JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

A Thorough Analysis of Quality by Design (QbD)

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ABSTRACT

The pharmaceutical industry is constantly looking for fresh methods to ensure and enhance the safety, efficacy, and quality of its products. But medication recalls, Contrary evidence has recently been shown by manufacturing failure costs, scaling up challenges, and regulatory complexity. With the conventional approach of quality by testing (QbT), end product testing plays a key part in ensuring the performance and quality of the item. Process understanding is limited, and important parameters for the process. Therefore, regulatory authorities are concentrating on putting quality by design (QbD) into practice. QbD is a science-based strategy that reduces process variation and enhances process understanding by enabling process-control solutions. The pharmaceutical sector is presently experiencing a substantial shift to optimize its research and development procedures, offer enhanced flexibility and control over manufacturing processes, and lessen the weight of regulations. However, there are significant issues and a lack of knowledge surrounding the application of QbD guidelines in the medical industry. Therefore, the goal of this review paper is to address implementation-related issues and offer a thorough grasp of the numerous facets of QbD.

Keywords: critical material attributes, critical process parameters, design space, Quality by design, Quality risk management, Design space, Quality target product profile

INTRODUCTION

The developing a superior product and production process to reliably achieve the intended functionality of the product is the goal of pharmaceutical development. The creation of the design space, specifications, and production controls are supported by scientific understanding thanks to the data and expertise gathered from research on pharmaceutical development and production expertise. One source of in formation for quality risk management is data frompharmaceutical development studies. The understanding that goods can not be assessed for quality means that quality should be included into the design from the beginning. It is important to see modifications to the activities involved in formulation and manufacturing that take place during development and lifecycle management phases as chances to learn more and strengthen the foundation of the design space. Likewise, it might be beneficial to include pertinent information discovered through studies yielding unexpected outcomes. The applicant proposes the design space, which is subject to regulatory review and approval. It is not

deemed a change to work inside the design space. Exiting the design area is seen as a change, and doing so would often result in the start of a regulatory post approval change procedure[1].

In every situation, the product's design should take the demands of the patients and its intended functionality into account. Product development strategies vary from company to company and from one product to the next. Additionally, the strategy may differ and must to be included in the proposal. An application may decide to design a product using an empirical technique, amore methodical one, or a combination of the two. A more methodical approach to development also known as quality by design might involve, among other things, using quality risk management, incorporating existing knowledge, and study findings from trials. The application of knowledge management (ICH Q10) during the course of the product's lifecycle. This kind of methodical approach can improve the product's ability to meet quality standards and aid regulators in comprehending a company's business plan. Knowledge acquired throughout the course of the product lifecycle may be used to refresh understanding of the product and process[2].

Quality by Design (QbD)

Regulators believe that, when applied alone, gradual and haphazard process operations improvement would have minimal impact on overall process quality or performance.

In order to ensure product quality, a more comprehensive approach offered by QbD has to be utilized. "An organized method of development that starts with predetermined goals and places a strong emphasis on understanding the product and the process as well as process control, all supported by high-quality risk management and solid science " is how the ICH Q8 guideline defines QbD. (3) QbD may assist in anticipating the risk potential of different operations throughout the manufacture of new or marketed products, ensuring that appropriate control techniques can be implemented on schedule. Qbd offers a foundation for streamlining and enhancing the manufacturing process without requiring extra regulatory filings or attention because it is a science-based methodology. Additionally, QbD-generated process understanding can facilitate a more seamless technology transfer[4].

Definition [ICH Q8 (R1)]

A systematic development strategy based on well-defined goals and a strong emphasis on process control, well-founded on sound science and high-quality risk management, as well as product and process understanding[5].

Pharmaceutical Quality by Testing

Testing of raw materials, manufacturing processes for drug substances, specified drug products, in-process material testing, and final product testing all guarantee the quality of the final product. They can be utilized in the production of the products if they fulfill the FDA-approved parameters set out by the producer or other standards like USP for drug substances or excipients[6]. Drug makers are often asked to do thorough internal testing, such mix homogeneity, tablet hardness, etc., since only a small percentage of the millions of tablets examined are tested. This is done to make sure the results of the Moreover, in-process testing satisfies FDA approval requirements criteria. Additionally, without submitting modifications to the FDA, manufacturers are not allowed to alter any process parameters or the operational parameters included in the batch record. Consequently, the volume of Chemistry, Manufacturing, and Controls (CMC) amendments submitted to the FDA in the last several years has been over whelming. For instance, the Received by the FDA Office of Generic Drugs more than three thousand CMC supplements a year between 2005 and 2006[7]. In the conventional approach, quality is guaranteed by a series of predetermined production procedures and thorough testing. Due to a lack of variability

characterization, a lack of knowledge on the identification and measurement of crucial process factors, and regulatory caution, excessively strict and unyielding criteria are created, which restrict the release of goods with potentially acceptable clinical performance[8].The FDA and industry invest a great deal of resources in the debate over allowable variability, the necessity of further testing controls, and the creation of specification acceptance criteria. These discussions frequently center on acceptance limitations or statistical issues. Manufacturers may not know how drug ingredients, manufacturing procedures, and other factors impact the quality of their goods, or they may choose not to tell FDA reviewers about this, which leads to the conservatism of FDA reviewers. All items are evaluated identically under the existing regulatory framework, regardless of the danger to the customer[9]. This has the dual impact of giving low-risk items an excessive amount of review time and, more importantly, detracting from the evaluation of high-risk products by taking away necessary resources. The CMC review evaluations of medications with narrow therapeutic index (NTI) and complicated dosage forms (transdermals, topicals, and modified release products) are essentially the same as those of simple dosage forms (many oral solid products with instant release). Furthermore, applications may examine all CMC data identically, without regard to criticality, necessitating the extensive use of resources for each application[9].

