based on the ICH Guidelines. ICH guidelines govern the development of pharmaceuticals and the implementation of quality assurance systems. Pharmaceutical development and production can benefit from Quality by Design (QbD).

**Keywords:** Concept & background of QbD, Traditional vs QbD Approach, Key elements, PAT, Challenges, Current & Future perspective.

## INTRODUCTION

### Quality

While talking about Quality by Design, the word "quality" is often mentioned (QbD). Quality is defined as "suitability for the intended use" in a qualitative sense. As a general rule, keep in mind that your identity encompasses all aspects of potency and purity.

### Quality by Design

Product quality, safety, and efficacy are of paramount importance to this group of people. Product quality has improved as a result of the use of QbD and other scientific methods (Quality by Design). Product development and manufacturing will be more efficient and effective if scientific methods are used. It's not just that these Quality by Design tools increase productivity and quality; they also lower risk. A QbD-based approach was used to successfully develop industry standard formulas. Qualified by Design (QbD) guidelines issued by the FDA apply to both immediate and extended-release pharmaceuticals, as well as biotechnological goods. ICH quality guidelines from Q8 to Q11 are always recommended by regulatory bodies <sup>1</sup>.

According to the Q8 guidelines for quality driven development, "a systematic approach to development that begins with predefined objectives and emphasize product, process understanding, and process control, based on sound science <sup>2</sup>".

Precision in the formulation and production processes is required for a high-quality final product. To be successful in business, you need to know how the quality of the final product is affected by product and process variables. A methodical approach is necessary to ensure a high-quality final product. Implementing QbD entails determining which product quality traits and process parameters affect the final product's quality, as well as how much a variation in one of these can affect the product's quality.

## CONCEPTS AND BACKGROUND OF QbD

Since its inception, the phrase "Quality by Design" has appeared in a variety of publications. To him, it was possible to predict a product's quality. Product quality cannot be tested, according to ICH Q8's two recommendations. Quality should be embedded into products by design.

Toyota pioneered a number of QbD concepts while improving their early automobiles in the 1970s. This encompasses a wide range of subjects, from computer networking to aerospace. Many new design elements appeared in medical devices in the late 1980s and early 1990s. However, the FDA has already published an article in 2002 on the topic of 21st century cGMP. Businesses were urged to incorporate quality, safety, and efficacy into new products as soon as possible in light of these documents <sup>3</sup>.

## KEY CHARACTERISTICS OF QbD

This is a useful tool for speeding up the development of new drugs.

- Is based on the notion that quality can be continuously incorporated into the design;
- It has the potential to be used in the development of pharmaceutical products and substances (chemicals and biologics).
- It can be beneficial to analytical methods.
- It is possible to implement in full or in part.
- Is appropriate for use at every stage of the drug's life cycle.
- It is always encouraged by regulators <sup>4</sup>.

## BENEFITS OF QbD

- Batch failures must be eliminated, and deviations must be kept to a minimum, in order to avoid regulatory issues.
- Empowerment of technical personnel
- a quick-response system that is agile and flexible

- Many businesses want to reduce waste and project rejections while increasing manufacturing efficiency.
- Create a scientific knowledge base for all products.
- On science-related topics, collaborate more closely with industry.
- Ascertain that all data is consistent.
- Include a risk assessment and management component.
- Reduce the amount of time spent testing the final product.
- The ability to make a decision on a release date quickly <sup>5</sup>.

## Pharmaceutical Aspects: Traditional vs. QbD Approach

In comparison to the traditional approach, QbD can be utilised to demonstrate how the pharmaceutical development and manufacturing process has been explained (Table 1).

