Review Article

Quality by Design: A Roadmap for Quality Pharmaceutical Products

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Abstract

Quality by design (QbD) refers to a new approach to product development that could increase efficiencies, provide regulatory relief and flexibility, and offer important business benefits throughout the product life cycle. QbD is increasingly becoming an important and widely used technique in the pharmaceutical industry. QbD can be considered to be system-based approach to the design, development, and delivery of any product or service to a consumer. It is an approach to pharmaceutical development that begins with predefined objectives and emphasizes product and process understanding and process control. Process parameters and quality attributes are identified for each unit operation. Benefits, opportunities, and steps involved in QbD of pharmaceutical products are described. The aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product. Quality cannot be tested into products, but quality should be built in by design. It includes the quality target product profile, critical quality attributes, and key aspects of QbD. It also gives comparison between product quality by end product testing and product quality by QbD. The foundation of QbD is ICH guidelines. Hence, if we identify the cause and effect relationship between the various inputs and responses by carefully designed experiments, we can control the quality of the product by simply controlling the inputs such as raw material specifications or process parameters.

Keywords: *Critical quality attributes, pharmaceutical manufacturing, process analytical technology, quality by design*

Introduction

Quality by design (QbD) means designing and developing formulations and manufacturing processes to ensure predefined product quality objectives. In pharmaceutical industry, QbD identifies characteristics that are critical to quality from the perspective of patients and health care team, translates them into the attributes that the drug product should possess, and establishes how the critical process parameters (CPPs) can be varied to consistently produce a drug product with the desired characteristics. The main concept of QbD is that all final product critical quality attributes (CQAs) are affected by raw materials and process parameters. Hence, if we identify the cause and effect relationship between the various inputs and responses, we can control the quality of the product by simply controlling the inputs such as raw material specifications or process parameters. As a result, the final product will always conform to the quality specifications.[1]

In all cases, the product should be designed to meet patients' needs and the intended product performance. Strategies for product development vary from company to company and from product to product. The approach can also vary and should be outlined in the submission. An applicant might choose either an empirical approach or a more systematic approach to product development or a combination of both. A more systematic approach to development (also defined as QbD) can include, for example, incorporation of prior knowledge, results of studies using design of experiments, use of quality risk management (QRM), and use of knowledge management (ICH Q10) throughout the lifecycle of the product. Such a systematic approach can enhance achieving the desired quality of the product and help the regulators to better understand a company's strategy. Product and process understanding can be updated with the knowledge gained over the product lifecycle.[2]

Quality by Design

This concept was first outlined by well-known quality expert Joseph M. Juran

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on QbD (J.M.: "Juran on QbD"). With assistance of several biopharmaceutical companies, pilot programs were started to explore QbD application and understandings.[3]

As per ICH Q8 (R2) Pharmaceutical Development 2009, QbD is defined as "A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management." It means designing and developing formulations and manufacturing processes to ensure predefined product quality objectives.[4]

Benefits of Quality by Design

- QbD is good business[5]
- Eliminate batch failures
- Minimize deviations and costly investigations
- Avoid regulatory compliance problems
- Organizational learning is an investment in the future
- QbD is good science
- Better development decisions
- Empowerment of technical staff.

Opportunities of Quality by Design

- Efficient, agile, flexible system
- Increase manufacturing efficiency, reduce costs, and project rejections and waste
- Build scientific knowledge base for all products
- Better interact with industry on science issues
- Ensure consistent information
- Incorporate risk management.

Components of Quality by Design

Quality target product profile

The Food and Drug Administration (FDA) defines quality target product profile (QTPP) as the quality attributes related to safety and efficacy of the product. It may include route of administration, dosage form, delivery systems, dosage strength (s), container closure system, pharmacokinetic consideration, and drug product quality criteria (e.g. sterility, purity, stability, and drug release).[6]

It is important to acknowledge that QTPP should only include patient relevant product performance elements. For example, tablet density or hardness may be included as a specification for process monitoring but may not be included in QTPP. Furthermore, if particle size is critical to the dissolution of a solid oral product, then the QTPP should include dissolution but not particle size.

