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Quality by Design (QbD): Building and Enhancing Quality of Pharmaceuticals

Kanchan T. Sawarkar*, Alpana J. Asnani, Dinesh R. Chaple, Jaya S. Ikhar
Pharmaceutical Chemistry Department
Priyadarshini J. L. College of Pharmacy, Nagpur, Maharashtra, India

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ABSTRACT
Pharmaceutical industries are facing problems in quality control of pharmaceuticals. The traditional OFAT approach involved testing of finished products. It is time consuming, requires more cost and materials. The new AQbD approach instead aims to build a quality in the product during the process, so that the chances of product failure are minimized. In analytical process highly robust method can be developed by applying DoE tools. The MODR provide flexibility to method and avoid out of specification results. Earlier these procedures were carried out by conventional approach and finished product was tested by Quality by testing (QbT) approach but this approach was tedious, required more financial investments and many times failed to prove quality of pharmaceutical products. So, the new approach of Quality by design (QbD) was introduced in various synthetic and analytical procedures by USFDA in 2004. This new approach was more robust, fast and economical. It involves designing of experiments (DoE) in such a way that it will build Quality in product during the process thus reducing approval time from regulatory authorities.

KEYWORDS: Quality by testing (QbT), Quality by design (QbD, USFDA (United State Food and Drug Administration, Design of experiments (DoE).

I. INTRODUCTION

Dr. Joseph M. Juran, a quality scientist, coined the term "quality by design" (QbD). Quality, according to Dr. Juran, should be designed into a product, given the fact that the majority of quality issues and problems stem from how a product was designed in the first spot. According to Woodcock, quality product is one that is free of harmful substances, avoiding toxicities and giving desired therapeutic response.[1] According to US Food and Drug Administration increased testing does not always imply a better product. It is necessary to incorporate quality into the product. This goal can be achieved only when the experiments are designed properly in predefined way before performing actual procedure. Using various mathematical models and statistical tools we can determine various CPPs (Critical Process Parameters as independent variables) and CQAs (Critical Quality Attributes as dependent variables).[2]QbD concepts are well defined in ICH guidelines Q8 (R1): pharmaceutical development, Q9: quality risk management, and Q10: pharmaceutical quality system.[3] During late 2013 and early 2014, there were a few conferences that emphasised the application of the existing QbD concept to analytical method development processes. Several studies have found that analytical methods have similar opportunities for applying QbD to them as manufacturing processes do. AQbD aids in the development of a robust and cost-effective analytical method that is applicable throughout the product's lifecycle, thereby facilitating regulatory flexibility in analytical method. It refers to the ability to change method parameters within a method's design space, also known as the method operable design region (MODR).[4]

To date, there is no or little experience or exposure with the AQbD approach for analytical methods among analytical researchers. As it stands today, the pharmaceutical industry has many questions and requires a lot more discussion about AQbD implementation and its relationship with other components of pharmaceutical quality A review of the literature reveals that many researchers have applied QbD principles to the development of analytical methods, which are referred to as analytical QbD.[5] (AQbD)systems. Certainly, the majority of works were insufficient to define the method of AQbD implementation, because people believed that implementing DoE in an analytical method is QbD, which is incorrect. Furthermore, these reports have revealed a lack of knowledge about analytical target profiles (ATP), method performance characteristics, risk assessment, the selection of a DOE tool in the QbD

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process, the optimization of the MODR region and its verifications, and so on [6].

The analytical chemist's primary concern is to develop a suitable analytical method that works exactly as intended. In the current state of analytical chemistry, two approaches to analytical method development are used. The former is based on trial and error and studies one factor at a time (OFAT), where only one parameter is optimised for the expected results. Others remained constant in their response. This practise always results in a method for instrumental analysis with a narrow robust behaviour [7]. As a result, the analytical method development strategy (i.e., OFAT) is fraught with danger, and it always necessitates a revalidation protocol after method transfer or during alternative method development; as a result, it has been increasing the method's cost. The latter approach is Analytical Quality by Design (AQbD), which investigates scientific understanding in method implementation sequences and begins with product quality, which relates the risk assessment in method choice, then between method parameter and expected method results, and finally a region for high robustness and cost effectiveness. The AQbD paradigm is a preferred and recommended analytical method strategy in order to achieve regulatory flexibility and reduce out-of-specification (OOS), out-of-term (OOT), and out-of-control (OOC) (OOC) results.[8]

We know that USP and FDA require system suitability testing (SST) for an analytical method to ensure the ongoing performance of an analytical system and relevant methods. The United States Pharmacopoeia (USP-NF) and European Pharmacopoeia (EP) have recently updated related chapters in which flexibility is granted for an analytical method that can be changed without the need for revalidation if the AQbD approach has been implemented. The USP chapter 1058 states that SST can be used to replace an instrument's performance qualification; however, no further guidelines are provided. As a result, there are numerous questions which are still prevalent among regulatory experts, and thus QbD concept in analytical method development became a continuing topic of discussion and to find out more scope and applications [9].