Table 1: Traditional vs. QbD Approach

| Aspects                    | Traditional  | QbD   |
|----------------------------|--|---|
| Pharmaceutical Development | Empirical  | Systematic, multivariate experiments.                     |
| Mfg. 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 the 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 with in design space.        |

## KEY ELEMENTS OF QbD

These parts of a QbD approach to developments that are:

- Because quality, safety, and effectiveness can now be linked, the TPP can be refined. As a starting point for product planning and development, the standard characteristics of the product are identified.
- Characteristics of Importance Material properties that must be within acceptable limits, ranges, or distributions are known as attributes.
- In Risk Assessment, CPPs and material attributes are compared to CQAs. The CPPs will be determined through the use of risk assessment tools like the FMEA or the bone diagram. ICH Q9 lists the risk management tools that will be used <sup>6</sup>.
- An important connection between CQAs and CPPs can be established and represented in a stylistic area through the use of experiment style (DOEs).
- The company's long-term strategy In the event of an unexpected event, it is important to identify and address the problem as soon as possible.
- Management of the product lifecycle and continuous improvement in quality (Fig. 1).

The ICH-Q10 standard can be used to set up, maintain, and improve the quality management system for QbD products at all stages of their lifecycle <sup>7</sup>.

### TPP

The TPP specifies how a drug product should look for purposes of labelling and drug development. The product's

intended use, target audience, administration route, and other critical features and quality design are all defined by TPP.

### Target quality product profile (TQPP)

The term TQPP may be a logical follow-up to the term TPP when discussing product quality. The QTPP is required in order to comprehend and trace data that cannot be passed down from one generation to the next. This is accomplished by laying out the desired characteristics of a drug product while also considering the product's potential side effects and safety concerns. TQPP's indefinite-quantity type and purity include quantity, strength, instrumentation closure system, and identity <sup>8</sup>.

### CQA's

CQA can be applied in a variety of ways to ensure a product's quality, safety, efficacy, and stability (certificates of conformity, or CQA for short). It is also possible to define, measure, and monitor the final product's quality to ensure that it remains within acceptable limits. Quality attributes include clinical safety and efficacy, as well as the parameter boundary approaching failure. Manufacturing is also a quality attribute. It's possible that the criticality of the APT manufacturing process will change, raising the criticality risk level.

### Critical material attributes (CMAs)

It is critical to fail when a true change in a parameter causes it impossible for a product to meet a QTPP. It's important to consider how much adjustment one is willing to make as well as the uniqueness of each input material when deciding which parameters are important. CMAs that fall within an acceptable range or ranges must meet drug substance, excipient, and in-process material quality.