For a new drug application (NDA), the QTPP is under development, while for the abbreviated NDA (ANDA) product, the QTPP is well established based on the properties of the drug substance (DS), characterization of the reference listed drug (RLD) products, RLD label, and intended patient population. Therefore, a generic drug product is expected to have the same QTPP as that of brand or reference product.[7]

Critical quality attributes

Once QTPP has been identified, the next step is to identify the relevant CQAs. A CQA is defined as "a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality." This indicates that CQAs are subsets of QTPP that has a potential to be altered by the change in formulation or process variables. For example, QTPP may include additional quality attributes of the drug product such as strength and dosage form, which are not the part of CQA as it will not change during drug development process. However, QTPP attributes such as assay, content uniformity, dissolution, and permeation flux will also be a part of CQA as they may be altered by formulation or process variables.[8]

Identification of CQA can be performed based on prior knowledge and/or QRM. Prior knowledge may be attained by literature review, manufacturing experience, technology transfer, stability reports, raw material testing data, adverse event report, and recalls. QRM, on the other hand, applies various tools to identify and prioritize potential CQA.[9]

Quality risk management

The FDA defines QRM as a systematic process for the assessment, control, communication, and review of risks to the quality of the drug product across the product life cycle. The goal of QRM is, therefore, to identify risks within a process or event, analyzing the significance of these risks, and takes appropriate measures to mitigate such risks if deemed unacceptable.[10]

QRM is integral part of QbD as it helps in identifying the extent of the impact of critical material attributes (CMA) and CPP on CQAs, which can eventually assist in prioritizing the CQAs. They are particularly important in complex processes, especially which are involved in cases of biologics or biosimilar. The FDA suggests various tools that can be applied for QRM, among which the relevant ones are discussed below:

Failure mode effects analysis

Failure mode effects analysis is one of the most commonly used risk assessment tools in the pharmaceutical industry. It is a systematic and proactive method to identify and mitigate the possible failure in the process. Failure modes represent any errors or defects in a process, material, design, or equipment. Once failure modes are established, FMEA tool evaluates the effect of these failures and prioritizes them accordingly. Risk control activities can then be performed to avoid such failure modes. Since FMEAs require a good understanding of cause and effects, a thorough process understanding is essential.[11,12]

Fault tree analysis

The fault tree analysis (FTA) was first introduced by Bell Laboratories and is one of the most widely used methods in system reliability, maintainability, and safety analysis. FTA is a deductive analysis approach for resolving an undesired event into its causes in a top-down fashion. Typically, assumed failures are listed at the top as a main event and all of the associated elements in that system that could cause the event are listed as subsequent branches till the root condition or cause is identified. The results are represented pictorially in the form of a tree of fault modes and their relationship is described with logical operators such as "AND" and "OR."[13]

Hazard Analysis and Critical Control Points

The Hazard Analysis and Critical Control Points (HACCP) provides detailed documentation to show process or product understanding through identifying parameters to control and monitor.[14] The definition of hazard includes both safety and quality concern in a process or product. Examples of hazards within the pharmaceutical setting include environmental aspects of the facility (environmental conditions and hygiene aspects), material flow, manufacturing steps, personnel hygiene and gowning, and technical aspects relating to process design. HACCP consists of the following seven steps:

(i) Conduct a hazard analysis and identify preventive measures for each step of the process
(ii) Determine the critical control points
(iii) Establish critical limits
(iv) Establish a system to monitor the critical control points
(v) Establish the corrective action to be taken when monitoring indicates that the critical control points are not in a state of control
(vi) Establish system to verify that the HACCP system is working effectively
(vii) Establish a record-keeping system.