In conclusion, the old framework mostly relies on end product testing and limiting manufacturing process flexibility to achieve product quality and performance. The current

system of regulatory reviews gives little to no consideration to how the development of a successful and effective manufacturing process may ensure the end product's quality.. Consequently, the difficulties associated with process scale-up are frequently overlooked, especially when dealing with complicated dosage formulations. Mechanistic knowledge is not a major factor in the process of deriving product specifications, which are frequently developed using test data from one or more batches (sometimes not at production size). Lastly, continual improvement is hamperedbytheonerousregulatoryrequirementofsupplementsplacedonfirms for carrying out small, gradual modifications to production processes and controls[10].

Pharmaceutical Quality by Design

Based on clearly-defined objectives, quality by design (QbD) is a systematic approach to development that emphasizes understanding goods and processes, as well as process control based on sound science and quality risk management (ICH Q8(R)).

QbD is the process of designing and developing manufacturing processes and formulae to provide a defined level of product quality. Consequently, knowledge of how formulation and manufacturing processes impact product quality and their control is essential to QbD.

Relevant documents from the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), such as ICH Q8, Pharmaceutical Development, ICH Q9, Quality Risk Management, and ICH Q10, Pharmaceutical Quality Systems, can be used to obtain a general understanding of how quality by design contributes to drug product quality. The definition of quality provided by ICH Q8 is "the suitability of either a drug substance or drug product for its intended use". This expression captures attributes such as uniqueness, perseverance, and innocence. As stated in ICH Q6A, "Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities," highlighting the significance of specifications[11].

Pharmaceutical QbD is a methodical, scientific, risk-based, comprehensive, and proactive approach to drug development that starts with predetermined goals and places a strong emphasis on understanding products and processes as well as process control[12]. It comprises developing production processes and formulations to satisfy

preset requirements for product quality. QbD identifies the attributes that patients believe are crucial to quality, transforms those attributes into attributes that the medication product ought to possess, and ascertains how the crucial process parameters may be altered to consistently produce a therapeutic product with the intended attributes[13].This is achieved by the establishment of connections and the identification of sources of variability between the features of the product and the formulation and manufacturing process elements (drug ingredient and excipient quality, process parameters, etc.). Using this knowledge, a robust and flexible manufacturing process that can consistently produce a product over time is then put into practice[13].

Quality by Design (QbD)

Regulators believe that, when applied alone, gradual and haphazard process operations improvement would have minimal impact on overall process quality or performance.

In order to ensure product quality, a more comprehensive approach offered by QbD has to be utilized. The ICH Q8 guideline describes QbD as a systematic approach to development that starts with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management."(14) QbD may assist in anticipating the risk potential of different operations throughout the manufacture of new or marketed products, ensuring that appropriate control techniques can be implemented on schedule. Qbd offers a foundation for streamlining and enhancing the manufacturing process without requiring extra regulatory filings or attention because it is a science-based methodology. Additionally, QbD-generated process understanding can facilitate a more seamless technology transfer[15].

Advantages of QBD

- Good business is QbD
- Get rid of batch errors
- Reduce deviations and expensive inquiries
- Learning inside an organization is an investment in the future.
- QbD is an excellent science.
- Better choices for growth
- Encouraging technical personnel
- Prevent issues with regulatory compliance (16)

PRODUCT QUALITY IMPLEMENTATION STEPS

1. Creation of a novel molecular entity

a) Preclinical research

b) Nonclinical research

c) Clinical research

d) Scale up

e) Market submission Acceptance

2. Manufacturing

a) Design Space

b) Analytical Technology Processing

c) In-the-moment Quality Assurance

3. Third Strategy of Control a)Risk-based

decision-making

b) continuous improvement

c) product performance (17)

Components of QbD

A] QTPP, or quality target product profile

The FDA defines QTPP as the product's quality attributes linked to safety and effectiveness. It may involve the following: the administration route, dosage form, distribution strategies, dose strength(s), container closure mechanism, pharmacokinetic consideration, and requirements for the quality of the drug product (such as stability, sterility, purity, and drug release).

Recognizing that QTPP should only contain patient-relevant product performance information is crucial. Tablet hardness or density, for instance, could be specified for process monitoring but might not be in QTPP. Furthermore, if a solid oral product's ability to dissolve depends on particle size, then solubility but not particle size should be included in the QTPP[18]. The QTPP is being developed for an NDA, however it has already been established for an ANDA product based on the drug substance (DS) attributes, RLD product characterization, targeted patient population, and RLD label.(19) The Consequently, it is anticipated that a generic medicine product will have the same QTPP as a brand-name or reference product. The following is a typical example of QTPP for instant release dosage form in the development of generic products[20].

B] Critical quality attributes (CQA)

Finding the pertinent CQAs comes next after QTPP has been determined. To assure the intended product quality, A physical, chemical, biological, or microbiological property or feature must fall within the proper range, distribution, or limit. This is referred to as a CQA. (21) By modifying formulation or process factors, it is implied that CQAs are subsets of QTPP that are susceptible to modification. As an illustration, QTPP could also contain the drug product's potency and dose

form, among other quality aspects, which are not covered by CQA since they won't change while the medication is being developed. But as formulation or process factors may change QTTP properties including assay, content uniformity, dissolution, and permeation flux, they will also be included in CQA. A list of possible CQAs is provided for the instant release dosage form in the development of generic products[22].