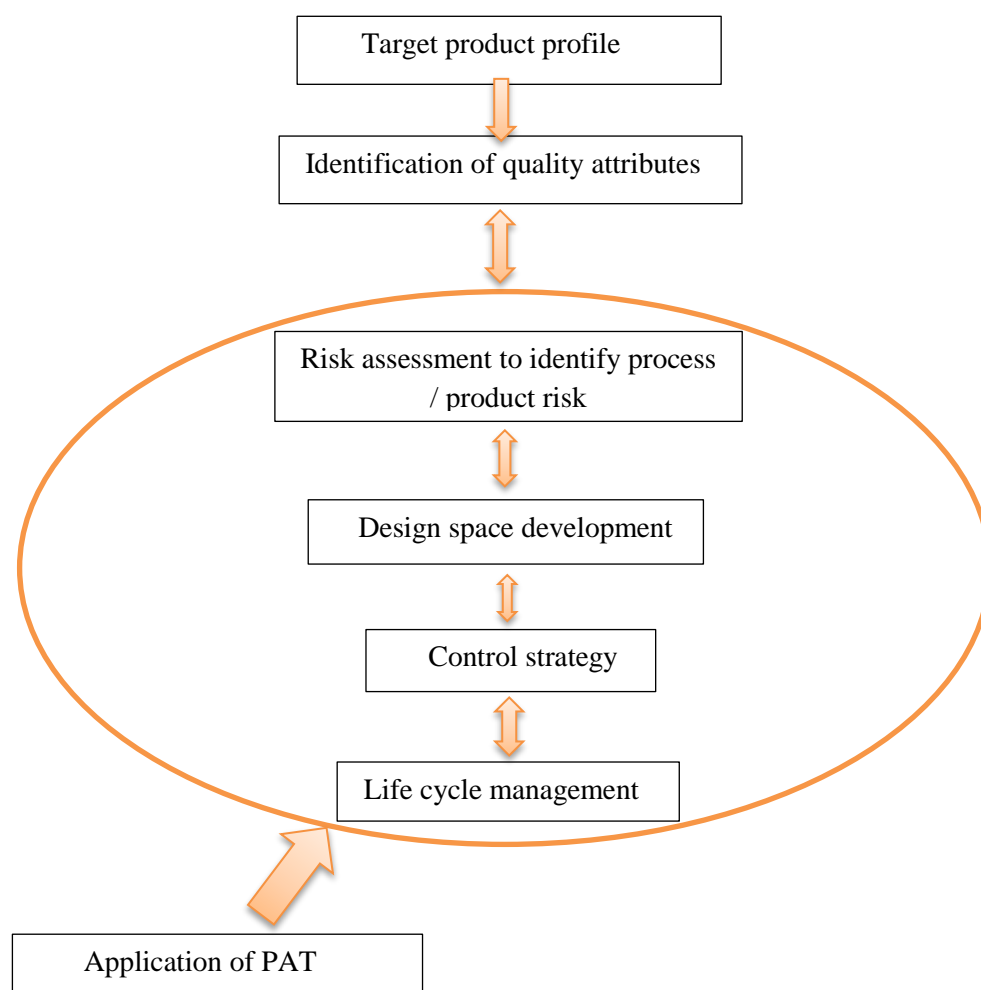


Figure 1: Key elements of QbD

### CPP's

This means that any measurable input or output of a method step must be managed in order to achieve the required product quality and method consistency. Each item in this read would be a method parameter. Here's how it'd work: Parameters are examined before or during procedures that can have a significant impact on the appearance, purity, and yield of the finished product <sup>9</sup>.

### Risk assessment

When we talk about "risk," we're referring to both the possibility and the magnitude of harm. By assessing the risks involved, the overall quality of a technique or process can be improved. A risk assessment's goal is to identify the critical characteristics that influence the quality of a finished product. A risk assessment can help improve communication when the FDA, trades, R&D/prototype, and multiple production sites are all involved. The methods for determining risk are as follows: A few risk assessment methods are described in ICH guideline Q9:

- ✓ Failure Mode Effects Analysis (FMEA)
- ✓ Failure Mode, Effects and Criticality Analysis (FMECA)

- ✓ Fault Tree Analysis (FTA)
- ✓ Hazard Analysis and critical control points (HACCP)
- ✓ Hazard Operability Analysis
- ✓ Preliminary Hazard Analysis
- ✓ Risk ranking and filtering
- ✓ Supporting applied mathematics tools <sup>10</sup>.

### Design space

The multidimensional combination and interaction of input variables (such as material qualities) and method parameters unquestionably ensures that the quality will be done appropriately. Moving out of the designated planning area is required for the more time-consuming post-approval amendment process (Fig. 2). The relevant authorities must review and approve an individual's projection of the planning area. The area for the scientist's style could be  $Y = F$  if  $Y = F$  is a function of the (critical) method parameters and the (critical) quality attributes/material attributes (Process Parameters, Material Attributes).

