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Review Article

Comprehensive Review of Quality by Design (Qbd)

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ABSTRACT

A unique approach to maintaining pharmaceutical product quality is called Quality by Design, or QbD. Quality is customer satisfaction such as product service, product design and product process. This article is about quality medicine by design. The main application of (QbD) is to develop quality of medicine analysis. Below this document shows the growth of products. To identify product characteristics such as Quality Assurance Product (QTPP), Critical Quality Attributes (CQAs), design stage, based on drug analysis, risk assessment, establishing ICH guidelines for quality design. The ICH guidelines Q8 (pharmaceutical development), Q9 (quality risk management) and Q10 (pharmaceutical quality system) are the basis for design quality. QbD can also be applied to produce pharmaceutical and quality products.

INTRODUCTION

The goal of pharmaceutical development is to design a quality product and its manufacturing process to continuously provide the desired performance of the product. Information and knowledge gained from drug development research and manufacturing experience provide scientific understanding to support the creation of design sites, specifications and controls[1]. Information obtained from drug development studies forms the basis for quality risk management. It is important to note that quality in products cannot be tested. For example, the attribute should be included in the design. Changes in manufacturing and production processes during development and life cycle management should be considered as an opportunity to gain more knowledge and support the creation of the design space[2]. In addition, incorporating relevant knowledge gained from experiments generating unexpected results can also be useful. The design space requested by the applicant is subject to regulatory review and approval. Work in design space is not considered a change[3]. Moving beyond the design point is considered a change, and the change process begins after legal approval. At all times, the product must be designed to meet the needs of the patients and the performance of

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the product. Product development strategies vary from company to company and product to product. There is another way to explain it in the presentation[4]. An applicant can choose an experimental approach, a more systematic approach to product development, or a combination of the two. A more systematic approach to development (also defined as quality by design), for example, the synthesis of prior knowledge, research results through the design of experiments, the use of quality risk management and using knowledge management (ICH Q10) in the product life cycle[5]. Such a systematic approach can increase the achievement of the desired product quality and help managers to better understand the company's strategy. Product and process understanding can be updated with knowledge gained throughout the product's life cycle[6].

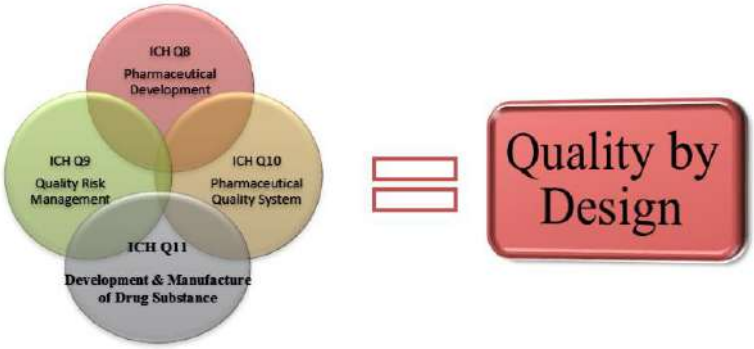

Figure 1 Content of Quality by Design

The pharmaceutical industry knows the product's quality, safety and effectiveness. Product quality has increased by implementing scientific tools called QbD (Quality by Design)[7]. Scientific approaches can provide clear and sufficient knowledge from product development to production. This QbD tool reduces risk by increasing production and quality. Today, the QbD approach has been successfully used in the development of common formats. The USFDA has published specific QbD guidelines for immediate and extended release drug products and biotechnology products[8]. Regulatory authorities continue to recommend the implementation of ICH quality guidelines such as Q8, Q9, Q10 and Q11. The concept of "Quality by Design" (QbD) was proposed as an approach that encompasses a better scientific understanding of critical processes and product quality, the design of controls and tests based on Scientific limitations of understanding in the field of development and use[9]. Product life cycle to work in a continuous improvement environment. QbD describes a pharmaceutical development approach that involves the design and development of manufacturing and manufacturing processes to maintain the quality of the specified product[10]. Instruction based on mathematical models is used to ensure that subject knowledge is constructed and applied independently and in combination. QbD means not just fewer diagnostic tests, but the right diagnosis at the right time, based on science and risk assessment[11]. The implementation of QbD helps to develop a strong and robust (robust) process that helps to adhere to the ICH, and therefore the pharmaceutical industry participates in the QbD program. Factors affecting robustness are assessed for the development of a QbD environmental analysis method[12]. This approach helps to continuously improve the method. Parallel approaches for using QbD in an analytical sense as a production process are available in the literature. An approach such as benchmarking, quality assurance attributes (CQA), design phase, risk

assessment can also be used for the analysis process. While not yet adopted by all pharmaceutical companies, what is coming is the products that management teams need[13]. This concept can be adopted by businesses because of its many benefits and easy controls. The Pharmaceutical Research and Manufacturers of America (PhRMA), Analytical Technology Group (ATG) and the European Federation of Pharmaceutical Industries and Associations (EFPIA) provide clear recommendations for the parallel implementation of QbD[14].

