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A Review: Analytical Method Development and Validation by QbD Approach

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ABSTRACT

Quality by design is a modern approach to pharmaceutical product quality. The goal of drug development is to create a quality product and its manufacturing process to consistently deliver the product's intended function. Quality cannot be tested in products, but quality must be built into the design. It is an important part of the modern approach to medical quality. As part of the concept of QbD throughout the design and development of products, it is important to define the performance profile of the desired product [Target Product Profile (TPP), Target Product Quality Profile (TPQP)], Critical Quality Attributed(CQA). Based on this, we can create a product design and process to meet product specifications. This leads to understanding the impact of the material [Critical Material Attributes (CMAs)], Critical Process Parameters (CPPs), and CQAs and identifying and controlling the sources of variation.

INTRODUCTION

Quality: In Quality by Design, Quality is an important word. So Quality is “standard or suitability for the intended use.” This term includes identifying features, strengths, and purity. Quality by Design: Multiple approaches to the development of pharmaceutical products and their subsequent manufacture have been recommended by the USFDA and the International Council Harmonization (ICH). This system has been mounted as 'Quality by Design' (QbD) and it is defined as- “A systematic approach to development that begins with a predefined objective and emphasizes product and process understanding and process control, based sound science and quality risk management.”

The concept of "Quality by Design" (QbD) is described as a method that covers the better scientific method understanding of critical processes and product quality, management control, and testing based on scientific limitations of understanding during the development process and using knowledge acquired during the life cycle of products that work and always better environment. QbD describes a pharmaceutical development method for design planning and the development and production process to supervise the prescribed product quality. Guidelines associated with mathematical models are used to ensure the establishment and use of knowledge on the subject in an independent and integrated way. (1-5)

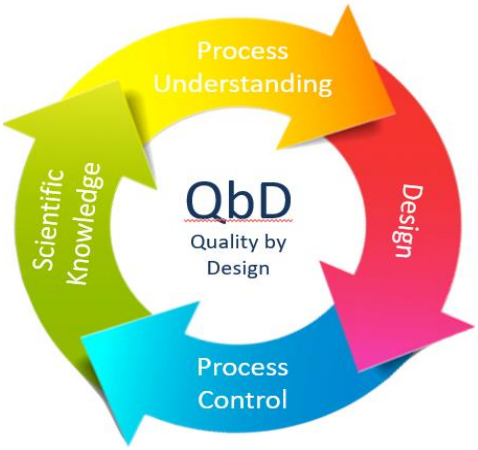

Figure no.1: **Content of Quality by Design**

QbD doesn't mean fewer research tests, rather it means proper analysis at the right time, and is based on science and risk assessment. Implementation of QbD helps to develop a robust (strong) process that helps with ICH therefore, for this reason, the pharmaceutical industry is taking QbD design. Factors that affect the robustness are considered for the development of the analytical method in the QbD environment. This one approach makes a continuous

improvement system. Similar opportunities to apply QbD and the research process are similar to that of the production process available in the literature. It put forth approaches like target profile, Critical quality attributes (CQA), design space, and risk assessment that apply to analytical methods also. Though it's not adopted by all pharmaceutical industries its future perspective as a result of it's become necessary by regulatory bodies. Acceptance of this concept voluntarily by the company is possible because of its various benefits and ease of compliance with regulators. Pharmaceutical research and manufacturers of America (PhRMA), Analytical Technical Group (ATG), and the European Federation of Pharmaceutical Industries and Association (EFPIA) provide clear ideas regarding the parallel implementation of QbD to analytical method. (7-10)

APPLICATION OF QBD

The implementation of QbD helps to develop a strong/hard process that helps with ICH guidelines hence for that reason pharmaceutical industries are adopting this concept of QbD. This approach facilitates continuous improvement in the method. (6)

1. Chromatographic methods such as HPLC (For stability studies, method development, and determination of impurities in pharmaceuticals).
2. Karl Fisher titration for determination of moisture content
3. Use of biopharmaceutical systems
4. Dissolution studies
5. Hyphenated methods such as LC-MS
6. Advanced techniques such as mass spectroscopy, UHPLC, capillary electrophoresis
7. Analysis of genotoxic impurities.

