A Review on Quality by Design Based approach for the optimization of Analytical Method development

Mandhare Shubham

Pravara Rural College Of Pharmacy Loni

Rahul Godge

Pravara Rural College Of Pharmacy Loni

ABSTRACT

Quality by Design (QbD) is a strategic process used to continuously produce high-quality goods in a variety of industries, such as manufacturing, product development, and medicines. It entails a methodical, proactive strategy that incorporates quality considerations at every stage of the product lifecycle, from development to manufacturing.

Quality-based drug development (QbD) in the pharmaceutical business aims to improve safety, efficacy, and overall quality through process optimization in drug development, production, and control. This method necessitates a deep comprehension of the key process parameters (CPPs), which are the factors that affect the manufacturing process, and the critical quality attributes (CQAs), which are the measurable features that define the performance of the product. Finding and comprehending the connections between a product's CQAs and the CPPs that affect them is the fundamental tenet of quality by design. The range of CPPs that guarantee the product's CQAs are within allowable bounds is defined by the design space. It offers process optimization flexibility while preserving the necessary quality qualities. To guarantee consistency and predictability in product performance, producers can set up suitable process controls, monitoring strategies, and quality assurance systems within this design space. Putting quality by Design into Practice has several benefits. It helps producers to lower variability, minimize risks, and gain a deeper understanding of their processes. Potential quality concerns can be found and fixed early on by including quality into the product development and manufacturing stages, which lowers the possibility of post-production issues. Furthermore, QbD promotes continuous improvement by offering a structure for continuing process innovation and optimization.

KEYWORDS: - Quality by Design (QbD), Critical Quality Attributes (CQAs), Design of Experiment (DOE), Analytical Quality by design.

INTRODUCTION: Identifying the essential process parameters and starting material properties that must be controlled to produce the intended final product features. A well-defined acceptable performance envelope and a clear understanding of the acceptability bounds are necessary for a flexible process. To improve process performance, an approach-like Design of Experiments (DoE) may be employed. creation of a comprehensive control plan encompassing every facet of the production process. In the control process, risk assessment for each stage should be considered. The PAT technique could be used as a component of the overall control plan. To ensure the quality of the finished product, the manufacturing process is continuously audited and revised as needed. The product's composition design and the meticulous specification of the quality attributes that must be maintained to meet the product quality profile. creation of an adaptable process for the product with the specified quality attributes. [1-2]

The implementation of an analytical quality by design a QbD strategy can help to overcome these constraints. Now, A QbD is well-liked due to its consistency and method performance [3]. Many benefits are provided by A QbD, including complete process understanding, minimal failure, a more successful control strategy, a robust analytical method that increases confidence, successful method transfer from research to the quality control department, continuous improvement throughout the process life cycle, avoidance of post approval changes, and increased compliance with regulatory authorities [2]. Preassigned objectives, risk assessment (RA), process comprehension, sufficient control, and ongoing improvement are often the first steps in the implementation of a QbD [4-5]. Moreover, it is feasible to get the intended outcomes in a shorter amount of time with less experimenting [1,5] Acquiring the analytical target profile (ATP) in the A QbD framework requires a thorough comprehension of the correlation between key analytical attributes (CAAs) and critical method parameters (CMPs). Fishbone diagrams, failure mode and effect analysis (FMEA), risk screening, and other quality assurance (RA) tools are used to determine which pieces to include. To incorporate quality into a technique, A QbD is a methodical approach to analytical development across the entire life cycle [6-10]. Figure 1 depicts the potential flow of systematic QbD events for the development of analytical methods. The QbD-based strategy, which summarizes the complete development of a quality product that depends on solid scientific knowledge and quality risk management, was highlighted in International Conference on Harmonization (ICH) Q8 (R2) [11] (As the new ICH Q14 standards for analytical method development covering A QbD are being developed, the A QbD paradigm has been applied in the pharmaceutical sectors [1,8]