CQA can be determined using historical data and/or quality risk management (QRM). Prior knowledge may be obtained through literature reviews, manufacturing experience, technology transfer, stability reports, raw material testing data, adverse event reports, and recalls. However, on the contrary, quality risk management uses a number of instruments to find and rank possible CQA. The next section goes into further information about QRM.

C] Quality risk management (QRM)

As per the FDA, QRM is a systematic process that involves recognizing, controlling, revealing, and evaluating risks related to the quality of a drug product across its entire life cycle. It is therefore the goal of QRM to identify risks inside a process or event, assess the significance of these risks, and, if deemed unacceptable, take appropriate action to mitigate such risks[23].

QRM is a crucial component of QbD since it aids in determining the degree to which key material attributes (CMA) and critical process parameters (CPP) have an influence on CQAs. This information can then be used to help prioritize the CQAs. They have a specific role in intricate procedures, notably those involving biologics or biosimilars[24].

The FDA recommends using a number of tools for QRM, some of which are covered below and are pertinent:

Analysis of failure mode and effects (FMEA)

One of the instruments for risk assessment that is most frequently used in the pharmaceutical sector is the FMEA. It is a methodical and proactive way to find and reduce the possibility of a process failure. Any mistakes or flaws in a procedure, substance, design, or piece of machinery are represented as failure modes. Following the identification of failure modes, the FMEA tool assesses the impact of these failures and ranks them appropriately. Then, risk control procedures may be followed to steer clear of these failure scenarios .A comprehensive process understanding is crucial since FMEAs need a solid grasp of causes and consequences[25].

Case study: FME Approach to QRM of a typical manufacturing process

Using prior knowledge about the drug's substance, excipient, and manufacturing process, risk assessment was first conducted in this case study. Subsequently, risk assessment and analysis were conducted based on the potential damage associated with each identified risk[26].Fault tree analysis (FTA)

Developed by Bell Laboratories, the fault tree analysis (FTA) is one of the most used techniques for analyzing system dependability, maintainability, and safety. FTA is a top-down deductive analytical method for determining the reasons of an undesirable event. Until the primary condition or cause is identified, assumed failures are frequently shown as the primary event at the top, followed by a list of all the connected system components that may have produced the event as branches. The links between the failure modes in the tree of results are explained by logical operators like "AND,""OR," and so on. A case study on cross-contamination between two goods utilizing an FTA is shown in Figure. A fault tree diagram may develop quickly and become rather complicated, as this graphic illustrates. (27)

D] Hazard analysis and critical control points (HACCP)

Through the identification of control and monitoring criteria, HACCP offers comprehensive documentation to demonstrate process or product expertise. A process or product's concern for both quality and safety is included in the definition of danger. The facility's surroundings (hygiene and environmental elements), material flow, production procedures, staff hygiene and gowning, and technical aspects of process design are a few examples of dangers in the pharmaceutical industry. HACCP includes the following. aaThere are seven steps in the process: (i) Create a system to monitor the critical control points; (ii) decide what corrective action should be taken if monitoring indicates that the critical control points are not under control; (ii) create a system to ensure that the HACCP system is operating efficiently; and (iii) create a record-keeping system. The first two tasks involve analyzing potential hazards and determining preventive measures for each step. The other tasks involve

identifying critical control points, establishing critical limits, and creating a system to monitor the critical control points. (28)

TARGET PRODUCT PROFILE (TPP)

The TPP not only outlines the medication at a certain stage of development but also outlines the general objectives of the drug development program., according to a new FDA guidance. Typically, the TPP is structured in accordance with the main parts of the medicine label and connects the development of drugs to certain ideas meant to be mentioned in the label. As per ICH Q8, pharmaceutical development should include "identification of those attributes that are critical to the quality of the drug product, taking into consideration intended usage and route of administration." This means that the intended usage and route of administration would be considered through the TPP. (29)

The TPP, which is centered on the patient and labeling, is comparable to the medicinal product's "user interface."

Therefore, one would anticipate that a generic version's TPP and that of its reference product would be identical. The TPP may be implemented differently in a generic product by a modified formulation or design. A drug product's features and efficacy assessments might vary between a reference and generic version depending on how it was implemented.

Modifications to the TPP may necessitate fresh safety or effectiveness evidence for a novel medication. Regarding Reformulation, It's possible that reformulation-related changes to a product's performance or features won't call for such information.

The TPP influences formulation and process development scientists' decisions in several ways. A pharmaceutical scientist's job is to convert the qualitative TPP into the target product quality profile (QTPP), which is then used in a quality by design procedure[30].

QUALITY TARGET PRODUCT PROFILE

An overview of the medication development program that focuses mostly on safety and efficacy and is explained in terms of labeling ideas.

1 Overview

2 Clinical Pharmacology

3 Indications and Usage

4 Contraindications

5 Warnings

6 Precautions

7 Adverse Reactions

8 Drug Abuse and Dependency

9 Over dosage

10 Dosage and Administration

11 How Supplied

12 Animal Pharmacology and/or Animal Toxicology

13 Clinical Studies [31]

A logical progression of the target product profile in terms of quality. The drug product's quality features are what it needs to consistently deliver the therapeutic benefit stated on the label in order to build a formulation strategy and maintain an efficient and targeted formulation effort.

