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A REVIEW ON: QUALITY BY DESIGN APPROACH TO ANALYTICAL METHOD DEVELOPMENT

Pratiksha B. Sonawane[1]*, Ramanlal N. Kachave[2] and M. J. Chavan[3]

[1]Amrutvahini College of Pharmacy, Sangamner, Department of Quality Assurance, Savitribai Phule Pune University, Maharashtra, India.

[2]HOD of Pharmaceutical Chemistry, Amrutvahini College of Pharmacy, Sangamner, Savitribai Phule Pune University, Maharashtra, India.

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***Corresponding Author**
Pratiksha B. Sonawane
Amrutvahini College of Pharmacy, Sangamner, Department of Quality Assurance, Savitribai Phule Pune University, Maharashtra, India.

ABSTRACT

QbD is the latest approach to pharmaceuticals quality. QbD is gaining a lot of publicity for maintaining quality among the pharmaceutical industries. It functions as a bridge between industry and drug regulatory authorities to transfer towards scientific, risk-based pharmaceutical product development. It has been decided that during the manufacturing process quality of pharmaceutical product should be designed and built. Most of the quality concerns are connected to the manner in which pharmaceutical products have been manufactured. Poorly designed pharmaceutical products can demonstrate poor safety and effectiveness, no matter how many experiments or analyses have been performed to validate their performance. Thus, QbD starts with quality and does not merely improve by expanding pharmaceutical research. The concept of QbD is focused on enhancement of process and product understanding with the help of risk assessment, identifying critical quality attributes and critical process parameters to be controlled via right control strategy. In the review, QbD and its elements are given. Benefits, opportunities and steps involved in QbD of pharmaceutical products are described. It also gives application of QbD in pharmaceutical development and manufacturing of pharmaceuticals.

KEYWORDS: QBD, FDA, ATP, CQA, NDA, ANDA, BLAs, PAT, QTPP, MODR, CAPA, DOE.

1. INTRODUCTION

Quality: The quality of any product or process in measured as compared to its standard and it suitable for their intended use. This includes such attributes like identity, safety, strength and purity. The quality is nothing but the addition of characteristics and features of product or services that has willingness to meet the customers need.

Quality by design

- **Definition [ICH Q 8(R1)]**

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.

The main focus of pharmaceutical organization is to design a quality product and its manufacturing process to deliver consistent performance and results of the product. It is necessary to understand that the quality can't be tested into the products; it should be built by the design. Changes made in formulation and manufacturing process during management of lifecycle should be seen as an opportunity for understanding establishment of design and manufacturing control of process or product. That helps to gain the further extra knowledge about specification and manufacturing control. All regulatory bodies have given much more importance to quality for development and manufacturing process. Quality means satisfaction of the customers in terms of service, product and process. None of the main quality goals are discussed by ICH (International Council for Harmonization). There are three main guidelines of ICH used for Quality by Design is: Q8 (Pharmaceutical Development), Q9 (Pharmaceutical Risk Management), Q10 (Pharmaceutical Quality System).The Q8 guideline consisting two parts:

i. That deals with Pharmaceutical Development and
ii. That states principle of QbD.

In all cases, regarding to the quality, the main demand of customer about the product is low cost, good performance, and perfection in quality. The techniques of product development will be differed from business to business and product to product. The customer can be satisfied by the following means like functions of product and the product that is free from defects. To avoid the failure, quality should be built into the product, for that manufacturer should have strong focus on some strategies like ease of use, service of product, trustworthiness etc. to produce the product that is free from defects.

There are various factors included in lifecycle of QbD like ATP, risk Assessment, CQA, method optimization, method development, control strategy, continuous monitoring etc. Regarding the analytical, QBD is important for helping to build quality in any analytical method from selection to finalization. There are various factors like robustness, ruggedness should be needed to establish in HPLC during method development for implementation of QbD. It takes too much efforts and resources to redevelop and revalidate if non-robust, and non-rugged method is adopted. The design space and QbD both in combination provides deep understanding of analytical system.

The concept of QbD has been designed by well-known quality practitioners Joseph Moses Juran. He believes that the quality should be planned in first priority. The plan designed by the applicant will undergoes regulatory assessment first and then to for the approval. Thus, the principle of QbD used to enhance the quality of product and formulation/ manufacturing process in industry.

2. Historical background

In 2007, FDA received more than 5000 requests, but apparently it was reaching the increase in number of manufacturing applications to New Drug Applications (NDA), Abbreviated New Drug Applications (ANDA), Biological License Applications (BLAs). Guidance on Process Analytical Techniques (PAT) has been published as part of Good Manufacturing Practices i.e. GMP in 21st century, which increases acceptance of modern and flexible techniques in pharmaceutical industries.