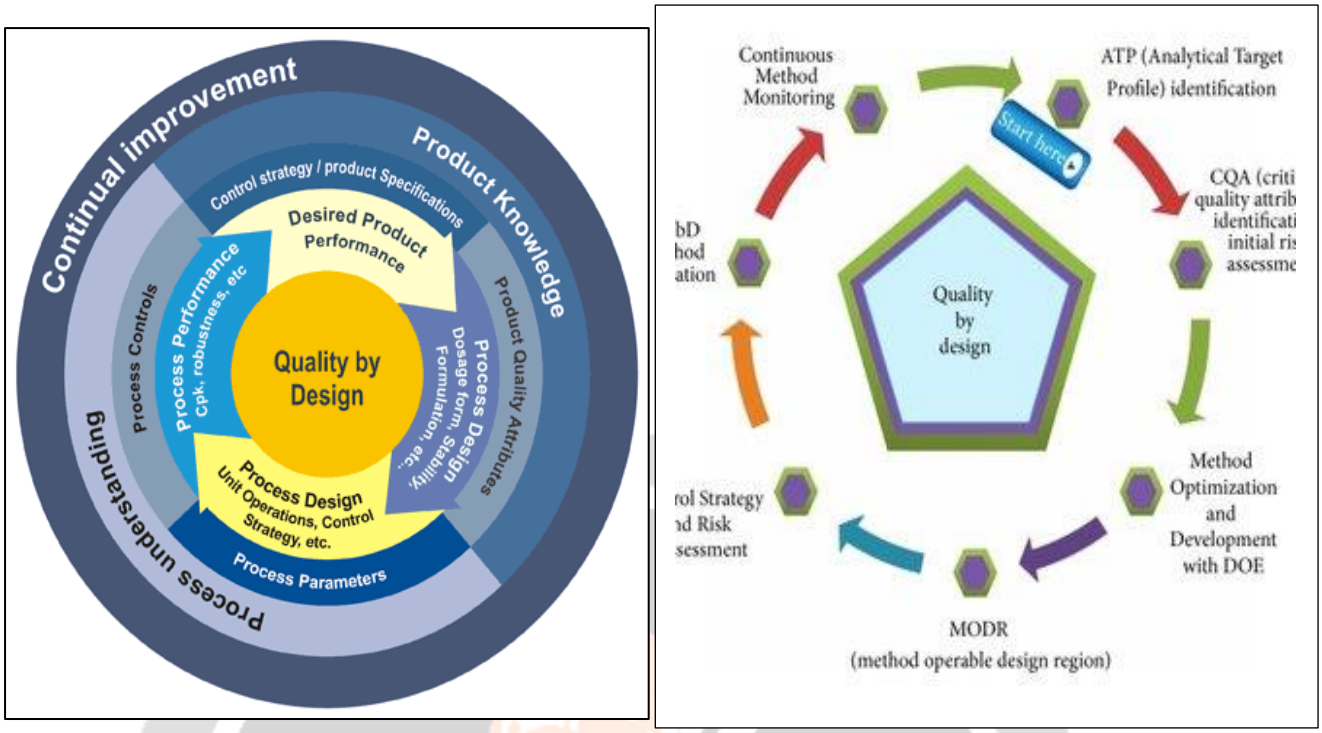

Fig:1 Tools and process understanding of QbD

Steps Synthetic development (QbD)	Analytical development (AQbD)
QTPP identification	ATP (Analytical Target Profile) identification
CQA/CMA identification, Risk Assessment	CQA identification, Initial Risk Assessment
Define product design space	Method Optimization and development with DOE (Design of Experiment)
Define process design space	MODR (Method Operable Design Region)
Control Strategy with Risk Assessment	Control Strategy with Risk Assessment
Process validation	AQbD Method Validation
Continuous process monitoring	Continuous Method Monitoring

Table 1: QbD tools for synthetic development and analytical development.

2. ATP (Analytical Target Profile)

The identification of ATP involves choosing the necessary method parameters, such as target analytes (product and contaminants), the kind of analytical technique, and the product specifications [11]. As a preliminary measure of risk assessment, the method requirements and analytical criticalities would be anticipated. ATP for analytical procedures consists of the following:

(a) choosing target analytes (API and contaminants).
(b) selecting an analytical technique (e.g., HPLC, GC, HPLC, Ion Chromatography, etc.)
(c) selecting the necessary method parameters.

a) Target Analytes Selection:
Numerous regulatory agencies including ICH Q3 provide information on the consideration of contaminants in the synthetic route of API.

b) Technique Selection:

Analytical technologies are numerous and varied, and while there is a lot of overlap in their applications, each method has advantages and disadvantages. An appropriate analytical technique can be chosen based on the type of the analytes. The test's requirements are crucial for choosing the right approach. The following are examples of analytical test items and analytical techniques:
1. Using an FT-IR spectrophotometer for IR identification
2. Chromato-logical impurity profile: HPLC using a UV detector
3. HPLC with RID/ELSD for non-chromophore impurity profile
4. HPLC (non-chromophore) assay: HPLC with RID/ELSD; HPLC (chromophore) assay: HPLC with UV detector