Design[15]

- The product is designed to meet patient needs and functional requirements.
- The process is designed to be consistent with product quality requirements.
- The effect of initial raw materials and processing parameters on product quality is clear.
- Identify and control major sources of process variation.
- The process is monitored and updated to ensure constant quality over time.

DEFINITION[16, 17]

Quality: Quality is a very important word in Quality by Design, quality is defined as good or good enough to ensure the identity, purity, strength of the product for the intended purposes.

Quality by Design

According to the ICH guideline Q8 (R1): QbD is a systematic approach to development that begins with previously defined objectives and emphasizes product and process understanding and control, in based on good science and quality risk management.

According to the FDA PAT guidelines: QbD is a system for designing, analyzing, and controlling production through real-time (i.e., in process) measurement of critical quality. The performance characteristics of new and processed materials, and the process affects the quality of the product Security."

History of the QbD: Dr. Joseph M. Joran was the first to recognize quality through design and applied engineering. Since 1986, Edwards Deming has also discussed the concept of quality by design. In 2002, the FDA proposed a new formulation (cGMP for the 21st century risk approach). Quality by design concepts can be used for new product development, industrial quality processes and automated pharmaceutical research, development and production[18].

Objectives of QbD[19, 20]

QbD's main goal is to achieve product quality:

- Maintain product quality.
- Discounts
- During development, it's time to get practical knowledge.
- Increasing product efficiency can reduce product variation and efficiency by increasing the product process and understanding design control.
- To achieve a good performance test.
- QbD Foundation

ICH guidelines Q8, Q9 and Q10 related to drug development, quality risk management and quality system structure by QbD.

Benefits of QbD[21]

The main advantages of QbD are

- QbD helps to improve the quality of the product and easy understanding of the process.
- QbD is very scientific.
- QbD is the highest level of business.
- To learn technical skills.
- To develop the quality of products.
- QbD is correct.
- Fix stack crash.
- Good development decisions.
- Building technical skills.
- To delete the entire bath.
- To avoid compliance issues.

Opportunities of QbD[22-24]

- To increase productivity, reduce costs and eliminate projects and waste.
- Create knowledge on all products
- Scientific problems in high-end business
- Economical, flexible and versatile systems
- Including risk management.

Activities in QbD / Elements of QbD

➢ Clinical development
- Preclinical research
- Non-clinical research
- Clinical research
- Scale-up
- Market acceptance

➢ Production
- Spatial Design
- Quality control in real time.
- Technical process analysis

➢ Management strategy
- Risk decision making
- Continuous improvement
- Product performance

The following seven steps are the QbD implementation plan:

- Contract quality through professional design
- Review the business and methods of professional gap evaluation
- Organize a meeting on design quality for all employees
- Review expert findings and recommendations
- Develop planning, implementation strategy and cost estimates.
- Outsource the work and hire someone else
- Retain an impartial staffing expert as a "Project Management Consultant".

Important attributes about QbD[25-31]

➢ **Quality Target Product Profile (QTPP):** Product Specification Quality measures include developing the basic design of the product. QTPP mainly emphasizes safety and effectiveness.
- Pharmaceutical Form
- Appearance
- Identity
- Quality
- Promotion
- Preparation
- Purity/Contamination
- Stability and Dissolution
- Fracture of medicine and bioequivalence
- Dosage and administration

Considering the use and administration, the QTPP specifies the properties necessary for the quality of the medicinal product. For the patient or consumer, the simple identification in the product profile quality measures (such as quality attributes or CQA) can be decisive or important.

Advantages of the QTPP:

➢ To identify risk and effectively manage risk.
➢ LifeChanging Process A sudden decision to m ake a medical intervention will help the patient.
➢ Creation and sharing knowledge license.
➢ The medical product has been developed and manufactured to meet product requirements for quality objectives, while meeting release/launch approval standards and other parameters consistent with product performance in vivo.
➢ **Critical Quality Attributes (CQAs):** The terms "physical, chemical, biological and microbiological quality" (CQA) refer to these properties. CQA must be maintained within product quality parameters distribution, locations or regions. CQAs are the same for pharmaceutical substances, excipients and intermediates in pharmaceutical products. In some cases, the product directly affects the quality and safety of the product, it also affects the development of the method, and the inspection of important quality factors can also be made using the HPLC method. for a specific

drug product. The scope of an API manufacturing company's operations may vary with respect to a drug product and manufacturing process.