- It makes it easier to identify in the Quality Target Product Profile what the patient or consumer needs or considers important (such important Quality Attributes, or CQAs).
- Determines the best ways to mitigate risks.
- Makes optimal use of tools and enablers (e.g., integrating biopharmaceutics and QbD).
- Produces and facilitates information exchange.

A patient-centered, iterative, learning life-cycle method that maximizes therapy results and decision-making.A medicinal product designed, developed, and manufactured in accordance with the Quality Target Product Profile, with parameters (such dissolving rates and release/acceptance criteria) that correspond to the product's intended in vivo performance[32].

Risk assessment:

- Risk is characterized as the result of combining the likelihood that harm will occur and the seriousness of that harm.
- Risk assessment involves identifying and assessing potential threats associated with a given circumstance[33].
- ICH Q9 According to quality risk management, there is some risk involved in the production and use of pharmaceutical products. Therefore, scientific information should be used to evaluate the danger to quality. The identification of critical and non-critical variables will aid in the development of control strategies for in-process, row material, and final testing.

Risk assessment approaches can be used to identify and rank variables (e.g., process, equipment, input materials) that may have an impact on the quality of the final product, based on historical knowledge and early experimental results. Although the first set of possible parameters maybe rather long, additional research may be able to refine and rank the list (for example, by combining mechanistic models with experimental design). Experimentation may be used to further narrow the list by identifying the importance of individual factors and any relationships. After the identification of the important factors, a deeper degree of process understanding may be attained by further studying them (for example, by combining experimental design, mathematical modeling, or investigations that result in mechanistic understanding)[34].

Risk Assessment Method

The following are some of the several ways that risk can be determined:

1. Failure Mode Effect Analysis

2. Failure Mode Effect And Criticality Analysis

3. Fault Tree Analysis
4. Hazards Analysis and Critical Control Point
5. Hazard Operability Analysis
6. Preliminary Hazard Analysis
7. Risk ranking and Filtering

1. Failure mode effects analysis (FMEA):

One of the risk-assessment instruments that is most frequently employed in the pharmaceutical sector is the FMEA. It is a methodical and proactive way to find and lessen the possibility of a process breakdown. Failure modes are any errors or defects in a process, material, design, or piece of equipment.. After failure modes are identified, the FMEA tool assesses their impact and ranks the failures in order of importance. Then, risk control procedures may be followed to steer clear of these failure scenarios. A deep comprehension of the process is necessary since FMEAs need a solid grasp of causes and consequences[35].

2. Fault tree analysis (FTA):

Fault tree analysis (FTA), created by Bell Laboratories, is one of the most used methods for evaluating the dependability, maintain ability, and safety of systems. FTA is a top-down deductive analytical method for identifying the reasons of an undesirable event. Assumed failures are usually displayed as the primary event at the top, followed by any related system components that may have contributed to the event as branches, until the underlying issue or cause is found. Logical operators such as "AND", "OR," and soon are used to explain there relationships between the fault modes in the tree of results[36].

3. Hazard analysis and critical control points (HACCP):

Through the identification of control and monitoring criteria, HACCP offers comprehensive documentation to demonstrate process or product expertise. A process or product's concern for both quality and safety is included in the definition of danger. The facility's surroundings (hygiene and environmental elements), material flow, production procedures, staff hygiene and gowning, and technical aspects of process design are a few examples of dangers in the pharmaceutical industry. The following seven elements make up HACCP: The steps involved in this process are as follows: (i) do a hazard analysis and develop preventative measures for eachphase; (ii) identify critical control points; (iii) create critical limits; and (iv) set up a system to monitor the critical control points.(v) specify the course of remedial action to be followed in the event that monitoring shows that the critical control points are not under control. (vi) set up a method to ensure the HACCP system is operating efficiently, (vii) put in place a mechanism for keeping records[37].

4. Hazards Analysis and Critical Control Point:

The HACCP management system analyzes and controls physical, chemical, and biological hazards at every stage of the production process, from the handling and procurement of raw materials to the manufacture, distribution, and consumption of the finished product[38].

5. Hazard Operability Analysis:

A planned or ongoing process or operation is examined systematically and methodically in a Hazard and Operability (HAZOP) analysis to find and assess issues that might endanger people or property, hinder effective operation, or both.

Originally designed to study chemical process systems, the HAZOP approach has now been expanded to include various kinds of systems, sophisticated operations, and software systems.

During a series of meetings, a multidisciplinary team known as the HAZOP team implements a qualitative approach known as a HAZOP that is based on guidelines[39].

6. Preliminary Hazard Analysis:

An early high-level screening tool called a preliminary hazard analysis (PHA) may be used to identify, characterize, and prioritize the most important risks at the conceptual stage of a facility design. Using the broad HAZID approach previously mentioned, this technique may also be utilized to determine potential outcomes and likelihood of occurrence and to offer recommendations for hazard reduction.

PHA delivers information early in the project's life cycle and takes very little time to complete. Still, it's a straightforward method that relies on team expertise, isn't methodical, and is mostly applied in situations when there isn't much information accessible regarding the pipeline design[40].

7. Risk ranking and Filtering:

The ELO system used in chess has been tweaked to create the RISK ranking system. Initial rating points are awarded to you, and you can gain or lose rating points by playing opponents.

The difference in your ranking points at the beginning of the game determines how much of a change there will be[41].