In 21st century, GMP practices have been continuously grown because of ICH quality activities were used. PAT includes some standards of FDA depends upon understanding the science, also includes some factors like design, analysis, and control of manufacturing process and another factors that effects on quality of final product. The risk-based approach was initiated by FDA to solve the problems regarding quality. Later, in 2005 the time has come to incorporate QbD concept for more systematic approach.

The QbD along with system transfer knowledge of product and process for development of any drug.

3. Basic consideration of QBD

- It involves designing the products and develops the processes.

- Science based risk assessment is carried.
- It focuses on patient safety and product effectiveness.
- It conducts empirical understanding of pharmaceutical processes and methods.
- It conducts systematic analysis of the processes and methods of pharmaceutics.
- Critical quality attributes are established and their effect on end product quality is analyzed.
- It provides robust method or system.

3.1: Difference between conventional and QbD approach.

Table no. 1: Difference between conventional and QbD approach.

Sr. No.	Traditional approach	Qbd approach
1.	Performance of assessed is evaluated during validation	Focus on performance by setting up ATP
2.	Start with the hit and trial approach in order to fulfill the purpose of the process.	Start with predetermined goals.
3.	Limited understanding of analytical variables.	Systematic assessment of single variables Interactions effect
4.	quality of method is based on method validation	Performance qualification is based on method quality.
5.	No regulatory flexibility on changes	Working inside MODR will not be considered as a change
6.	Method verification and transfer are two different parameters.	Performance qualification and method verification are continuous parameters during throughout the life cycle.

4. Start-up plan of qbd for analytical methods

- **Measurement of target**

For measuring the target, determine what is to be measured, where and when to measure. And develop the requirement depends on QTPP and CQA of product.

- **Selection of techniques**

Depending upon the requirements and measurements, select the analytical technique. And specify the criteria for method and its performance.

- **Risk assessment**

For this, analyze the risk for parameters that include in method and sample. And according to that choose risk assessment tools to avoid problems.

- **Development and Validation of method**

For development and validation, firstly analyze or examine the various multiple interactions. And understand the robustness and ruggedness of method, and determine design space.

- **Control strategy**

Define control space and system suitability that meets the performance criteria.

- **Continuous improvement**

For continuous improvement, the method performance plays important role, thus monitor performance of method and update in process and analytical technology as needed.

This is whole start up plan of QbD for analytical method development.

5. Qbd tools for analytics

QbD can be applied for various analytical methods like:

- For HPLC, UHPLC, UV
- LC-MS, Capillary electrophoresis.
- Karl Fischer titration for determination of moisture content.
- Dissolution studies.
- Method development, determination of impurities, stability study in various chromatographic methods.

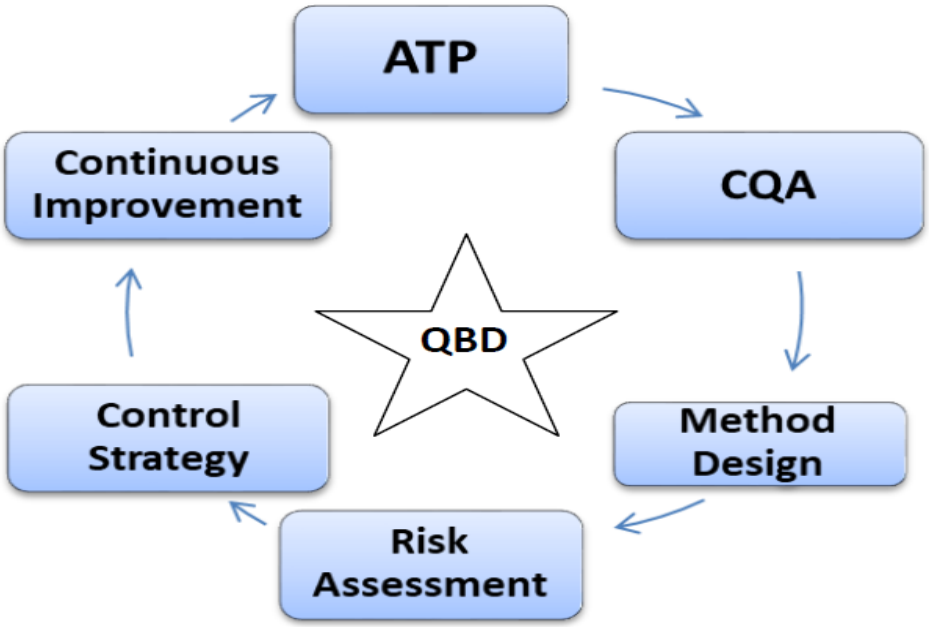

Figure no. 1: Tools of QbD.