- **Design Space:** The relationship between important material and process inputs can be linked at the design stage. A complete design process can be developed for single and multi-part projects. The FDA's guidance states that the design stage does not require you to understand the product and function, or to have full control over the system.

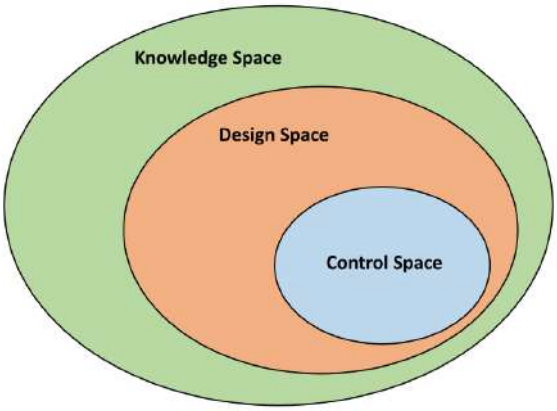

Figure 2 Design space

- **Risk Assessment:** The process of risk assessment is to combine and anticipate the potential harm and severity of that harm. Risk assessment is the analysis and formulation of risks associated with a situation that is considered a threat. Technical expertise and patient safety are the basis of quality risk assessment. ICHQ9 is a quality risk management system that is suitable for the manufacture and use of pharmaceutical products and understands the process management strategy, raw materials to final testing[32]. Risk assessment tools can be used to identify and determine parameters. Threat assessment is effective in improving communication when processes involve FDA, experts and R&D, modeling (sampling) and various production units. The following is a formal threat assessment There are several types of threat assessment presented in ICHQ9.
  - Analysis of the effects of failure modes
  - Analysis of effects and assessment of failure modes
  - Analysis of fault trees
  - Analysis of hazards and critical control points
  - Analysis of risk activities
  - Initial assessment Risk
  - Risk analysis and rating[33]
- **Process Analytical Technology:** PAT is a system that validates the design, analysis of operational measurements and the production process of high quality and processing characteristics of materials in the final production process[33]. PAT can use continuous manufacturing technology to improve product quality and eliminate waste. In the pharmaceutical industry, PAT represents a move from a dynamic approach to batch production. Since the CAQ of the final product affects the device of CPPs some time after refining the product of high quality, it reduces the waste and lowers the costs. In fact, real-time PAT assessment can provide immediate feedback and fundamental feedback to increase process robustness. PAT is a good primary tool for recording the Time Trial Test (RTRT) uniformity of particle size structure, concentration, uniformity of content, polymorphism and determination.

There are three main tools for PAT

1. Real-time/linear tools
2. Downstream processing programs
3. Multiple statistical methods[34].

- **Control strategy:** During the development of medicines, many sources of product variation are identified depending on the process and the product. Management strategy mainly affects process development, process resources, drug product materials and

components, facilities and equipment, operating procedures, process control, and final product requirements. Product quality to maintain the quality of the medicinal product throughout the life of the product cycle[35].

Elements of an Effective Strategy

- Methodology Testing
- Delivery Output Testing
- Compliance Testing
- In-Process control
- Procedural control[36]