BENEFITS OF QbD

For industries

1. In a variety of situations, the process will become stronger which gives more confidence level.
2. It helps to understand the process better.
3. This method gives more transfer success when the process is carried over from the research level to the quality management department.
4. The design space concept avoids post-approval changes that can lead to higher prices for any business.

5. It allows for the creation of new processes through continuous improvement throughout the life cycle.

For Food and Drug Administration (FDA)

1. Give more flexibility in decision making
2. Improving the scientific basis for research
3. Ensure that decisions are made scientifically and not on observed information.
4. Give more stability

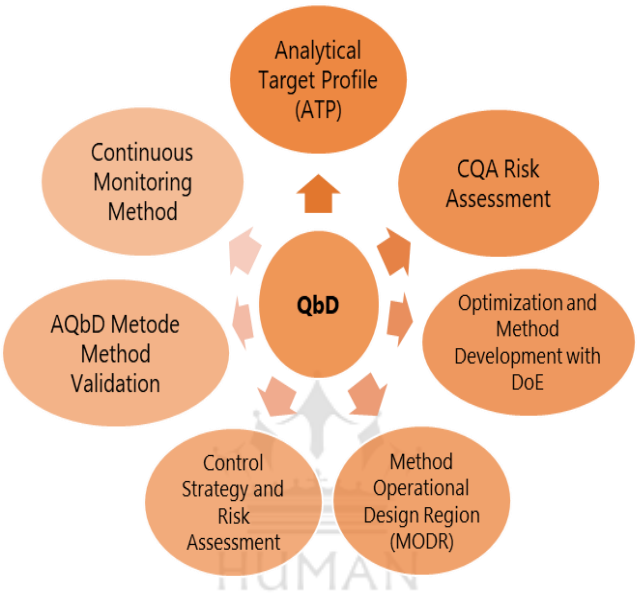

Figure no. 2: A QbD tools

Steps for scientific approaches for analytical method development.

1) ATP (Analytical Target Profile)

ATP (29,30) identification includes the selection of method requirements such as target analytes (product and impurities), analytical technique category, and product specifications. A preliminary risk assessment will be conducted to anticipate system requirements and research needs.

The general ATP for analytical procedures is as follows:

(1) selection of target analysis (API and impurity)
(2) method selection (HPLC, GC, HPTLC, ion chromatography, chiral HPLC, etc.)
(3) the choice of the required procedure (assay or impurity profile or residual solvents)

(A) Target Analytes Selection. ICH Q3 and all other regulatory guidance explained the consideration of impurities in the API synthetic route. The analytical target profile (ATP) impurities are as follows:

(1) starting material: it is starting material for DS
(2) stage 4 product: it is the final DS degradation product
(3) material-1: it is new additional material in stage 4 for the formation of stage 5
(4) material-2: it is new additional material in stage 6 for the formation of stage 7
(5) byproduct-1: it is a byproduct for stage-6
(6) byproduct-2: it is a byproduct of the final DS
(7) the product of step 6: this is what is left of the structure of the final DS;
(8) product of step 7: it reacts with the last/penultimate and last DS.

(B) Selection of procedures. Each analytical technique has a definition so the principle depends on the nature of the analytes, it can be chosen. However, analytical material and the purpose of the experiment are also important for the selection of the technique. Analytical test items and analytical techniques are as follows:

(1) identification by IR: FTIR spectrophotometer
(2) impurity profile (Chromophore): HPLC with UV detector
(3) impurity profile (non-chromophore): HPLC has RID / ELSD and others
(4) HPLC analysis (Chromophore): HPLC with UV detector
(5) HPLC analysis (non-chromophore): HPLC has RID/ELSD and others.

(C) Method Requirements Selection. The requirements can vary from system to system.