TOOLS OF QUALITY BY DESIGN:

Design of Experiments (DOE):

The Design of experiments (DOE) is a productive process for organizing tests in a way that allows for the analysis of the data collected to provide reliable and impartial results. "Design of experiment" refers to a systematic, ordered approach for figuring out how variables influencing a process relate to the process's outcome. In experiments, we purposefully alter one or more process variables (or factors) to see how the alteration affects other response variables. The efficient process of designing experiments to enable the analysis of collected data to provide reliable and impartial findings is known as the (Statistical) design of experiments (DOE). Establishing the goal of an experiment and choosing the study's process variables are the first steps in DOE.

Use of Design of experiment :

Experiment design is used to assess responses at various levels of controlled variables, identify conditions under which the ideal (maximum or lowest) response is attained, identify sources of response variance, and construct a response prediction model.

The first steps in DOE involvement. The planning of a comprehensive experiment is known as an experiment design.

Select experimental designs in advance of doing the experiment. Increase as much "Information" as possible for a given quantity of experimental effect. Choosing the process parameters for the investigation and establishing the goal of the experiment[42].

Advantages of using DOE approach are summarized as following:

- Comprehensive data from the fewest possible experiments
- As you concurrently alter every operational parameter, examine each consequence separately.
- Can take into account variations in the materials, operators, processes, or experiments Able to provide knowledge on how different factors interact
- Determine allowable ranges for crucial process parameters that help identify a design space[43].

Process Analytical Technology (PAT):

In order to ensure the quality of the end product, PAT is defined as "a system for designing, analyzing, and controlling manufacturing through measurements, during processing of critical quality and performance attributes of raw and in-process materials and processes.""Improving understanding and control over the manufacturing process is consistent with our current drug quality system: quality should be built-in or by design; it cannot be tested into products. "This is the stated purpose of PAT. The essential and crucial process parameters found in process characterization studies, along with their allowed ranges, establish the design space. The main emphasis of on-, in-, or at-line PAT applications is on these characteristics. Real-time process availability testing (PAT) evaluations have the potential to serve as the foundation for ongoing feedback loops and enhance process resilience. As a technique for PAT and beneficial in RTRT (Real Time Release Testing), NIR tracks the particle size, dissolution, polymorphism, blend uniformity, granulation, and content uniformity[44].

PAT steps

The design and optimization of medication formulations and manufacturing processes follow a three-step approach that combines Read et al.'s literature and guidelines: design, analyze, and control.

Experimentation is carried out in the design stage to determine which quality characteristics are associated with a particular unit operation and which raw material attributes and process factors have the greatest influence on the quality of the finished product. The QTPP, CPP, and CQA are then determined using this knowledge, and they must be taken into account while designing an efficient PAT-based control strategy for the process[45].

During the analysis stage, a process measurement system enables real-time(oral most real-time) monitoring of all CQAs and CPPs using direct or indirect analytical procedures with the required analytical instruments in order to detect the specified quality attribute, process parameters, and raw material characteristics.

Lastly, control strategies establish the understanding of relationships among CQAs, CPPs, and QTPPs and offer adjustments to guarantee control of all critical attributes. This allows decision-makers to know what to do in the event that process performance deviates from the ideal path or product quality deviates from the desired attributes[46].

PAT tools

The PAT framework offers a multitude of instruments to support the understanding of scientific, risk-managed pharmaceutical development, manufacturing, and quality control. They can be divided into four classes according to the PAT guidelines

(1)Multivariate tools for data collection, analysis, and design;
(2)Analyzers of processes;

(3)Tools for process control;

(4)Tools for knowledge management and ongoing development.

Whether the sample is removed or not, process analysis falls into three categories, which are at-line, on-line, and in-line, as stated by the FDA's PAT guidance paper[47]:

(1)On-line: Measurement when the sample is withdrawn from the manufacturing process and may be reintroduced into the process stream;

(2)At-line: Measurement where the sample is taken out of, separated from ,and examined in close proximity to the process stream;

(3)In-line: Noninvasive or invasive measurement in which the sample is not taken out of the process stream.

It is clear that PAT greatly aids in the implementation of QbD. It is capable of uninterrupted real-time process monitoring to get material and technical parameters online. PAT improves knowledge of technology, particularly the connection between CPP and CQA, which helps achieve registration simplification and quality improvement[48].

Utilizing PAT

Spectroscopic methods, such as nuclear magnetic resonance (NMR), Raman, and UV–VIS spectroscopy, are typically employed. In addition, various PAT analytical techniques such as focused beam reflectance measurements (FBRM), nanometric temperature measurement (MTM), near infrared spectroscopy (NIR), and tunable diode laser absorption spectroscopy (TDLAS), are widely used in the pharmaceutical manufacturing industry and are essential for the real-time monitoring of processes.

Since NIR is a speedy, non-invasive analytical technique that doesn't require a lot of sample preparation, it is one of the PAT instruments that has attracted a lot of interest in the pharmaceutical industry. NIR is described in both the United States and the European Pharmacopeia. Utilizing on-line, in-line, or at-line spectroscopic measurements, it has been used to the identification and characterization of raw materials and intermediates, dosage form production analysis, and the prediction of one or more variables in process streams or end product streams (composition). It is the tool in the production process that is most often utilized[49].

Comprehending QbD in pharmaceuticals

In 2002, the FDA introduced cGMP in order to address GMP's limitations. (50) During production, cGMP emphasizes the "software," or management level, and clearly and tightly defines staff responsibilities. On the other hand, GMP places more weight on an employee's credentials and training than their job description, and these comparatively laxer standards are still widely used in many developing nations.