Design space

A design space is a multidimensional combination of input variables (e.g. material attributes), their interactions, and process parameters that have been demonstrated to provide assurance of quality. A design space may be constructed for a single unit operation, multiple unit operations, or for the entire process. Although according to the FDA guideline, defining design space is optional since the product and process understanding can be established without a formal design space, nevertheless, such approach can assist to better understanding and attain overall control of a system.[15]

In this regard, one can apply one-factor-at-time approach, which varies only one factor or variable at a time while keeping others constant. However, design of experiments (DoE) approach that varies several input variables simultaneously is more efficient when studying two or more factors. Factorial designs (full or fractional) and the response surface methodology are characteristic tools for this kind of application. The key advantages of using DoE approach are summarized as follows:

- Exhaustive information from a minimum number of experiments
- Study effects individually by simultaneously varying all operating parameters
- Can account for variability in experiments, process, materials, or operators
- Able to provide understanding about the interaction between various variables
- Determine acceptable ranges of CPPs contributing to identification of a design space.

Basic steps involved in DoE approach are as follows:

Defining input and output variables and range

Based on prior knowledge and risk assessment, the input variables and their range can be defined. Screening design like full or fractional factorial design can also be utilized to identify the range of various variables. The response variable should be a CQA or closely related to them.[16,17]

Select appropriate experimental design and perform the run

The choice of experimental design may depend on the purpose of the study (e.g. a screening, optimization, or robustness study) and the factors and interactions involved in the studied and available resources (e.g. literature knowledge, time, labor, cost, and materials).[18,19]

Model diagnostic

After obtaining the initial model, foremost step is to check whether the model is appropriate or not. In general, the significance of a parameter is verified using the analysis of variance (ANOVA) method. ANOVA is a statistical method based on the *F*-test to estimate the significance of model terms. It involves subdividing the total variation of a data set into variation due to main effects, interaction, and residual error. Model terms can be added or eliminated from the analysis, depending on their significance. The new model, with more or fewer model terms, is again forced through this cycle until all terms included in the model satisfy *F*-test statistics.[20,21]

Once the overall model satisfies an ANOVA check, the next step is to determine what cannot be modeled (i.e. the errors resulting from the model). This is done using a residual analysis technique.[22]

Illustration of design space

The design space can be tabulated or graphically displayed using various methods. Graphically, the design space can

be illustrated by the following:

- Contour plots: A contour plot is a graphic representation of the relationships among three numeric variables in two dimensions. Two variables are for X-and Y-axes, and a third variable Z is for contour levels. You can interactively identify, label, color, and move contour levels, and change the resolutions of rectangular grids to get better contouring quality and performance
- Three-dimensional plots: These plots are used to illustrate and study the effect of two input variables on an output variable simultaneously. These plots are ideal for showing the process shape; however, contour plots are more useful for determining or displaying acceptable operating ranges for process parameters
- Overlay plots: When there is more than one quality characteristic in the design space, the use of overlay plots is helpful. The overlay window shows the design space, which indicates the various combinations of the factors that will provide results within the acceptable range.[23]

From the FDA perspective, regulatory submission in regard to design space should include the following aspects:

- Description of design space, including critical and other relevant parameters. The design space can be presented as ranges of material inputs and process parameters and graphical representations (contour, interaction or overlay plots) or through more complex mathematical relationships
- The interaction of various input variables (e.g. material attributes and/or process parameters) and their relationship with the CQAs. Interaction plots can be used to illustrate these relationships
- Data supporting justification of design space, which can include but not limited to historic knowledge base, conclusions from QRM, and experimental studies
- The relationship between the proposed design space and other unit operations or process steps
- Results and conclusions of the studies, if any, of a design space across different scales
- Justification that the control strategy ensures that the manufacturing process is maintained within the boundaries defined by the design space.

Control strategies

ICH Q10 defines a control strategy as "a planned set of controls derived from current product and process understanding that assures process performance and product quality.[24] The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in process controls, finished product specifications and the associated methods and frequency of monitoring and control." A control strategy ensures that the process is maintained within the boundaries described by design space.

Specifically, the control strategy may include:

1. Control of input material attributes (e.g. DS, excipients, and primary packaging materials) based on an understanding of their impact on processability or product quality
2. Product specifications
3. Procedural controls
4. Facility controls, such as utilities, environmental systems, and operating conditions
5. Controls for unit operations that have an impact on downstream processing or end product quality (e.g. the impact of drying on degradation, particle size distribution of the granulate on dissolution)
6. A monitoring program (e.g. full product testing at regular intervals) for verifying multivariate prediction models.