The following are the seven steps of the QbD startup plan:

1. Engage the services of an independent Quality by Design expert.
2. Conduct a gap analysis on your organisation and processes with the help of an expert.
3. Host a basic quality by design workshop for all of your employees.
4. Analyse the expert's report and recommendations.
5. Create an implementation plan, timelines, and cost estimates.
6. Distribute the resources (or contract out).
7. Keep the independent expert on your team as your "Project Assurance" advisor [10].

Definition of QbD as per ICH guidelines

Quality by design

International conference on hominization (ICH) Q8 (R1) guideline defines QbD 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" [11]

Characteristics of QbD

- An approach based on sound knowledge and predefined objective
- Systematic as well as dynamic process
- It believes in building up a quality in product during the process rather than directly testing a finished product [12,13]
- It is applicable to both synthetic as well as analytical procedures
- It can be incorporated in any stage of drug development
- Always beneficial for growth of pharmaceutical industry [14]

Objectives of QbD approach

A) For process manufacturing

To achieve the quality product which will meet the specifications given by regulatory authorities, by more rapid and economical method. [15]

B) For analytical method development

To develop robust analytical method for the drug by avoiding out of specifications results which is applicable to quantitative as well as qualitative analysis. [16]

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TABLE I: HISTORICAL BACHGROUND of QbD [17]

YEAR	ACTIVITIES
1950	Operation windows
1970	QBD created by Joseph M Juran
Sept 2002	QBD concept integrated by USFDA in cGMP
Sept 2004	USFDA release final report in "Pharmaceutical cGMP"
Sept 2004	USFDA Guidance for Industry: PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Control
Nov 2009	ICH: Q8(R2) Pharmaceutical Development
Nov 2005	ICH: Q9 Quality Risk Management
June 2008	ICH: Q10 Pharmaceutical Quality System

Advantages of QbD

- Ensures Product efficacy
- Assurance of patient safety
- Promise to significant improvement in pharmaceutical industries
- Process designing as per target profile
- Science based risk assessment [18]
- Accelerate regulatory review and approval process
- Minimize product recall from market
- Avoid need of revalidation
- Avoid out-of-trend (OOT), out-of-specification (OOS), out-of-control (OOC) and out-of-statistical-control (OOSC) results. [19]

Quality by design approach versus conventional approach

In traditional practise, the analytical approaches used were based on one factor at a time (OFAT), which optimises one parameter at a time, others remained constant while waiting for the expected results. This method always resulted in a restricted robust behaviour, failure to comply with results and the approach always necessitates a revalidation protocol. Overall, it increased cost of the method. As a result, in the current analytical strategy the development of a method (e.g., OFAT) is fraught with danger. [20]

The AQbD investigates scientific understanding in method implementation sequences, beginning with product quality, which is linked to risk assessment in method selection, and then moving on to method implementation sequences. Between a method parameter and the expected results of the method and finally, an area for a high-quality, cost-effective strategy. DoE is a component of AQbD that indicates interaction like one of the input factors that has an impact on the procedure, response and outcomes. It also aids in determining which parameters should be kept constant and which should be changed. [21]

TABLE II: DIFFERENCE BETWEEN CONVENTIONAL APPROACH AND QbD APPROACH

Conventional approach	QbD approach
Quality assured by testing and inspection	Quality is built into the product and process by design and scientific approach
Quality assured by testing and inspection	Submission with product knowledge and process understanding [22]
Specifications are based on batch history	Specifications are based on product performance requirements
Process is frozen, discourages changes	Flexible process with design space, allows continuous improvement
Focuses on reproducibility ignores variation	Focuses on robustness which understands control variation [23]

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WHAT ADDITIONAL VALUE WILL AQbD PROVIDE TO THE INDUSTRY'S METHOD VALIDATION PROCESS?

From the perspective of lifecycle management, AQbD provides some flexibility in application because any post-approval parameter changes within the MODR will not be deemed a change by regulatory authorities, removing the need for revalidation.

AQbD, as a science-driven approach, provides the solution to support the creation of complicated analytical methods, in addition to providing more robust methods, minimising batch failure occurrence, and lowering long-term expenses for method updates.[24] When opposed to old ways, establishing methods with a new approach, such as AQbD, needs an initial investment in time and cost, just like any other adjustment to an existing process workflow. However, once adopted as the preferred tactical technique, the time required to complete a method's development could be drastically shortened. [25]

STEPS INVOLVED IN QbD

1. Quality Target Product Profile (QTPP)

The FDA recently issued instructions on developing a target product profile**:** The target product profile (TPP) has been defined as a "prospective and dynamic summary of the quality characteristics of a drug product that ideally will be achieved to ensure that the desired quality, and thus the safety and efficacy, of a drug product is realized" It is the quality features that a drug product should have in order to deliver the therapeutic benefit promised on the label in a consistent manner.