Another problem that arose when cGMP was put into place is that pharmaceutical companies had significantly stricter standards than other industries, such the automotive, aerospace, and electronics sectors. It is, however, extremely difficult to maintain a steady state for all the parameters, and small-scale environmental fluctuations are unavoidable. The problem then occurs with the FDA clearance documentation for new products; the

corporation is only permitted to present a set number in the report since "details" and "the authenticity of the process" are seen to be crucial by cGMP. It is plausible that certain product batches may fail to satisfy the exacting requirements. In order to address this issue, the FDA and the International Conference on Harmonization (ICH) started studying other industries. In 2004,QbD was added to the chemical manufacturing control (CMC) review pilot program with the goal of enhancing the quality and safety of pharmaceutical drugs in order to attain a desired state for pharmaceutical manufacturing based on engineering and scientific knowledge. Through the CMC project, the roles of Design Space, QbD, and real-time release have been assessed. Years later, the ICH released a set of guidelines: the ICH Q11 Development and Manufacture of Drug Substances; ICH Q8 Pharmaceutical Development; ICH Q9 Quality Risk Management; and ICHQ 10 Pharmaceutical Quality System[46]. In line with the FDA's current drug quality system ideology, which states that "quality cannot be tested into products; it should be built-in or should be by design,"Quality by Design (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" in the ICH Q8 guideline[51].

Elements of QbD

Although there are several claims on the components of QbD, the most generally acknowledged one is that QbD is made up of the following characteristics. (52)

Information on the dosage form, distribution methods, dose strength(s), and other relevant details are included in the Quality Target Product Profile (QTPP). It is a prospective summary of the quality attributes of a drug product to be achieved, in addition to the variables affecting pharmacokinetic characteristics (like dissolution and aerodynamic performance) and drug product quality criteria (like sterility, purity, stability, and drug release) appropriate for the intended marketed product. This involves taking into account the medication product's dose strength(s) and container sealing mechanism. The characteristics of an output material, such as the final pharmaceutical product, that are related to its physical, chemical, biological, and microbiological aspects, are referred to as CQAs, or important quality attributes. Potential drugproduct CQAs come from the QTPP and/or prior information. These CQAs guide the development of the product and process and should fall within an acceptable range, limit, or attribute of an input material. CMAs must fall under the appropriate range, distribution, or limit in order to ensure that the medication component, excipient, or in-process material has the desired quality.

Critical Process Parameters (CPPs) are factors that are monitored before, during, or after a process that has a significant effect on the yield, purity, and appearance of the final product.

Different from CQAs, CMAs are identified as part of the product design and understanding phase in the Quality by Design (QbD) process. While CMAs are for input materials, such as drug substances, excipients, and in-process materials, CQAs are for output materials. For a stage in the manufacturing process that comes after, the CMA of an intermediate might become the CQA of that intermediate. While identifying CPPs and having a solid grasp of scale-up principles are part of process design and understanding, it is especially crucial to relate CMAs and CPPs to CQAs. According to QbD, CMAs and CPPs can differ within the defined Design Space without having a major impact on CQAs, and as a consequence, the finished product's quality will fulfill the QTPP[53].

Procedures for Implementing QbD in Pharmaceuticals

Generally speaking, the following procedures may be followed to practically apply QbD in the creation of novel pharmaceutical products[54]:

1. Describe the intended product performances and the QTPPs;

2. CQA identification;

3. 3. potential CMA and CPP identification;

4. Configuring and carrying out the DoE to connect CMAs and CPPs to CQAs and obtain sufficient data on the influence of these factors on QTPP. Following that, a process Design Space ought to be established, resulting in a final product with the intended QTPP;

5. Determine and manage the sources of variation in the production process and the raw materials;

6. Keep an eye on and refine the production process to guarantee a constant level of product quality. Thus far, the majority of pharmaceutical unit operations may be made more efficient by utilizing the QbD idea. (55)

CONCLUSION

The objective of a thoroughly documented method development process is to create a dependable technique that can be shown with a high level of assurance to

When working within predetermined parameters, consistently generate data that satisfies predetermined requirements. Analytical method development and assessment can benefit from the application of QbD.

To ascertain the linkages, all plausible components (the inputs) and all crucial analytical answers (the outputs) are examined throughout method development. A technique that mimics what is stated for process development in ICH Q8 and Q9 identifies critical analytical elements. Analytical scientists actively collaborate in the development and operational laboratories to actively partner in the process of quality by developing methods and identifying and controlling factors that may lead to potential method failures. Throughout the process, it is necessary to maintain a corporate knowledge repository to make sure important data is recorded. This repository can then be examined and expanded upon later, allowing lessons learned to be applied to both the particular method being considered and to other similar methods being applied to other products. A repository of this kind (following the principles outlined in the draft ICH Q10) will allow for method modification and continual improvement throughout the course of its existence.

A QbD strategy based on a risk-assessed change control mechanism should be used in place of ongoing analytical technology transfer exercises and ICH validation. A risk assessment needs to be done each time a method is modified. When a modification is found to have the potential to move the method outside of its established design space, it is important to evaluate the method and, if necessary, carry out an equivalency exercise to make sure the method's performance requirements are still met. This will make it possible to improve methods through internal change control processes, and it might even make switching between various techniques (like HPLC and NIR) more simpler to execute.

The QbD approach for analytical methods, which includes risk assessment, robustness testing, and ruggedness testing, is more rigorous than ICH validation requirements (Q2(R1)). It also assesses method variability compared to specification limits, a crucial attribute for determining method suitability. The new QbD process offers greater regulatory flexibility, as method performance criteria can be registered instead of the method itself. The method used can be used as an example of achieving required performance criteria, and any changes would be covered by internal change control procedures.