(c) Analytical method performance characteristics

The conditions needed for different methods can vary. Different methods have different performance characteristics. Method performance can be divided into two categories: intrinsic random (variance) and systematic (bias) components. Performance of the Commonly technique is assessed by both, not just one. There are numerous validation factors for chromatographic separations that are regarded as method performance characteristics, such as accuracy and precision, in accordance with USP and ICH guidelines. These are often regarded as method performance characteristics for substance quantification. Without sufficient specificity, linearity, and peak resolution, no approach can be both accurate and precise, but these factors do not indicate a robust method. The range is another essential element that must be established based on appropriate behaviour of both random and systematic performance parameters. To provide certain results, robustness specifies an operating range of technique factors. It is not necessary to include other method performance characteristics like linearity and specificity in the ATP because they are not directly related to understanding how well a measurement agrees with the true value.

3 CQA and initial risk assessment

A characteristic or property that is physical, chemical, biological, or microbiological and that needs to fall within a certain range, limit, or distribution to guarantee the intended level of product quality. Method parameters and attributes make up CQA for analytical procedures. CQA can vary depending on the analytical method used.

a) Buffers used in the mobile phase, pH of the mobile phase, diluent, column selection, organic modifier, and elution method are HPLC (UV or RID) CQA.
b) CQA for GC techniques include sample diluent, concentration, gas flow, injection temperature, oven temperature and program.
c) The CQA for HPTLC includes the TLC plate, mobile phase, injection volume and concentration, plate development time, colour development reagent, and detection techniques. To developing analytical methods, CQA is also described by the physical and chemical characteristics of the drug ingredient and contaminants, such as polarity, charged functional groups, solubility, pH value, boiling point, and solution stability. To demonstrate demonstrable control of the important quality attribute in the manufacturing process and stability testing, the method performance (e.g., specificity, accuracy, precision, linearity, range, and quantitation limits for contaminants) should be targeted.

4.RISK ASSESSMENT OR MANAGEMENT[12]

"A systematic process in the assessment, control, communication, and review of risks to the quality across the lifecycle" is what quality risk management (ICH Q9) is defined as. An essential component of the analytical QbD process is risk assessment.
Risk evaluations facilitate the identification and prioritization of factors that may negatively impact method performance and ATP compliance. Throughout a method's lifecycle, risk assessments are frequently iterated. They are usually carried out at the conclusion of method development, in conjunction with product changes (such as route, formulation, or process), and before a method is transferred. Potential disparities (e.g., Laboratory methods, environment, testing cycle times, reagents resources) are highlighted by these RAs. Major variations (such equipment availability) should be identified and taken into consideration throughout the technique selection and method development stages.

Risk assessment techniques: -

The following risk assessment techniques are included in ICH guideline Q9:

1. Failure Tree Analysis (FTA),
2. Hazard Analysis and Critical Control Points (HACCP),
3. Hazard Operability Analysis (HAZOP),
4. Failure Mode Effects Analysis (FMEA),
5. Failure Mode,

6. Effects and Criticality Analysis (FMECA),
7. Preliminary Hazard Analysis (PHA),
8. Risk ranking and filtering
9. Supporting Statistical Tools etc.

5. Method development using the QbD methodology [13]

1) **Specifying the method's-** The objectives of HPLC method development must be clearly specified since pharmaceutical QbD is a systematic, scientific, comprehensive, threat-based, and practical approach that starts with predefined objectives and places a strong emphasis on product and process understanding and control. The primary compound must be isolated and quantified as the final objective of the analytical process.
2) **Executing the experimental design:** Method optimization can be carried out quickly and methodically with the use of experimental design. An organized approach to experimentation is seen to be essential for achieving deep comprehension of the methodology and carrying out optimization. It creates a chromatographic database that aids in the comprehension, optimization, and selection of methods. Furthermore, if a method modification is required in the future for instance, if the chromatographic column used is no longer readily accessible on the market or if an impurity is no longer elevating it can be utilized to assess and execute the change.

3) **Selecting the ultimate technique conditions and assessing the experimental outcomes: -**

The three-tiered methodology must be used to assess the method's conditions. The initial step is to assess the criteria for peak symmetry, peak fronting, and peak tailing. Afterwards, these circumstances ought to be assessed once more using stricter standards, like the tailing factor having to be smaller than 1.5, etc.