For Product QbD: The quality target product profile (QTPP) includes, but is not limited to, the following elements, Dosage form, Route of administration, Strength, Release or Delivery of the drug Pharmacokinetic characteristics e.g., dissolution, aerodynamic performance Drug product quality characteristics for intended use e.g., sterility, purity. [26]

For Analytical QbD: Recently PhRMA and EFPIA provided the definition of ATP: "ATP is a statement that defines the method's purpose which is used to drive method selection, design, and development activities." i.e., performance level characteristics, such as precision, accuracy, range, sensitivity, and the associated performance criterion. The common ATPs of an instrument like LC-MS/MS could be noise, heat block temperature, buffer pH, flow rate, column temperature. [27]

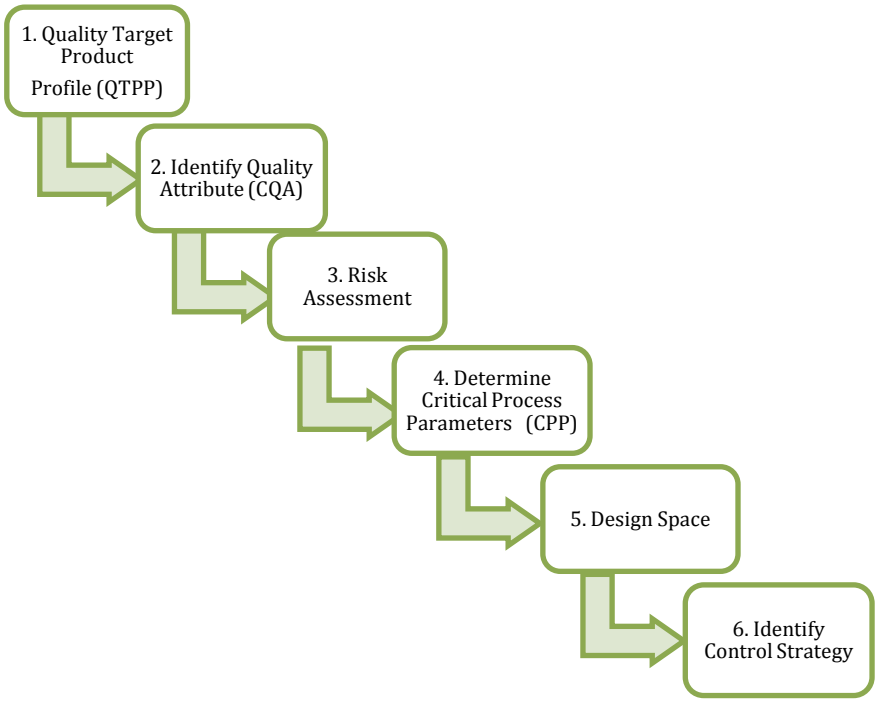

Figure I. Implementation strategy for QbD

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2. Identify Quality Attribute (CQA)

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".

For Product QbD: Appearance, Identification, Hardness, Uniformity of dosage, Physical form, Dissolution, Degradation products, Water content, Microbiological limits. [28]

For Analytical QbD: Typical CPAs for chromatographic experiments are sampling, sample preparation, standards, reagents, column chemistry, mobile phase composition, pH and flow of mobile phase, column temperature, detector selection etc. CQA's (responses) for the above parameters would be resolution, retention time, tailing factor, detection limit, robustness. [29]

3. Risk assessment

According to ICHQ9 guideline: "it is systematic process for the assessment, control, communication and review of risks to the quality across the method development". It entails a thorough examination of the aspects that may contribute to technique variability, like analyst methods, instrument configuration, measurement and method parameters, sample characteristics, sample preparation, and environmental conditions. [30]Traditional method development was based on testing the method after transfer whereas Analytical QbD necessitates the risk assessment step before method transfer and throughout the product life cycle. Risk Assessment can be carried out in three steps; (Figure II)

Principles of quality risk management are:

- Scientific knowledge-based evaluation of the risk to quality which eventually links to the protection of the patient.
- Adequate effort should be taken; formality and documentation of the quality risk management process should be done with the level of risk involved.

After identifying the ATP and CPA, AQbD focuses on a detailed risk assessment of the factors that may lead to possible method variability, such as analyst methods, instrument setup, measurement as well as method parameters, sample characteristics, environmental protection and sample preparation. [31]