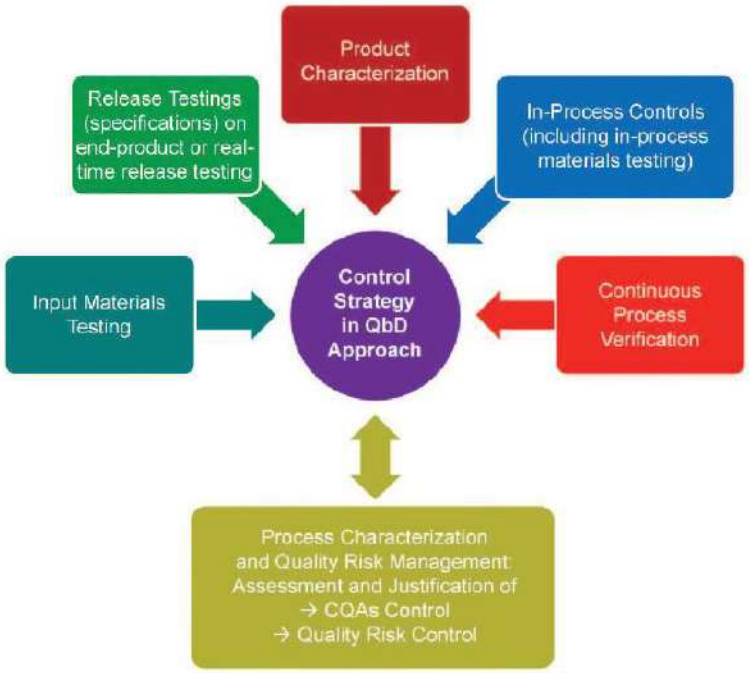

Figure 3 Control Strategy in QbD

Applications of QbD in analytical method development

The implementation of QbD helps in the development of robust and robust/robust process which helps to follow the ICH guidelines, so the pharmaceutical industry adopts this concept of QbD. This approach helps to continuously improve the method[37].

- Chromatographic methods such as HPLC (for stability studies, method development and determination of impurities in pharmaceuticals)
- Karl Fischer titration to determine moisture
- For biomedical processes
- Descriptive studies
- Linear methods such as LC-MS
- Advanced methods such as mass spectrometry, UHPLC, capillary electrophoresis
- Genotoxic contamination analysis[38].

ADVANTAGES OF QBD

For Industry[39]

- When conditions are different, the method developed becomes stronger and more reliable.
- It becomes more and more familiar with the meaning.
- This approach increases the success of the transfer when transferring the method from the research level to the quality control department.
- The room design project avoids post-approval changes that could be costly for both companies.
- It can create new processes and continuously improve throughout the life cycle.

For Food and Drug Administration[40]

- Provide easier decision-making
- Strengthen the scientific basis for analysis
- Ensure that decisions are made based on science and not on detected data
- Provide higher compatibility.

Pharmaceutical aspects: Traditional vs. QbD Approach[41]

Table 1 Difference Between Traditional vs. QbD Approach

Traditional Analytical Method Development	QbD (Lifecycle) Analytical Method Development
Methods validated as check box tools are defined in the International Conference on Harmonization (ICH) Guideline Q2, Validation of Analytical Methods: Text and Method.	The efficiency of the method is presented next to the analysis objective profile, which shows the specific characteristics and criteria required by the process control strategy.
The effect of changes in method parameters on method performance is not well known.	A structural, scientific approach to identifying and exploring methodological variables and their effects (methodology and characterization).
Transfer of customs is a separate process from authorization.	Culture transfer activities are viewed as part of a life cycle approach and consider change management activities. Implementation of the appropriate method and verification measures determined by the audit (method performance verification phase)
Words for example; Method verification, method, method validation and re-validation are confused in the traditional approach.	In the life cycle approach, clearer terms are used in terms of validation and tool specification terms.
Method validation is used to perform a single event after method development is complete.	Lifecycle Validation is used to perform all activities that ensure correct data is produced throughout its life cycle (ie from development to continuous operation environment and knowledge transfer from a transfer entity).
Method validation is the verification of the performance of medical methods under the conditions of use. Revalidation is performed after validating attributes are changed which may cause problems.	Method performance verification is the demonstration of the performance of a method after a change in the method's operating conditions or operating environment.
Process transfer is the process performed to transfer a process from the sending entity to the receiving entity and to demonstrate the equivalence between the two entities.	Process integration includes activities to ensure an effective process setup in a typical operating environment and includes knowledge transfer from the supply chain.

Analytical Quality by Design: Quality by design is very useful in analytical method development, the goal of analytical QbD (AQbD) is to develop a robust method that can be used throughout the entire life cycle of a medicinal product and similar products contain the same active ingredient[42]. QbD Analytical makes it easy to analyse APIs, pharmaceutical impurities and biological metabolites. The AQbD process includes defining process development goals, increasing product and process understanding, and creating an analytical goal specification (ATP), run an experimental design that includes a set of analytical methods, understand the method, and optimize the operation and design of the MODR, and finally, risk assessment and method validation are performed to prove that the method can be used with robustness and robustness throughout the product's life cycle[43].

PROCESS ANALYTICAL TECHNIQUE

FDA's PAT monitors drug manufacturing processes by following key process parameters (CPPs) (CQA). To reduce cancellations, to be more comfortable, and reduce excessive processing, they prefer to monitor their CPP online or online. Officials have announced restrictions

using PAT(44). In the pharmaceutical industry, PAT represents a transition from batch production to a more dynamic approach. As far as the CQA of the final product is concerned, the device CPP is important at some point in post-processing. Manufacturers can produce high quality products with minimal waste and at low cost[45]. The use of continuous manufacturing technologies leads to improved product quality and waste reduction (CMT). If you understand the up and down effects of a simple method, you will be better able to deal with common cause variations[46].