4) **Assessing risk using a robustness and ruggedness assessment: -**

After the ultimate approach is chosen based on method characteristics, there's a good chance it will be dependable and functional throughout the duration of the product. The evaluation of the robustness and ruggedness of the method, as well as its finalization, are the primary tasks of the fourth step in the method development process. To assess the robustness and ruggedness of a method, a risk-based methodology grounded on the QbD principles outlined in ICH Q8 and Q9 can be utilized. To detect the possible risk of a technique owing to a tiny change in method parameters or under a range of settings, such as different laboratories, analysts, instruments, reagents, days, etc., a fishbone diagram, such as structured methodologies for risk assessment, can be adopted.

6. QbD's regulatory aspects

1) The FDA's viewpoint [14]:

"QbD is a systematic approach to product and process design and development," according to the FDA approved this idea in 2004 and provided a thorough explanation in "Pharmaceutical cGMPs for 21st century – a risk-based approach." Stricter standards for product quality are set by the international conference on harmonization in its Q8 pharmaceutical development, Q9 quality risk assessment, and Q10 pharmaceutical quality system. By providing Process Analytical Technology (PAT), a Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance, the FDA further emphasizes the significance of pharmaceutical product quality. In the end, QbD aids in the implementation of Q8 and Q9. Risk-based regulatory approaches are used to govern connected processes for product performance and quality using scientific understanding.

2) QbD and the ICH guideline

The quality guidelines of the International Conference on Harmonization (ICH Q8 Pharmaceutical Development, ICH Q9 Quality Risk Management, and ICH Q10 Pharmaceutical Quality System) explain the fundamentals of QbD, which include science- and risk-based product development, risk assessment, lifecycle approach, and method design.

7. THE EXPERIMENTS' DESIGN [15]: -

Method optimization can be carried out quickly and methodically with the use of experimental design. Design of experiments (DOE) is a vital component of Quality by Design and a well-established method in process and product development.
Understanding the crucial process characteristics impacting the analytical method is made easier with the aid of method development. Accuracy and precision as well as to lessen their impact. DoE (Design of Experiment) is typically used to determine instrument operating parameter ranges, comprehend differences in sample preparation, and determine technique precision variations. In addition to specifying which analyte or analytes will be measured, in which matrix, and over what concentration range(s), the ATP also gathers a collection of attributes that dictate the necessary performance criteria of the method and the specifications for these latter ones. The purpose of DOE for method validation is to confirm the analytical method for a variety of concentrations such that, as they are adjustments within a defined design area, formulation or concentration modifications won't need further validation. Recently, using DOE to analytical methodologies has received increased attention. Three main applications exist for DOE in analytical procedures.

1. Developing new methods or improving existing ones.
2. Validating existing methods.
3. Quantitating the impact of analytical methods on process and product acceptability as well as rates of deviation from specifications.

QbD can be used with a variety of analytical techniques, such as [15]:

1. Chromatographic techniques such as HPLC (for method development, stability studies, and impurity determination in pharmaceuticals).
2. Hyphenated methods such as LC-MS.
3. sophisticated methods for figuring out moisture content include mass spectroscopy, Karl Fischer titration, UHPLC, and capillary electrophoresis.
4. Vibrational spectroscopy, such as the UV technique, for component identification and quantification. Examination of a genotoxic contamination.
5. research on dissolution and
6. procedures in biopharmaceuticals.

Advantages of QbD implementation for FDA [16].

1. Enhance scientific foundation for review.
2. Provides for better coordination across review, compliance and inspection.
3. Improves information in regulatory submissions.
4. Provides for better consistency. Improves quality of review.
5. Provides for more flexibility in decision making.
6. Ensures decisions made on science and not on empirical information.
7. Involves various disciplines in decision making.
8. Uses resources to address higher risks.

ADVANTAGES FOR THE INDUSTRY [17]: -

1.Assures improved product design with fewer manufacturing issues.
2. Lessens the quantity of manufacturing supplements needed for post-market adjustments; this is dependent on process comprehension, risk assessment, and risk mitigation.
3. Enables new technology to be implemented to enhance manufacturing without facing regulatory scrutiny.
4. Enables less waste and potential savings in production costs overall.
5. Assures quicker approvals, fewer deficiency, and less trouble during review.
6. Enhances communication with the FDA; deals with research rather than procedures.

CONCLUSION: -

It is acceptable to apply the QbD idea to analytical methods since a variety of factors, such as calibration model selection, sample characteristics, instrument settings, and method parameters, have a substantial impact on the method results. Chromatography is the most often used analytical method in pharmaceutical quality.