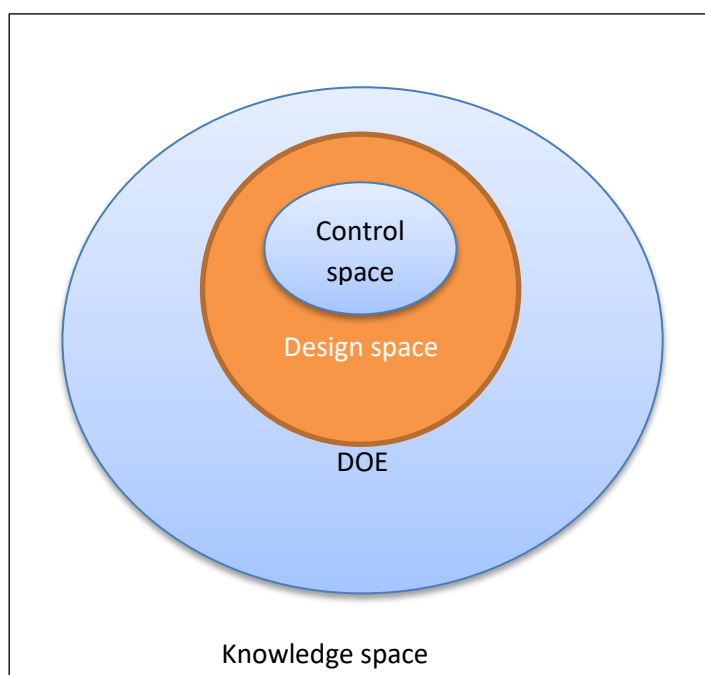


Figure 2: Design space

### Control strategy

An all-encompassing strategy for producing high-quality goods includes raw material specifications, method controls, and final product testing. This method provides a wealth of information for both the substance and the method you're researching. PAT is an excellent tool for this because it can be scaled back depending on the house's style.

#### Elements of an Effective Strategy

- Procedural controls
- In-process controls
- Batch release testing
- ✓ Method observation characterization testing
- ✓ Comparability testing
- ✓ Constancy testing

The risk management strategy of the QbD commonplace is based on the importance of CQAs.

### Product lifecycle management and continual improvement

Quality is constantly improved throughout the lifecycle of a product, giving companies a wide range of options for improving the quality of their products. It is standard practise to monitor the effectiveness of a method in order to ensure the highest level of quality control. From routine manufacturing, there is a wealth of new data and information that can be used to improve procedures and methods. The style area must remain unchanged in order to maintain a company's quality system, which is why traditional methods like the way frozen method are used <sup>11</sup>.

### PROCESS ANALYTICAL TECHNIQUE

The FDA's PAT keeps a close eye on pharmaceuticals manufacturing processes by tracking key process parameters (CPPs) (CQA). To reduce rejects, improve consistency, and reduce over-processing, they prefer in-line or online real-time

monitoring of their CPPs. The authorities have made the limitations on the use of PAT public.

In the pharmaceutical industry, PAT refers to the transition from batch production to a more dynamic approach. Because the CQA of the final product is affected, instrumentation CPPs take precedence at defined intervals after processing. Manufacturers can consistently produce high-quality products with less waste and lower costs.

Using Continuous Manufacturing Technologies can result in improved product quality and reduced waste (CMT). You can better manage common cause variability if you understand the upstream and downstream effects of a gentle state method.

### PAT TOOLS

All three main PAT tools must be used in order to complete a successful PAT project:

- To determine which parameters are CPP, multivariate knowledge acquisition and analysis necessitates the use of advanced software programmes, packages that assist in the design of experiments, a wide variety of raw data, and statistical analysis.
- In-line and real-time analysis are used to keep track of the CPP's various parameters. Fiber optics, Raman spectrometry, and biosensors are also included in this category (NIRS) <sup>12</sup>.

### CHALLENGES

Quality by Design (QbD) is an important part of improving pharmaceutical quality, but it can be difficult to implement because many people are unfamiliar with the pharmaceutical manufacturing process. In the pharmaceutical industry, a thorough scientific understanding of manufacturing has always taken precedence over an end product.

Pharmaceutical companies are unanimous in their support for QbD implementation. The FDA has requested that terms such as criteria for selecting and eliminating quality attributes, standards for evaluating control, and criteria for substituting analytic approaches be included in the final rule. Ten major

roadblocks stand in the way of QbD adoption. The importance of each of these issues is determined by the type of drug and its stage of adoption.