5.1. Analytical Target Profile (ATP)

Quality by Design (QBD) is a systematic approach. Hence identification of method and its goals is important. ATP is simple tool for method development which includes requirements which are expected to measure. It also contains analyte, analytical technique, specification of product and their associated risks. The important factor for chromatographic method is separation, quantification, identification of impurities and drug substances. The identification of impurity also helps in dealing with other traces and understanding the knowledge of manufacturing process and other possible ways.

The main requirement of method will be accuracy, precision, robustness, ruggedness described in ICH. It decides what to be measured and within limit it is required to be measure.

Examples. If any method is developed then their various parameters should be measured and they are within limit like:

- Linearity-Correlation coefficient should not be less than 0.999.
- Accuracy- Mean recovery should be in the range of 98.0% to 102.0%.
- Specificity- No interference with main peak.

- **Selection of target analyte**

Selection of target analyte is depending on nature of analysis and properties of analyte. The detection of analyte includes UV, IR, RI and other various methods.

- **Selection of analytical technique**

There are wide varieties of analytical techniques used for analysis; each technique has many advantages and applications. The selection of analytical technique for method development is depends on nature of analyte. The analytical techniques used are IR, FT-IR, UV, HPLC, UPLC, and Impurity profile etc. are used for different purpose.

Example

UV is used for structural elucidation and quantitative analysis.

HPLC is used because components are easy to fractionate and purify.

IR is used for identification of structure, functional group, symmetry of molecule.

This different analytical technique has different uses and advantages thus, depends upon analysis the selection of technique is done.

5.2. Method design

Method design is made for the availability of material and specific experimental design. In this various factor are checked regarding method and are made available like material, instrument, experimental designs etc. During method design various charts and trees are used for designing. In this, different experimental trials are taken like pH, temperature, solubility, column etc. and after that results are collected and obtained data is put into the software for performance of actual experiments. Then this saved data is used to check the effect of various parameters or result on actual result. Without performing actual experiment this data helps to predict the effects. This software also allows making changes.

The method design includes selection of different analytical techniques for development of any method. Example. Various analytical techniques are available like HPLC, UPLC, LC-MS, IR, UV, Raman etc. and from this one method is finalized. And finally, after selection of technique, if method fulfills the requirement then is implemented for development.

Throughout lifecycle, this method is able to modify and use again over period. Good understanding of method parameters will help to appropriate method design. Using method design, we able to knows the knowledge regarding existing method and from that we understand is which critical parameters are there and which effective controls are allowed to use is studied in method design.

5.3. Critical quality attributes (CQA)

The critical quality attributes include basic properties and characteristics i.e. physical, chemical, and biological etc. that should be within range. There are various critical parameters like polarity, solubility, pH, boiling point; melting point etc. and that should be come within limit.

CQA should be different for different analytical technique.

For example

- HPLC- mobile phase, pH, diluents, buffer, column, method, flow etc. are the critical parameters for this technique.
- UV- concentration, range selection, preparation of aliquots, cuvette etc. are the critical parameters for this technique.

- HPTLC- plate, mobile phase, volume, time, reagent for color development etc. are the critical parameters for this technique.
- LC-MS- extraction, filtration, chemical treatment, and bioassays are the critical parameters for this technique.

5.4. Risk assessment

Risk is characterized as the combination of the possibility of harm occurring and its severity. Risk assessment helps to increase the quality of method and process. From risk assessment one can recognize critical attributes that are going on affect final quality of product. The risk assessment is helpful for effective communication between FDA and industry.

Risk factor = Occurrence ×Severity ×Detectability

Risk management includes three main steps:

- Risk assessment
- Risk control
- Risk review

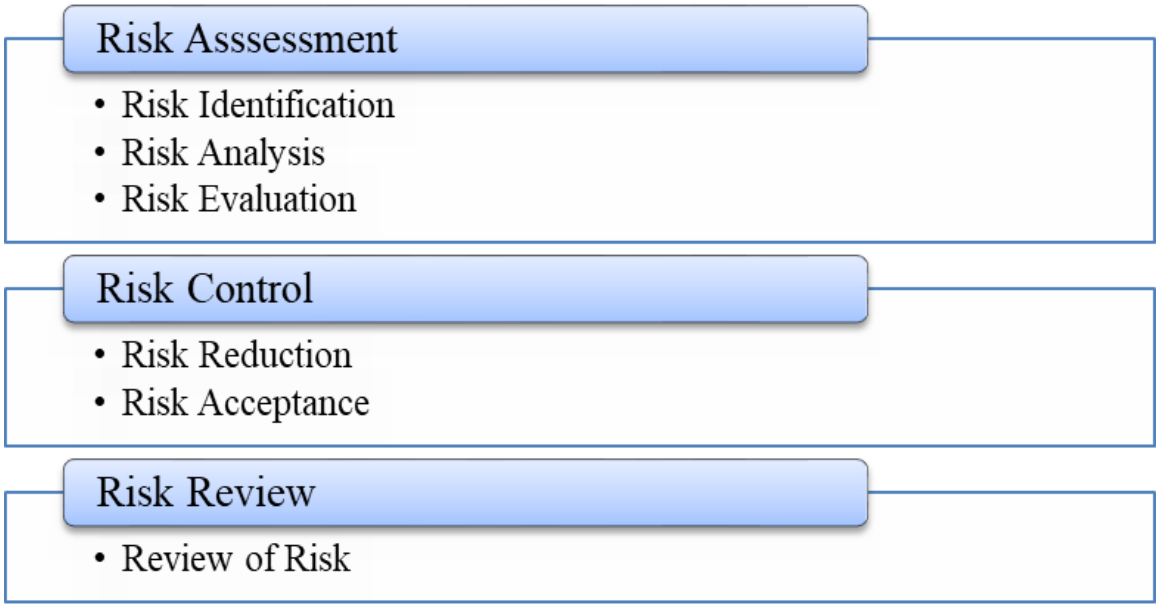

Figure no. 2: Three steps of risk assessment.

5.4.1. Principles of Quality Risk Management

The risk assessment contains two principles of quality risk management.

- Scientific knowledge based evaluation of the risk to quality with eventually links to the protection of patient.

- Adequate efforts should be taken; formality and documentation of the quality risk assessment process should be done with level of risk involved.

5.4.2. Method of risk assessment

There are eight method of risk assessment that is mentioned in ICH Q9 guidelines.

- 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.

For example, in chromatographic separation, the variability due to HPLC instrument configuration, flow rate, column selection, injection volumes, are kept constant for the experimental strategy, while the other of the variables like pH, column temperature, and mobile phase percent ration can be change to evaluate the robust behavior.

5.5. Control Strategy

The control strategy is consists of various controls focused on existing product and process understanding to ensure process efficiency and product quality. The controls can includes various parameters and attributes related to drug product, drug substance, and material equipment's, and finished product specifications etc.

In control strategy, there are various inputs for continuous improvement in the product These inputs are

-Manufacturing experience

-Performance monitoring

-Customer complaints

-Management reviews

-Material variance

-Deviation

-CAPA

-Continuous monitoring

These inputs are helpful for continuous improvement of product.

If the finished drug product meets the specification, then this product are sent for quality testing. Pharmaceutical quality is achieved through the understanding and monitoring of formulations and the processing of variables to ensure the consistency of the finished product. Final product testing confirms quality of product.

6. Continuous monitoring

Once a method has been developed for routine use, the performance of the method should be checked over time to ensure it remains in accordance with the given criteria. This can be achieved using control charts or other methods to monitor suitability of the data. Continuous monitoring helps the analyst to proactively detect any out-of-trend results and fix that. Established approaches should be regularly re-evaluated to resolve any deficiencies or opportunities for improvement found in the current methodology by enhancing the technique. Establishing an analytical method for quality control or routine testing, and evaluating the performance of the proposed method over time to ensure that the method remains in accordance with the defined ATP criteria. Established approaches should be routinely re-evaluated to overcome any deficiencies or opportunities for progress found in the current methodology by enhancing the technique, or by introducing a new approach as analytical technologies advance. This continuous monitoring helps an analyst to track, locate, and resolve any analytical system output that is irregular or out-of-trend. In pharmaceutical industry, it is representing by using control charts or other tool to track system suitability data and method related investigations.

7. Benefits of QBD

- Ensures effective production of products and less manufacturing complications.
- Allows a significant decrease in overall production costs.
- Problems in adopting QbD.
- Allows the development of new technologies to boost production without the need for government regulation.
- Reduces the number of production supplements needed to make post-market modifications.
- Eliminate batch failure and minimize costly investigations.
- Better interact with industry on science issues.
- Reduce end-product testing and Speed-up release decision.

- Build scientific knowledge base for all products.
- Avoid regulatory compliance problem.

8. Potential benefits of adopting qbd for analytical method

- It provides opportunities for the development of new techniques during life cycle through continuous improvement
- It offers greater compliance with regulatory bodies
- The method developed will be more reliable, which gives a higher level of trust in the event of conditions variations.
- Create space design which removes the post-approval modifications that can cause some of the businesses to pay a high cost.
- It helps make the process well understood.