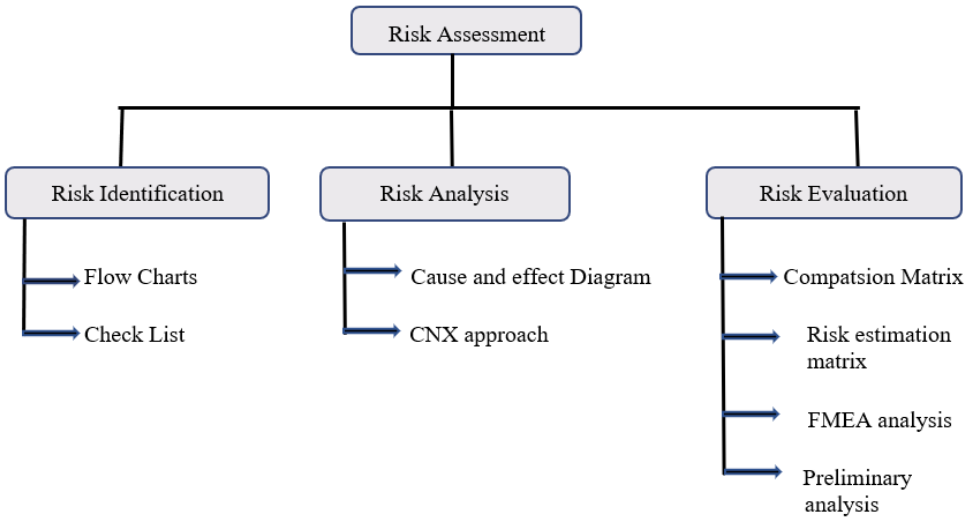

Figure II: Risk Assessment steps, management and tools (ICH Guidelines)

Methods of risk assessment as per the ICH guideline Q9 are as follows:

- Failure Mode Effects Analysis (FMEA)
- Failure Mode, Effects and Criticality Analysis (FMECA)
- Fault Tree Analysis (FTA)
- Hazard Analysis and Critical Control Points (HACCP)
- Hazard Operability Analysis (HAZOP)
- Preliminary Hazard Analysis (PHA)
- Risk ranking and filtering
- Supporting statistical tools [32]

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A. Risk Identification

Risk identification is critical for identifying and prioritising potential risks. These risks could include the instrument's operation method, reagent characteristics, cycle time, and so on. It is generally recommended to devise a backup method in case the primary method fails. To identify risk factors, flow charts and check lists are used. [33]

B. Risk Analysis

Second step in the process is Risk Analysis. Tools which are employed in this step include Ishikawa Fishbone Diagram and the CNX approach.

Ishikawa Fishbone Diagram: The Cause-and-Effect diagram, also known as the Ishikawa Fishbone diagram, categorises risks based on their source. It can also be identified by SIPOC by identifying the potential gap between (S= supplier, I- input, P= high level process, O= output, C= customer).

CNX approach: The risk factors are classified into the following categories using this approach [34]

High Risk Factors: e.g., Sample preparation methodology. These are to be fixed during the Method Development process.

Noise Factors: These are subject to an MSA study. Done through staggered cross nested study design and variability plots. These factors are subjected to robustness testing

Experimental Factors: e.g., Instrumentation and operation methods. Subjected to ruggedness testing and acceptable range is identified. The third step is Risk Evaluation which is done through Failure mode and effects analysis (FMEA) and the Matrix designs [35]

C. Risk Evaluation

Failure Mode Effect Analysis:

This is another way of risk analysis. In this process, the risks are given a number on a scale of 1 to 5, based on the severity, occurrence and detection, which on multiplying gives the Risk Priority Number. Then a bar graph is being plotted, considering RPN as the y-axis and the method attributes/factors as the x-axis. As per RPNs, all the factors are arranged in decreasing order by Pareto Chart & High-Risk Factors are categorized as 'Critical'. Method Attributes which got RPN more than 25 are given highest priority among all the risks, they should be taken into consideration as most Critical Material Attributes of API, which were required to be optimized &/or controlled. [36]

4. Determine Critical Process Parameters (CPP)

Any measurable input, such as an input material attribute, or output, such as an output material attribute, of a process step that should be regulated to achieve the desired product quality and process uniformity is referred to as a critical process parameter (CPP). For example, in the pilot and commercial processes, a material property such as moisture content should have the same target value. As the process scale changes, an operating parameter like air flow rate is expected to vary. [37,38]

5. Design Space

The ICH Q8 (R2) defines the design space as to ensure the quality of the product. The design space is defined as the multidimensional combination and interaction of the input variables and process parameters to provide assurance of the quality. One variable at a time experiments, statistically designed experiments, and modelling were all used to determine design space. Techniques for displaying design space are graphs (surface-response curves and contours). Equations can be used to explain it mathematically outlining the interrelationships of factors. [39]

Design of Experiments

a) Screening

It identifies the important method parameters (CMP) that must be taken into account during optimization studies. It also serves as a semioptimization tool for determining the required levels of CMA for an application.

b) Optimization

Quantitative metrics for critical method in variables (i.e., CMP) can be introduced at this point, either from screening or directly from risk assessment. It provides a scientific foundation for understanding the relationship between input variable quantities (CMP) and output response, which will have a significant impact on method performance and ATP. [40]

c) Selection of DOE Tools

The amount of input variables, knowledge of regulated parameters, and scientific understanding of the relationship between result and variable must all be considered while choosing a tool for DoE. statistical knowledge is essential to interpret the interaction and contribution of method variables (Xn) in method responses (Yn). [41] If the influence of all input variables and their interactions needs to be quantified, factorial design can be used, and RSM (response surface methodology) can be used to consider and optimise it. With fewer trial runs, the Taguchi method can be

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used. Plackett-Burman methods can be used to study large numbers of input variables without interaction effects. [42]

d) Method Operable Design Region (MODR) and Surface Plots

The contour plot is a 2D response plot representing the impact of two CPPs.