The first four challenges occur within companies:

- An internal body misalignment (Disconnect between cross functional areas, e.g., R&D and manufacturing or quality and regulatory).
- Among QbD implementers, is a major factor due to the uncertain implementation timelines and costs.
- Due to a lack of execution technology, there is a lack of understanding of the implications of Critical Quality Attributes (CQA) (e.g., data management issues).
- To implement QbD, how do we ensure that our suppliers and contract manufacturers are aligned?

The next six challenges are directly related to the regulatory authority:

- This is due to regulators not knowing how to deal with QbD applications due to a lack of concrete guidance for industry to follow.
- The existing method of distributing promised regulatory benefits does not make people feel protected.
- There is a lack of coordination among intergovernmental regulatory bodies.
- Interactions with businesses are currently not conducive to QbD.

Even though putting QbD into practice has its own set of issues and concerns, industry and government agencies can work together to address them.

## CURRENT STATUS

To guarantee a consistently high-quality product, the ICH Q8 Pharmaceutical Development guidelines emphasize the importance of establishing proper controls and comprehending your production method. Product attributes and processes, as well as product performance, must be taken into account in risk-based, holistic, and proactive pharmaceutical development. You don't have to check the final product for its quality or all of its characteristics. In-process and method analytical technology (PAT) data can be used to ensure that factory-made products meet predetermined quality standards with the help of regulators.

Regulators are required to be informed of the company's product knowledge and conclusions, along with its management strategy for ensuring product quality attributes, by law <sup>13</sup>.

"QbD could be a systematic approach to product and method style and development," says the FDA's Center for Drug Analysis and Analysis.

QbD involves the subsequent key elements:

- CQAs must be determined and the product profile must be targeted.
- Connect the raw material attributes and method parameters to CQAs to perform a risk assessment.
- It is necessary to create a design space.
- Come up with a solution to the problem and put it into action.
- Product management and continual improvement are inextricably linked.

For both the company and its government contracting agency, Quality by Design remains a top priority (QbD). Period unleash, on the other hand, allows for greater quality assurance while also allowing for the widespread use of more production and control methods <sup>14</sup>.

## FUTURE PERSPECTIVE

The QbD will become more widely accepted in the future. In both development and production, event-based approaches are widely used.

It's become a common issue for many businesses because factories are difficult to access, or because the PAT department is unwilling to cooperate. Our current output is fine as long as we don't exceed the capabilities of our instruments.

When we get to the more advanced and significant parts of the standard intentionally approach to PAT using controlled methods, we encounter significant resistance.'

So, for instance, the European Medicines Agency is collaborating on the QbD concept with other regulatory bodies (EMA). "Real-Time Release" was also published by the EU.

An application that shows a strong focus on quality will be given high consideration by the European Medicines Agency (EMA). The European Medicines Agency (EMA) only accepts applications that fully adhere to its quality concept on purpose (QbD).

Mathematics and analytical methods, as well as risk-management techniques, are used at various stages of drug design, development, and production to ensure that medicines meet quality standards.

For the purposes of implementing QbD, the US authority/EMA refers to the ICH Q8-Q12 document. Continuous Manufacturing and Analytical Technique Development are currently the focus of ICH's efforts. These new ICH tips should be available in the near future <sup>15</sup>.

## CONCLUSION

The QbD approach has several advantages, including a better understanding of products and methods, continuous improvement, and the ability to quantify TPPs. Drug development approach Quality-by-Design (QbD) improves the quality of medicines for patients, manufacturers and regulators. As a result of regulations, the adoption of QbD is greatly affected. QbD has become a promising scientific tool for quality assurance in the pharmaceutical industry. Prior to launching any product on the market, the pharmaceutical industry prioritises obtaining regulatory approval.

## CONFLICT OF INTEREST

Authors do not have any conflict of interest with each other.

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