  This approach provides greater success in moving method from research level to department for quality control

9. Implementation of qbd in current practise

Analytical QBD must be implemented in the process development phase and validated in accordance with the validation protocol for system results. For a given drug product, the following may be considered to implement analytical QbD

- Develop QTPP (product-based profile) the information as described in FDA approval.
- Analyze criticality of each component listed.
- Analyze and explain the production of the analytical method and its worthiness for maintaining criticality
- Choose the appropriate analytical method such as HPLC, UV, and IR to reach Analytical Target Profile and then Quality Target Product Profile.
- Perform risk assessment and evaluate risk for chosen system.
- Identify the quantitative and qualitative variable that influences the output of the methods to be evaluated and the method responses.
- Use the correct DOE experiment to enhance variable and develop understanding of science.
- Find the zone, models for evaluating the stable and economic growth of the variable method.
- Validate the models and MODR (method operable design region) region using experimental verification at different points to prove robustness.

- To prove robustness, validate the models and the MODR area using experimental testing at various points.
- Then validate the system for performance in the operation mode and be subject to strategy and enhancement of the function.

10. Problems in adopting qbd

- Current standards of analytical technology transfer and system validation must change, as existing validation guidelines do not result in methods that can always be run reliably
- External guidance in this field must be developed; ICH guideline Q2(R1) requires revision (or removal) and guidelines for the Drug Evaluation and Research Centre for analytical methods must be established
- A common language is needed for some of the new words, including analytical process design space, method control strategy and system performance criteria
- Acceptance must be obtained to record the success parameters of the system, rather than the requirements of the system
- Analysts must learn new tools and skills
- For this initiative to be successful, a consistent approach around the world is needed.

11. Application

11.1. Application to analytical QbD

❖ For spectroscopic measurement

- In mass spectroscopy
- In near infrared.
- In handling complex spectroscopic data

❖ For hyphenated technique

- In LC-MS for method development
- In bioanalytical method development
- In dissolution study

❖ For chromatographic technique

➢ **In determination of impurity**

Traditional HPLC gradient methods can isolate 13 of these impurities, while using QbD approach with ACQUITY UPLC column separation of as many as 26 impurities could be

possible. In screening of column used for chromatography in development of HPLC method for drug product/ substance.

- **In stability studies**

An application of quality by design (QbD) concepts to the development of a stability indicating HPLC method for a drug product containing drug substance, preservatives, and their degradants are described.

- **In screening of column used for chromatography**

The evaluation and experimental criteria is used and most common analytical columns are used from reputed column manufactures. And evaluate some RP-HPLC columns against predefined performance criteria.

And the data generated from this evaluation is used to provide help to analyst to develop robust and rugged methods for use in QbD.

- **In development of HPLC method for drug product/ substance**

Apply QbD approach for HPLC method development. In this some common and critical parameters of HPLC like temperature, pH, stationary phase, retention time etc. are evaluate and used development and optimization of an analytical method by using QbD approach.

- **In capillary electrophoresis**
- In analysis of excipients and API
- For chromatographic technique used for purification.

11.2. Application to Industry

1. Ensures better design of products with minimum problems in manufacturing.
2. Ensures less hassle during review with reduced deficiencies with quicker approvals.
3. Allows for implementation of new technology to improve manufacturing without regulatory scrutiny.
4. Reduces number of manufacturing supplements required for post market changes rely on process and risk understanding and risk mitigation.
5. Allows for continuous improvements in products and manufacturing process
6. Allows for possible reduction in overall costs of manufacturing with less waste.
7. Improves interaction with FDA which deals on a science level instead of on a process level.

CONCLUSION

In the pharmaceutical field, QbD is well established for analytical methods. The analytical QbD plays key role in pharma industry for ensuring product quality. Qbd is an integral aspect of the new reliable concept and is a creative approach towards pharmaceutical industry. The impacts of developing methods through QbD principles include improving the awareness of risk factors that could contribute to poor robustness of the system, and helping to meet quality standards in the process. From product development to commercial production the results of analytical QbD are understood. Initially it allows scientists to recognize risk quickly, so that quality can be enhanced. The application of the QbD definition to the analytical method is justifiable, as several variables significantly affect the results of the method. Qbd plays an important role in understanding processes and providing opportunities for risk analysis and the development of control strategy in formulation and method development. The long term benefit of the QbD strategy is improved testing skills, reduced variance, reduced development costs and reduced time consumption. The long term benefit of the QbD strategy is improved testing skills, reduced variance, reduced development costs and reduced time consumption.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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