If the response is nonlinear and the relationship between the input variable and the technique response has a higher curvature effect, this contour is appropriate. Then, using mathematical models, MODR can be picked from contours. (Figure III) [43]

e) Model Validation

Following the development of the design space, a minimum of three confirmatory experimental runs should be done within the design space's designated range for verification. These observed results of experimental runs will be compared to predicted results from the Model Prediction equation using the Correlation Coefficient R2, which should be greater than 0.9**.** [44,45]

f) Method Verification

Validation of an analytical method is always carried out in accordance with the ICH Q2 (R1) recommendations under normal operating conditions (NOC) or under optimised conditions involving a collection of variables at one time. A joint accuracy and precision assessment at multiple method factor sites inside the chromatographic separation space can be used to verify a method (from MODR). This MODR multipoint verification certainly provides the highest probability on the method's ability to meet the ATP criterion [47].

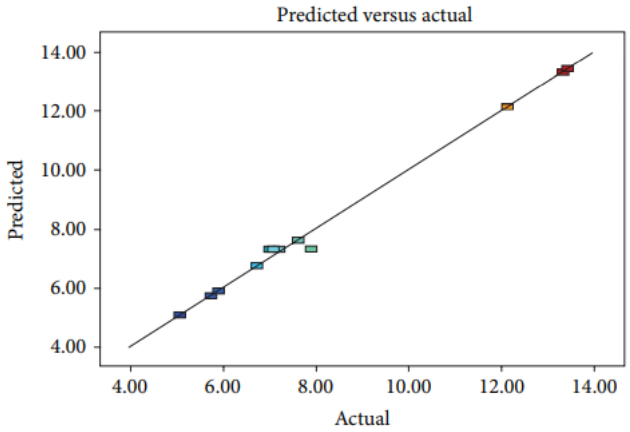

Figure III. Graph shows significant correlation between the predicted results and actual (experimental) values with good correlation coefficient

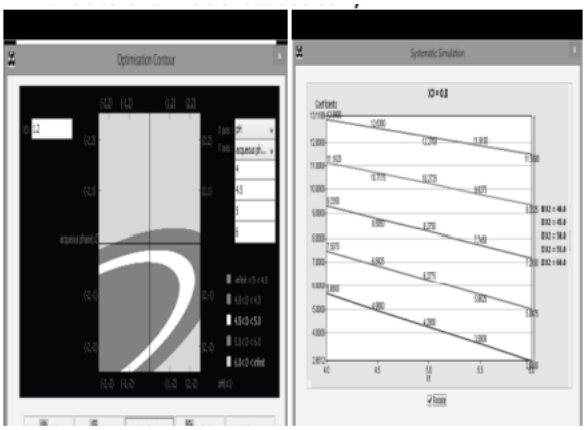

Figure IV: (a) Contour plot for MODR (retention time as metho response).
(b) Systematic simulation graph for retention time (*y*-axis) asmethod response at constant flow rate with change in pH [46]

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PAT and QbD

The FDA has generally accepted and defined PAT as "Systems for the analysis and control of manufacturing processes based on timely measurements during processing of critical quality parameters and performance attributes of raw materials, in-process materials, and processes to assure acceptable end-product quality at the completion of the process." [48]

The goal of PAT is to reduce costs while improving understanding and control of the manufacturing process. A set of scientific principles and PAT tools are
explained in guidance that can be used to gain a better understanding of the process and control [49]. QbD combined with Process Analytical Technology (PAT) tools improves process control and increases assurance that product quality attributes are consistently achieved. PAT is based on two major components: (a) knowledge of the scientific and engineering principles involved in the manufacturing process; and (b) identification of the variables that affect product quality [50]
A properly implemented PAT system should be capable of:

- Identify, understand, and manage the sources of variation;
- Establish a connection between raw materials, process parameters, and final product quality attributes.
- Control raw materials and processes to ensure CQAs are met. [51,52]

The language of QbD and PAT is constantly changing. Control Space or Normal Operating Ranges (NOR), Proven Acceptable Ranges (PAR), Experience Space, Knowledge Space, Continuous Improvement to Continual Improvement, Multivariate Data Analysis (MVDA) and the list continues. [53]
The PAT development action plan should include key components such as;

- Risk assessment
- Selection and evaluation of the feasibility of the appropriate PAT tool
- Deployment and in-process application development
- Monitoring, data collection and analysis
- Implementation [54].