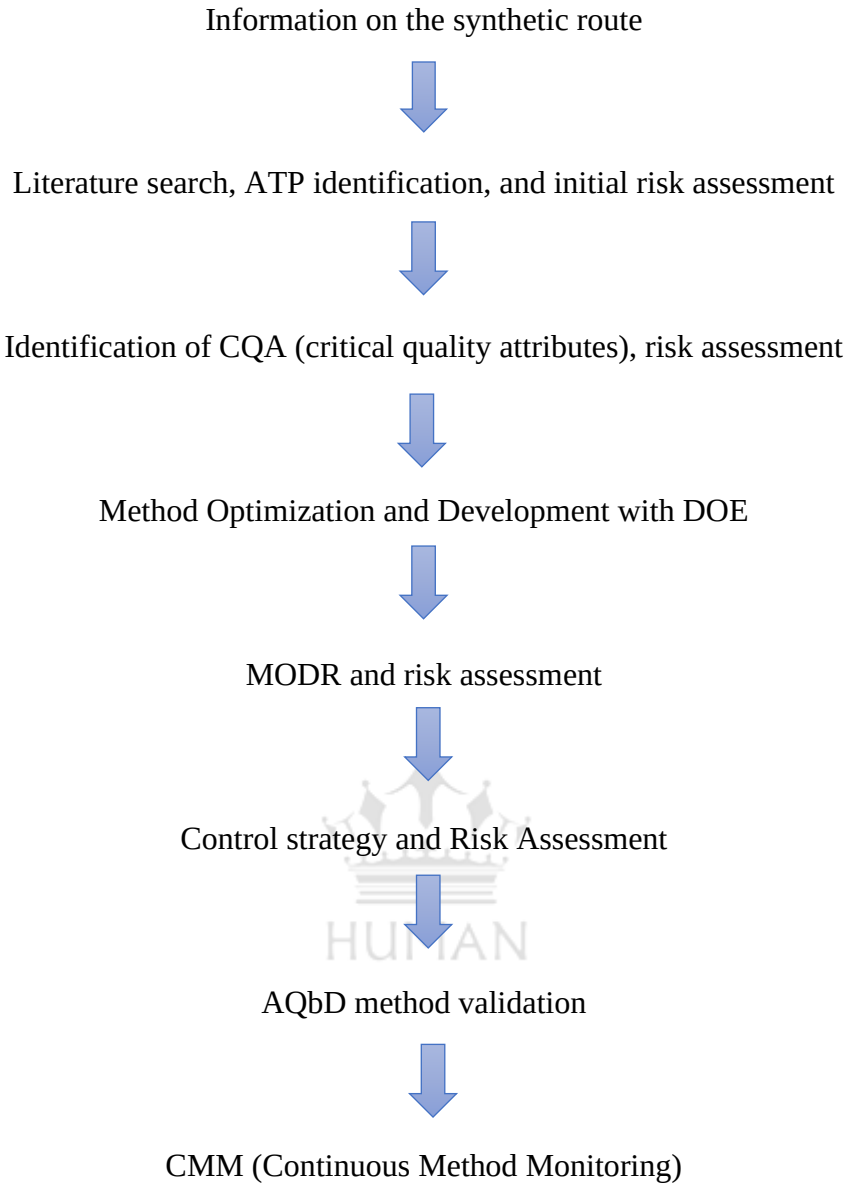

Fig. 3: **A QbD approach for analytical method development**

2) CQA (Critical Quality Attributes) and Initial Risk Assessment

(i) CQA (Critical Quality Attributes). CQA for analytical methods includes method attributes and method parameters. Each analytical technique has a distinct CQA. In HPLC, CQA methods are mobile phase buffer, pH, diluent, column selection, organic modifier, and elution method.

In GC, CQA methods are gas flow, oven temperature, program, Injection temperature, sampling, and concentration. In HPTLC, the CQA method is a TLC plate, mobile method,

injection concentration and volume, plaque development time, color developing reagent, and detection method. The nature of impurities and DS can define the CQA for analytical method development such as solubility, pH value, polarity, charged functional groups, boiling point, and solution stability.

(ii) Risk assessment. Risk assessment is a science-based process used in quality risk management and it can identify the characteristics and process (ATP). A risk assessment can be carried out from the initial stage of the development process to monitor ongoing processes. A QbD approach includes risk identification at the early stages of development followed by proper mitigation plans with control strategies that will be developed. Ishikawafishbone diagram can be used for risk identification and assessment.