Implementing QbD offers a chance to achieve regulatory flexibility, but it also necessitates a high level of robustness, product quality, and analytical method understanding. control, and the number of variables involved in the analytical method development phase is almost equivalent to the number of variables involved in formulation and development protocols for dosage form. For analytical techniques, method transfer in QbD is possible and will allow for better, more effective, and ongoing improvements for subsequent methods.

REFERENCES: -

1. Bonde, S., Bonde, C.G., Prabhakar, B.; Quality by design-based development and validation of HPLC method for simultaneous estimation of paclitaxel and vinorelbine tartrate in dual drug loaded liposomes; Microchemical Journal, (2019); 149: 103982. doi: 10.1016/j.microc.2019.103982.
2. Sangshetti, J.N., Deshpande, M., Zaheer, Z., Shinde, D.B., Arote, R.; Quality by design approach: Regulatory need; Arabian Journal of Chemistry, (2014); 10: S3412–S3425. doi: 10.1016/j.arabjc.2014.01.025.
3. Musters, J., Bos, L.V., Kellenbach, E.; Applying QbD principles to develop a generic UHPLC method which facilitates continual improvement and innovation throughout the product lifecycle for a commercial API; Organic Process Research and Development, (2013); 17: 87–96. doi: 10.1021/op300292a.
4. Dangre, P.V., Phad, R.D., Surana, S.J., Chalikwar, S.S.; Quality by design (QbD) assisted fabrication of fast dissolving buccal film for clonidine hydrochloride: Exploring the quality attributes; Advances in Polymer Technology, (2019); 2019: 1–13.
5. Thakur, D., Shivhare, U.S., Katare, O.P., Jain, A., Ghoshal, G.; RP-HPLC method development using analytical QbD approach for estimation of cyanidin-3-o-glucoside in natural biopolymer-based microcapsules and tablet dosage form; Journal of Pharmaceutical Investigation, (2016); 47: 413–427. D
oi: 10.1007/s40005-016-0269-5.
6. Orlandini, S., Pinzauti, S., Furlanetto, S.; Application of quality by design to the development of analytical separation methods; Analytical and Bioanalytical Chemistry, (2013); 405: 443–450. doi: 10.1007/s00216-012-6302-2.
7. Parr, M.K., Schmidt, A.H.; Life cycle management of analytical methods; Journal of Pharmaceutical and Biomedical Analysis, (2018); 147: 506–517. doi: 10.1016/j.jpba.2017.06.020.
8. Zigart, N., ˇ Casar, Z.; Development of a stability-indicating analytical ˇ method for determination of venetoclax using AQbD principles; ACS Omega, (2020); 5: 17726–17742. doi: 10.1021/acsomega.0c02338.
9. Hashem, H., El-Sayed, H.M.; Quality by design approach for development and validation of a RP-HPLC method for simultaneous determination of co-administered levetiracetam and pyridoxine hcl in prepared tablets; Microchemical Journal, (2018); 143: 55–63. doi: 10.1016/j.microc.2018.07.031.
10. Mohammed, A.Q., Sunkari, P.K., Srinivas, P., Roy, A.K.; Quality by design in action 1: Controlling critical quality attributes of an active pharmaceutical ingredient; Organic Process Research and Development, (2015); 19: 1634–1644. doi: 10.1021/op500295a.
11. Zhang, L., Mao, S.; Application of quality by design in the current drug development; Asian Journal of Pharmaceutical Sciences, (2017); 12: 1–8. doi: 10.1016/j.ajps.2016.07.006.
12. Ian House Process Understanding for Scale up and Manufacturing Method of Active Ingredients, First edition, Wiley VCH veer lags GMbH and co. KGaA (2011).
13. M. Deepa, K. Ravindra.A Review on Quality by Design Approach for Analytical Method Development.
14. Patrica V.A., 2007.Available on http://www.Pharmtech .com/pharmtech /article. 15. Ramalingam P, Kalva B, and Reddy Y. Analytical Quality by Design: A Tool for Regulatory Flexibility and Robust Analysis Hindawi Publishing Corporation International Journal of Analytical Chemistry volume 2015,9.
16. Tang Y., Quality by Design Approaches to Analytical Methods-FDA perspective US. Food and drug Administration, 2011.
17.Gholve SB, Angunde RR, Bhusnure OG, Thonte SS, Analytical method development and validation by QBD approach.A review Pelagia Research Library,Der Pharmacia Sinica,6(8),2015,18-24.