6. Identify Control Strategy

According to ICH Q10, a control technique is "an arranged arrangement of controls got from current item and procedure understanding that guarantees procedure execution and item quality. The controls can incorporate parameters and ascribes identified with medication substance and medication item materials and segments, office and hardware working conditions, in procedure controls, completed item determinations and the related techniques and recurrence of observing and control." [55]

Based on current process and product knowledge, the control strategy provides an integrated overview of how quality is ensured. This phase also includes the eventual replication of optimised experiments, as well as data collection and analysis to ensure that the method remains under control. [56,57]

Lifecycle Management

When going through all of the elements of AQbD for a specific analytical method, the key steps that ensure the method's fitness for its intended use include method validation, verification, and transfer. The process of combining all of these elements is known as "lifecycle management of analytical procedure." If any unexpected method variability is found, appropriate steps will be taken to correct, anticipate, and prevent future problems, ensuring that the process remains under control. [58]

AQbD IN FUTURE …

Finally, it should be noted that regulators are currently evaluating the broad application of QbD principles to analytical methods. The MHRA launched a consultation titled: Application of Analytical Quality by Design concepts to pharmaceutical pharmacopoeial standards. This emphasises the growing importance of AQbD in providing better methods for ensuring efficient, cost-effective, and robust monitoring of drug products in terms of quality, efficacy, and safety, and ultimately protecting public health. [59]
The AQbD approach also encourages the use of innovative analytical methods in line with technological advancements, which can continue to evolve throughout the lifecycle of a drug product. [60]

II. CONCLUSION

An accurate data analysis tool is required to evaluate any process or system to ensure that it works as intended on a consistent basis. Implementing QbD is one of the approaches that is fervently advocated. QbD has optimised the process. Some regulatory bodies have made it mandatory. This review explains us, QbD is rapidly becoming a significant and widely used method in

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pharmaceutical item development. In case of Product QbD it fastens the approval-time and avoids revalidation of the Process. For AQbD, in the pharmaceutical industry, it is critical to ensure method reliability and non-variability in results. The end result of AQbD is an understanding of the process from method development to method transfer.

CONFLICT OF INTEREST

There is no conflict of interest.

REFERENCE

[1]. Mohurle, Mr Shrikant M., et al. "Quality by Design (QbD): An Emerging Trend in Improving Quality & Development of Pharmaceuticals." Saudi J Med Pharm Sci (2019): 1132-1138.

[2]. Jetani, Jay M., and K. Girish Pai. "A comparative review of the USFDA guidelines on process validation focusing on the importance of quality by design (QbD)." Research Journal of Pharmacy and Technology 10.4 (2017): 1257-1260.

[3]. Peraman, Ramalingam, Kalva Bhadraya, and Yiragamreddy Padmanabha Reddy. "Analytical quality by design: a tool for regulatory flexibility and robust analytics." International journal of Analytical chemistry 2015 (2015).

[4]. Das, Vedantika, Bhushan Bhairav, and R. B. Saudagar. "Quality by design approaches to analytical method development." Research Journal of Pharmacy and Technology 10.9 (2017): 3188-3194.

[5]. International Conference on Harmonization (ICH). "Tripartite Guidelines. ICH Q8 (R2): Pharmaceutical Development." (2009).

[6]. Gupta, A., and Neeraj Kumar Fuloria. "Short review on Quality by design: A new Era of Pharmaceutical drug development." Int. J. Drug Dev. & Res 4 (2012): 19-26.

[7]. Elliott, Phillip, J. Bi, and H. Zhang. "Quality by design for biopharmaceuticals: a historical review and guide for implementation." (2013).

[8]. Ganorkar, A., and K. Gupta. "Analytical quality by design: a mini review." Biomed. J. Sci. Tech. Res 1.6 (2017): 1555-1558.

[9]. Panda, Sagar Suman, et al. "Analytical quality by design (AQbD)-oriented RP-UFLC method for quantification of lansoprazole with superior method robustness." Journal of Liquid Chromatography & Related Technologies 40.9 (2017): 479-485.

[10]. Tome, Tim, Zdenko Časar, and Aleš Obreza. "Development of a unified reversed-phase HPLC method for efficient determination of EP and USP process-related impurities in celecoxib using analytical quality by design principles." Molecules 25.4 (2020): 809.

[11]. Rathore, Anurag S., and Helen Winkle. "Quality by design for biopharmaceuticals." Nature biotechnology 27.1 (2009): 26-34.

[12]. Rathore, Anurag S. "Quality by design (QbD)-based process development for purification of a biotherapeutic." Trends in biotechnology 34.5 (2016): 358-370.

[13]. Vogt, Frederick G., and Alireza S. Kord. "Development of quality-by-design analytical methods." Journal of pharmaceutical sciences 100.3 (2011): 797-812.