REFERENCES

1. Woodcock J. The concept of pharmaceutical quality. American Pharmaceutical Review. 2004 Nov 1;7(6):10-5.
2. Singh, J. (2015). International conference on harmonization of technical requirements for registration of pharmaceuticals for human use. Journal of Pharmacology and Pharmacotherapeutics, *6*(3), 185-187.FDA U. Guidance for industry. Q8 (R2) pharmaceutical development. Maryland: Food and Drug Administration. 2009.
3. Looby M, Ibarra N, Pierce JJ, Buckley K, O'Donovan E, Heenan M, Moran E, Farid S.S, Baganz F. Application of quality by design principles to the development and technology transfer of a major process improvement for the manufacture of a recombinant protein. Biotechnology progress. 2011 Nov; 27(6):1718-29.
4. Ojha A, Bhargava S. International council for harmonisation (ICH) guidelines. In Regulatory affairs in the pharmaceutical industry 2022 Jan 1 (pp. 47-74). Academic Press.
5. Nasr M. Risk-based CMC review paradigm. In Advisory committee for pharmaceutical science meeting 2004 Jul 20.
6. Hussain A.S. A collaborative search for efficient methods of ensuring unchanged product quality and performance during scale-up of immediate-release solid oral dosage forms. In Pharmaceutical Process Scale-Up 2001 Dec 12 (pp. 347-374). CRC Press.
7. Scale-Up N.S, Changes P. Chemistry, Manufacturing, and Controls. vitro release testing and in vivo bioequivalence documentation. 1997 May.
8. Narke R.M, Singh R.P. Overview of QbD: A challenge to the pharmaceutical industry. Asian Journal of Pharmaceutical Research and Development. 2014 Jul 1:42-53.
9. Elder D. ICH Q6A Specifications: test procedures and acceptance criteria for new drug substances and new drug products: chemical substances. ICH Quality Guidelines: An Implementation Guide. 2017 Sep 27:433-66.
10. Sheinin E, Williams R. Chemistry, manufacturing, and controls information in NDAs and ANDAs, supplements, annual reports, and other regulatory filings. Pharmaceutical research. 2002 Mar; 19:217-26.
11. Patel H, Parmar S, Patel B. A comprehensive review on Quality by Design (QbD) in pharmaceuticals. development. 2013; 4(5).
12. Benny P, Nair S.K, Krishna kumar K, Dinesh kumar B. Artificial Intelligence in Drug Discovery and Development.
13. Food U. Administration, D. Guidance for Industry: Q8 (R2) Pharmaceutical Development. Center for Drug Evaluation and Research: Silver Spring, MD, USA. 2009.
14. Looby M, Ibarra N, Pierce JJ, Buckley K, O'Donovan E, Heenan M, Moran E , Farid S.S, Baganz F. Application of quality by design principles to the development and technology transfer of a major process improvement for the manufacture of a recombinant protein. Biotechnology progress. 2011; 27(6):1718-29.
15. Pawar M.A, Khandelwal M. H. An Overview-International Conference on Harmonisation and ICH (Q1) Stability Testing Guideline for Pharmaceutical Development.
16. Munson J, Freeman Stanfield C, Gujral B. A review of process analytical technology (PAT) in the US pharmaceutical industry. Current Pharmaceutical Analysis. 2006 Nov 1;2(4):405-14.
17. Lionberger R, Johnston G, Yu L, Buehler G, Olson M, Winkle H. Quality by design for generic drugs. Pharmaceutical Technology. 2009 Oct 2;33(10).
18. Lionberger RA, Lee S.L, Lee L, Raw A, Yu L.X. Quality by design: concepts for ANDAs. The AAPS journal. 2008 Jun; 10:268-76.
19. US Food and Drug Administration. Quality by design for ANDAs: an example for immediate-release dosage