It is important to appreciate that when developing a control strategy, a manufacturer can consider implementing single or multiple points of control for a specific CQA, depending on the risk associated with the CQA and the ability of individual controls to detect a potential problem. For example, with sterilized DSs or biotechnological/biological products, there is an inherent limitation in the ability to detect low levels of bacterial or viral contamination in the DS. In these cases, end product testing is considered to provide inadequate assurance of quality, so additional points of control (e.g. attribute and in-process controls) are incorporated into the control strategy.[25]

Quality by Design and Abbreviated New Drug Application

Historically, FDA ensured high quality of generic drug products by requiring two fundamental evidence during ANDA filling pharmaceutical equivalence and bioequivalence. Drug products are considered pharmaceutical equivalents if they contain the same active ingredient (s) are of the same dosage form, route of administration, and strength or concentration. Bioequivalence, on the other hand, refers that the rate and extent of absorption of the test drug have no significant difference with that of the reference drug, when administered at the same molar dose under similar experimental conditions in either a single dose or multiple doses.[26]

While this approach has been successful, it should be acknowledged that majority of generic drug products approved under this paradigm were solution and immediate release oral products, which are inherently simple in design.[27]

However, three key observations were found in the recent QbD-based ANDA filling:

1. Exhaustive information being presented with no justification or interpretation of data. Often, there were no conclusions from the data presented
2. Improper use of basic QbD terminology, such as CQAs, CPPs, and in particular, design space

3. Prior knowledge is often presented without necessary context.

Such issues may indicate an ineffective communication and collaboration between FDA and generic drug companies in regard to QbD implementation. It is expected that as the time will progress, more effective knowledge database will be developed and communicated from both sides that can help in resolving these critical issues.[28]

Advantage of Implementing Quality by Design

1. The ability to design products and processes and bring fewer setbacks at critical stages such as scale-up, validation, and transfer
2. Since the operation is working in a well-defined design space, it allows greater flexibility of adjusting variables within such space
3. Greater regulatory flexibility based on a science-based approach to risk management
4. Ability to continue to optimize and improve the manufacturing operation without facing additional regulatory filings or scrutiny
5. Faster time to market and reduced rework, resulting in reduced costs and increased revenues.[29,30]

Challenges

1. Lack of understanding regarding the QbD is the cause and also the major limitation for QbD implementation. Pharmaceutical companies are traditionally tuned to care more about the end product, with little emphasis on the science-based understanding of the process involved
2. Collaboration and consensus between field inspectors and the FDA review and compliance sectors on how to handle QbD remains an unmet challenge
3. The majority of pharmaceutical companies feel that there is a need for more tangible guidance on how to actually implement QbD. Companies want clarification from the FDA on QbD terminologies, acceptable methods, criteria to select and deselect CQAs, standards by which to judge adequacy of controls, and criteria for analytical method substitution
4. There is a need for greater cooperation across multiple disciplines within the company, including process development, manufacturing, and quality control for effective implementation of QbD
5. Pharmaceutical companies also feel that QbD would decrease time to file approval application or could provide unnecessary information to the regulatory authority that might create an obstacle in the approval process.[31]

Conclusion

The goal of a well-characterized method development effort is to develop a reliable method that can be demonstrated with a high degree of assurance to consistently produce data meeting predefined criteria when operated within defined boundaries. QbD can be applied to the development and evaluation of analytical methods.

QbD is a common understanding on the concepts of ICH Q8, Q9, and Q10 and will be essential in the process of formulation. It also explains application of QbD principles and tools to drug product and process development. It can be concluded that QbD principles and tools play an important role in facilitating a higher level of process understanding and create opportunities for investigation and developed control strategies in formulation and process development.

The regulatory authorities also need to harmonize the regulatory requirement. It is accepted that the challenges and concerns associated with the implementation of QbD can only be resolved if there is efficient communication between the industry and the regulatory bodies.

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Conflicts of interest

There are no conflicts of interest.

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