[14]. Mhatre, Rohin, and Anurag S. Rathore. "Quality by design: an overview of the basic concepts." Quality by design for biopharmaceuticals (2009): 1-8.

[15]. Weigl, Debbie, and Chester Meyers. "QbD and GMPs: How the Convergence of Science and Compliance Will Change the Way We Work." (2009).

[16]. Bhutani, Hemant, et al. "Quality by design (QbD) in analytical sciences: an overview." Quality Assurance 3 (2004): 39.

[17]. Bhadra, Rinkal M., Shailesh V. Luhar, and Sachin B. Narkhede. "A brief review on Quality by Design [QbD] a Systematic Approach." development 7: 9.

[18]. Malhotra, Girish. "QbA→ QbD: An imagination and creativity challenge." chimica oggi/Chemistry Today 29.2 (2011).

[19]. Drakulich, Angie. "Critical challenges to implementing QbD: A Q&A with FDA." (2009).

[20]. Peraman, Ramalingam, et al. "Analytical quality by design approach versus conventional approach: Development of HPLC-DAD method for simultaneous determination of etizolam and propranolol hydrochloride." Journal of Liquid Chromatography & Related Technologies 44.3-4 (2021): 197-209.

[21]. Alhakeem, Maher Abdulrazzaq, et al. "Analytical quality by design with the lifecycle approach: A modern epitome for analytical method development." Acta

Marisiensis-Seria Medica 65.2 (2019): 37-44.

[22]. Ramalingam, P., and B. Jahnavi. "QbD considerations for analytical development." Pharmaceutical Quality by Design. Academic Press, 2019. 77-108.

[23]. Kochling, Jianmei, et al. "A platform analytical quality by design (AQbD) approach for multiple UHPLC-UV and UHPLC–MS methods development for protein analysis." Journal of pharmaceutical and biomedical analysis 125 (2016): 130-139.

[24]. Fukuda, Isa Martins, et al. "Design of experiments (DoE) applied to pharmaceutical and analytical quality by design (QbD)." Brazilian Journal of Pharmaceutical Sciences 54 (2018).

[25]. Hubert, Cédric, et al. "Towards a full integration of optimization and validation phases: an analytical-quality-by-design approach." Journal of Chromatography A 1395 (2015): 88-98.

[26]. Vogt, Frederick G., and Alireza S. Kord. "Development of quality-by-design analytical methods." Journal of pharmaceutical sciences 100.3 (2011): 797-812.

[27]. Raman, N. V. V. S. S., Useni Reddy Mallu, and Hanimi Reddy Bapatu. "Analytical quality by design approach to test method development and validation in drug substance manufacturing." Journal of chemistry 2015 (2015).

[28]. dos Santos Moreira, Camila, and Felipe Rebello Lourenco. "Development and optimization of a stability-indicating chromatographic method for verapamil hydrochloride and its impurities in tablets using an analytical quality by design (AQbD) approach." Microchemical Journal 154 (2020): 104610.

[29]. Dobričić, Vladimir, et al. "AQbD-oriented development of a new LC method for simultaneous determination of telmisartan and its impurities." Chromatographia 80.8 (2017): 1199-1209.

[30]. Chandran, S., and R. S. P. Singh. "Comparison of various international guidelines for analytical method validation." Die Pharmazie-An International Journal of Pharmaceutical Sciences 62.1 (2007): 4-14.

[31]. Kumar, Palakurthi Ashok, et al. "simultaneous determination of related organic impurities of ibuprofen and paracetamol in combination solid dosage form by rp-hplc with qbd approach." Oriental Journal of Chemistry 33.3 (2017): 1461-1468.

[32]. Palakurthi, Ashok K., Thirupathi Dongala, and Lakshmi Narasimha R. Katakam. "QbD based development of HPLC method for simultaneous quantification of Telmisartan and Hydrochlorothiazide impurities in tablets dosage form." Practical laboratory medicine 21 (2020): e00169.

[33]. Nadpara, Nishendu P., et al. "Quality by design (QBD): A complete review." Int J Pharm Sci Rev Res 17.2 (2012): 20-8.

[34]. Mishra, Vijay, et al. "Quality by design (QbD) approaches in current pharmaceutical set-up." Expert opinion on drug delivery 15.8 (2018): 737-758.

[35]. Bandopadhyay, Shantanu, et al. "Integrated analytical quality by design (AQbD) approach for the development and validation of bioanalytical liquid chromatography method for estimation of valsartan." Journal of Chromatographic Science 58.7 (2020): 606-621.

[36]. Watts, C. "PAT–A framework for Innovative Pharmaceutical Development Manufacturing and Quality Assurance." FDA/RPSGB Guidance Workshop. 2004.

[37]. Juran, Joseph M. Juran on quality by design: the new steps for planning quality into goods and services. Simon and Schuster, 1992.

[38]. Jain, Shashank. "Quality by design (QBD): A comprehensive understanding of implementation and challenges in pharmaceuticals development." Int. J. Pharm. Pharm. Sci 6 (2014): 29-35.