forms. US Department of Health and Human Service (FDA, Rockville, MD, 2012). 2012.
20.Chang RK, Raw A, Lionberger R, Yu L. Generic Development of Topical Dermatologic Products, Part II: Quality by Design for Topical Semisolid Products. The AAPS Journal. 2013; 3(15):674-83.
21.McConnell J, Nunnally B.K, McGarvey B. Quality Risk Management and Variability Reduction. Journal of Validation Technology. 2011 Aug 1;17(3).
22.Fahmy R, Kona R, Dandu R, Xie W, Claycamp G, Hoag S.W. Quality by design I: application of failure mode effect analysis (FMEA) and Plackett–Burman design of experiments in the identification of "main factors" in the formulation and space for roller-compacted ciprofloxacin hydrochloride immediate-release tablets. AAPS pharmscitech. 2012 Dec; 13:1243-54.
23.White E. Risk management for aseptic processing. Journal of Validation Technology. 2009 Apr 1; 15(2):25.
24.Frank T, Brooks S, Murray K, Reich S, Sanchez E, Hasselbalch B. Defining process design space: A risk-management case study (Part 1). Pharmaceutical Technology. 2011; 35(7):77-9.
25.Thomson N.M, Singer R, Seibert K.D, Luciani C.V, Srivastava S, Kiesman W.F, Irdam E.A, Lepore J.V, Schenck L. Case studies in the development of drug substance control strategies. Organic Process Research & Development. 2015 Aug 21; 19(8):935-48.
26.Ward S.E, Davis A, editors. The Hand book of Medicinal Chemistry. The Royal Society of Chemistry; 2023 Feb 3.
27.Yu L.X, Furness M.S, Raw A, Outlaw K.P, Nashed N.E, Ramos E, Miller S.P, Adams R.C, Fang F, Patel R.M, Holcombe F.O. Scientific considerations of pharmaceutical solid polymorphism in abbreviated new drug applications. Pharmaceutical research. 2003 Apr; 20:531-6.
28.Miller S.P, Raw A.S, Yu L.X. Scientific considerations of pharmaceutical solid polymorphism in regulatory applications. Polymorphism: in the Pharmaceutical Industry. 2006 Feb 6:385-403.
29.Remy B, Glasser B.J, Khinast J G. The effect of mixer properties and filll level on granular flow in a bladed mixer. AIChE journal. 2010 Feb;56(2):336-53.
30.Leuenberger H, Puchkov M, Krausbauer E, Betz G. Manufacturing pharmaceutical granules: Is the granulation end-point a myth?. Powder Technology. 2009 Jan 31;189(2):141-8.
31.Miller CE. Chemometrics and NIR: A match made in heaven. Am. Pharm. Rev. 1999;2(2):41-8..
32.Chang RK, Raw A, Lionberger R, Yu L. Generic development of topical dermatologic products, part II: quality by design for topical semisolid products. The AAPS journal. 2013 Jul;15:674-83.
33.M c Connell J, Nunnally B, Mc Garvey B. Quality risk management and variability reduction. Journal of Validation Technology. 2011 Jul 1;17(3):12.
34.Gad SC, editor. Development of therapeutic agents handbook. John Wiley & Sons; 2011 Oct 24.
35.Akers J, Agalloco J.P. A revised aseptic risk assessment and mitigation methodology. Pharmaceutical Technology. 2017 Nov 2; 41(11):32-9.
36.Roy S. Quality by design: A holistic concept of building quality in pharmaceuticals. International Journal of Pharmaceutical and Biomedical Research. 2012; 3(2):100-8.
37.Hulebak K.L, Schlosser W. Hazard analysis and critical control point (HACCP) history and conceptual overview. Risk analysis. 2002 Jun; (3):547-52.
38.Viegas R.A, da Silva Mota F.D, Costa A.P, dos Santos F.F. A multi-criteria-based hazard and operability analysis for process safety. Process Safety and Environmental Protection. 2020 Dec 1; 144:310-21.
39.Fang H, Duan M. Offshore operation facilities: equipment and Procedures. Gulf professional publishing; 2014 Sep 5.
40.Haimes Y.Y, Kaplan S, Lambert J.H. Risk filtering, ranking, and management frame work using hierarchical holographic modeling. Risk Analysis. 2002 Apr;22(2):383-97.
41.Yu L.X, Amidon G, Khan M.A, Hoag S.W, Polli J, Raju G.K, Woodcock J. Understanding pharmaceutical

quality by design. The AAPS journal. 2014 Jul;16:771-83.
42.Sangshetti J.N, Zaheer Z, Mahaparale P.R, Chitlange S.S. Quality by design (QbD) in pharmaceuticals. Unique Publication, Aurangabad. 2015;20.
43.Mogal V, Dusane J, Borase P, Thakare P, Kshirsagar S. A review on quality by design. Pharm Biol Eval. 2016; 3:313-9.
44.Read E.K, Park J.T, Shah R.B, Riley B.S, Brorson K.A, Rathore A.S. Process analytical technology (PAT) for biopharmaceutical products: Part I. Concepts and applications. Biotechnology and Bioengineering. 2010 Feb 1; 105(2):276-84.
45.Read E.K, Shah R.B, Riley B.S, Park J.T, Brorson K.A, Rathore A.S. Process analytical technology (PAT) for biopharmaceutical products: Part II. Concepts and applications. Biotechnology and bioengineering. 2010 Feb 1; 105(2):285-95.
46.Scott B, Wilcock A. Process analytical technology in the pharmaceutical industry: a toolkit for continuous improvement. PDA Journal of Pharmaceutical Science and Technology. 2006 Jan 1;60(1):17-53.
47.Reich G. Near-infrared spectroscopy and imaging: basic principles and pharmaceutical applications. Advanced drug delivery reviews. 2005 Jun 15;57(8):1109-43.
48.Food and Drug Administration. Pharmaceutical current good manufacturing practices (cGMPs) for the 21st century—a risk based approach.
49.Mahapatra A, Meyyanathan S.N. Approach of analytical quality by design and regulatory need. IJHS.. 2022; 6:2572-92.
50.Chew W, Sharratt P. Trends in process analytical technology. Analytical Methods. 2010;2(10):1412-38.
51.Schweitzer M, Pohl M, Hanna-Brown M, Nethercote P, Borman P, Hansen G, Smith K, Larew J. Implications and opportunities of applying QbD principles to analytical measurements. Pharmaceutical Technology. 2010 Feb 2;34(2):52-9.
52.Yu L.X. Pharmaceutical quality by design: product and process development, understanding, and control. Pharmaceutical research. 2008 Apr;25:781-91.
53.Tomba E, Facco P, Bezzo F, Barolo M. Latent variable modeling to assist the implementation of Quality-by-Design paradigms in pharmaceutical development and manufacturing: A review. International journal of pharmaceutics. 2013 Nov 30; 457(1):283-97.
54.Rathore A.S. Roadmap for implementation of quality by design (QbD) for biotechnology products. Trends in biotechnology. 2009 Sep 1; 27(9):546-53.