PAT TOOLS

Three main PAT tools must be used to complete a successful PAT project:

- To determine which parameters are the CPP, knowledge acquisition and multivariate analysis must be used using advanced software programs, packages such as Design of Experiments, large. selection of raw data, and statistical analysis.
- On-line and real-time analysis are used to track various CPP parameters. Fiber optics, Raman spectroscopy and biology are also in this category (NIRS)[47].

CHALLENGES

Quality by Design (QbD) is an important part of medical quality improvement, but it is difficult to implement because many people do not know how to do medicine. In the pharmaceutical industry, a complete scientific understanding of manufacturing is paramount to the final product[5]. Pharmaceutical companies are united in their support for the implementation of QbD. FDA has requested that wording such as criteria for selecting and rejecting quality attributes, regulatory review standards, and criteria for other analytical methods be included in the final rule. Ten major barriers to QbD adoption. The importance of each of these questions is determined by the type of medicine and its area of acceptance[48].

The first four challenges arise in companies:

- Internal justice (disruption between cross-functional areas, for example R&D and production, or quality and legal);
- Among QbD practitioners, this is a major issue due to unknown implementation time and costs.
- Lack of understanding of Critical Quality Attributes (CQA) concepts (eg data management issues) due to lack of implementation technology.
- To implement QbD, how do we ensure the investment of our suppliers and contract manufacturers?[49]

The following six challenges are directly related to management:

- This is because managers are not familiar with QbD programs due to the lack of clear guidelines for the industry.
- Current distribution mechanism Legal benefits promised do not protect people.
- Lack of coordination among inter-governmental agencies.
- Interaction with companies is currently not required for QbD.
- Although implementing QbD in practice has its problems and concerns, businesses and government agencies can work together to address them[50].

CURRENT STATUS

To ensure a high quality product, the ICH Q8 drug development guidelines emphasize the importance of ensuring proper controls and understanding of the manufacturing process. Product characteristics and processes, including product performance, must be assessed in drug development in terms of risk, totality and efficacy[51]. You don't need to check the final product for quality and all its features. Data processing and analytical technique (PAT) can be used to ensure that factory products meet predetermined quality standards with the help of managers. Legislators should be informed

by law about the company's product knowledge and decisions, as well as its management strategy to ensure product quality conditions[52]. The FDA's Center for Research and Analysis says, "QbD enables a systematic approach to product and process design and development"[53].

QbD includes the following key elements:

- The CQA must be determined and the product specification specified.
- Methodology and parameters Link raw materials to CQAs to perform risk assessment.
- Create a design space.
- Find a solution to the problem and put it into action.
- Product management and continuous improvement are inextricably linked.

For the company and its public contracting business, quality by design (QbD) is a priority. On the other hand, delivery time provides greater quality assurance when production methods and controls can be used[54].

FUTURE PERSPECTIVE

QbD will be widely used in the future. In development and production, event-based methods are used extensively. This is common for many companies because the factories are difficult to access or the PAT department is unwilling to cooperate. Our current output is fine as long as it doesn't exceed the capacity of our hardware. When we get to the most advanced and critical parts of the standard approach set for PAT using control methods, we run into a big hurdle. So, for example, the European Medicines Agency cooperates on the basis of QbD with other regulatory bodies (EMA)[55]. The "deferral" was also introduced by the EU. The project shows a strong focus on quality recognized by the European Medicines Agency (EMA). The European Medicines Agency (EMA) accepts applications that fully comply with the Quality through Policy (QbD) concept. Mathematical and analytical methods, including risk management methods, are used at various stages of drug design, development and production to ensure that drugs meet quality standards. For QbD implementation purposes, the US/EMA reference is to the ICH document Q8-Q12. The continued development of manufacturing and analytical methods is the focus of ICH work at this time. These new ICH notes should be available in the near future[56].

CONCLUSION

The QbD approach has many advantages, including better understanding of products and processes, continuous improvement and the ability to measure TPP. A quality-based (QbD) approach to drug development improves the quality of medicines for patients, manufacturers and regulators. As a result of the law, the impact of the introduction of QbD will be strong. QbD has become an influential scientific tool for quality assurance in the pharmaceutical industry. Before launching a product on the market, the pharmaceutical industry's priority is to obtain regulatory approval.

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