[39]. Trivedi, Bhagyesh. "Quality by design (qbd) in pharmaceuticals." International Journal of Pharmacy and Pharmaceutical Sciences 4.1 (2012): 17-29.

[40]. Gandhi, Arijit, and Chandrani Roy. "Quality by Design (QbD) in pharmaceutical industry: tools, perspectives and challenges." PharmaTutor 4.11 (2016): 12-20.

[41]. Terzić, Jelena, et al. "Application of Analytical Quality by Design concept for bilastine and its degradation impurities determination by hydrophilic interaction liquid chromatographic method." Journal of pharmaceutical and biomedical analysis 125 (2016): 385-393.

[42]. Wu, Huiquan, Maury White, and Mansoor A. Khan. "Quality-by-Design (QbD): An integrated process analytical technology (PAT) approach for a dynamic pharmaceutical co-precipitation process characterization and process design space development." International journal of pharmaceutics 405.1-2 (2011): 63-78.

[43]. Urmi, Khandokar Farjana, Md Nawaz, and S. M. Islam. "Analytical quality by design approach to RP-HPLC method development and validation for simultaneous estimation of esomeprazole and naproxen in modified-release dosage form." Future Journal of Pharmaceutical Sciences 8.1 (2022): 1

[44]. Gurrala, Sunitha, et al. "Quality-by-Design Approach for Chromatographic Analysis of Metformin, Empagliflozin and Linagliptin." Journal of Chromatographic Science 60.1 (2022): 68-80.

[45]. Kala, Shabari Girinath, and Santhivardhan Chinni. "Bioavailability Enhancement of Vitamin E TPGS Coated Liposomes of Nintedanib Esylate Formulation Developed Using Quality by Design Approach." (2022).

[46]. Alhakeem, Maher Abdulrazzaq, et al. "Analytical Quality by Design with the Lifecycle Approach: A Modern Epitome for Analytical Method Development." Acta Medica Marisiensis 65.2 (2019).

[47]. Gayakwad, Ashwini, et al. "Quality by design: A new approach to analytical method development." World J. Pharmacecutical Res 4 (2015): 586-601.

[48]. Luttmann, Reiner, et al. "A comprehensive study in PAT-applications for a QbD-compliant development of continuous biopharmaceutical production." (2017).

[49]. Das, Parag. "The significance of collective role of QbD and PAT Tools in the Pharmaceu-tical Process Automation." International Journal of Pharmaceutics and Drug Analysis (2017): 369-375.

[50]. Das, Parag, S. Mishra, and B. Nayak. "The colossal role of QbD and PAT tools in the pharmaceutical process automation." Int. J. Pharma Res. Health Sci 5 (2017): 1909-1923.

[51]. Wu, Huiquan, and Mansoor A. Khan. "Quality-by-design: an integrated process analytical technology approach to determine the nucleation and growth mechanisms during a dynamic pharmaceutical coprecipitation process." Journal of pharmaceutical sciences 100.5 (2011): 1969-1986.

[52]. Munson, James, C. Freeman Stanfield, and Bir Gujral. "A review of process analytical technology (PAT) in the US pharmaceutical industry." Current Pharmaceutical Analysis 2.4 (2006): 405-414.

[53]. Hinz, Dirk C. "Process analytical technologies in the pharmaceutical industry: the FDA's PAT initiative." Analytical and bioanalytical chemistry 384.5 (2006): 1036-1042.

[54]. Vogt, Frederick G., and Alireza S. Kord. "Development of quality-by-design analytical methods." Journal of pharmaceutical sciences 100.3 (2011): 797-812.

[55]. Gurrala, Sunitha, et al. "Quality-by-Design Approach for Chromatographic Analysis of Metformin, Empagliflozin and Linagliptin." Journal of Chromatographic Science 60.1 (2022): 68

[56]. Guideline, ICH Harmonised Tripartite. "Quality risk management." Q9, Current step 4 (2005): 408.

[57]. Frank, T., et al. "Quality risk management principles and industry case studies." Pharm Qual Res Inst Manuf Technol Comm [Internet] (2008): 1-9.

[58]. Debevec, Veronika, Stanko Srčič, and Matej Horvat. "Scientific, statistical, practical, and regulatory considerations in design space development." Drug development and industrial pharmacy 44.3 (2018): 349-364.

[59]. Chordiya, Mayur Ashok, Hemant Hiraman Gangurde, and Vikram Nirmal Sancheti. "Quality by design: A Roadmap for quality pharmaceutical products." Journal of Reports in Pharmaceutical Sciences 8.2 (2019): 289.

[60]. Bhattacharya, Joymalya, M. Pharm, and M. Phil. "Quality Risk Management–Understanding and control the risk in pharmaceutical manufacturing industry." International Journal of Pharmaceutical Science Invention 4.1 (2015): 29-41.