3) DoE Design of Experiments (Method Optimization and Development) (11)Once the potential and critical analytical method variables are defined in the original risk assessment, then the DoE may be designed to support and facilitate critical change processes based on statistical needs. It can be determined function or combination of several selected variable processes and their interactions and responses (critical method attributes). This method provides a good opportunity to filter multiple conditions from a limited number of experiments. Then, data analysis uses statistical tools that are essential to identify critical method variables in the optimal ratio for the method variables where a robust region for the critical method attributes can be acquired. According to ICH Q8 guidelines, process robustness is defined as the "Ability of a process to tolerate variability of materials and changes of the process and equipment without negative impact on quality." Characteristics of the starting material to be affected by the drug substance synthetic process robustness, impurity profile, physicochemical properties, processing capacity, and stability. Process understanding will provide complete knowledge for establishing robustness parameters by considering different operating conditions, different scales, and different tools.

4) MODR (Method Operable Design Region). Method operable design region (MODR) is used for the establishment of a multidimensional space placed on method factors and settings; MODR can present desirable method performance. It is also used to establish important method controls such as system suitability, RRT, and RRF. Further method verification exercises can be employed to develop ATP conformance and ultimately define the MODR.

5) Control Strategy and Risk Assessment. Control strategy (31-34) is a planned set of controls, obtained from MODR understanding and an analyte nature. A control strategy can be developed based on statistical data collected during the DoE and MODR processes discussed above. Using these experimental data, connections can be made between the process and the analysis quality for the ability to meet ATP criteria. Control strategy this method will solve the parameters unpredictably (e.g., reagent grade, instrument brand or type, and column type). The control strategy method does not appear well and is different under the A QbD method compared to that traditional methods. However, method controls are obtained based on CQA, DoE, and MODR experimental data to establish a stronger link between the performance and objectives of the system.

6) A QbD Method Validation. A QbD (12-21) method validation is focused on the validation of analytical methods over a range of distinct API batches. It utilizes both DoE and MODR knowledge for designing method validation for all kinds of API manufacturing replace without revalidation. This system provides the required ICH supporting material and social information, uncertainty measurement, control strategy, and continuous development. This perspective requires rare resources than the traditional validation perspective without compromising quality.

7) Continuous Method Monitoring (CMM) and Continual Improvement (22-28). Life cycle management is a control strategy applied for the execution of design space in the commercial phase. CMM is the last step in the A QbD life cycle; it is an ongoing process of sharing knowledge gained through the development and implementation of design space. This includes the results of a risk assessment, assumptions based on prior knowledge, statistical analysis concepts, and bridges between design spaces, MODR, control system, CQA, and ATP. Once a method validation is done, for routine purpose method can be used and the performance of the system can be monitored continuously. It should be done using control charts or tracking systems suitability data, process-related analysis, etc. CMM recognizes the analyst to proactively identify and address any out-of-trend operation.

Benefits and recommendations. A QbD is a method that goes from reactive troubleshooting to proactive reduction of damages. Types and scope of risk assessment depend on the stage of the project and development time series. The success rate of AQBD depends on the right approach. Proper planning, tools use, and execution of work at a suitable time. Applying

appropriate risk assessment tools at the correct timing can prevent the failure of the method and a better understanding of design space and control strategy (35-37).

Elements of QbD to the analytical method:

In the determination of impurities: Experiments are used to improve the conditions and demonstrate the robustness of the method for the separation of impurities. HPLC/assay pharmaceutical impurity analysis methods, i.e., multi-column/mobile ring analysis, forward separation optimization using multiple organic variables and mobile systems, and multi-component system optimization using experimental design Plackett-Burman. Computer simulations were performed using Dry Lab, a commercial chromatography optimization software.

In Screening columns used for chromatography: Experimental design, endpoints used, and some of the most commonly used analytical columns from reputable column manufacturers. A systematic approach is used to evaluate seven of His RP-HPLC columns against defined performance criteria. This approach is an essential part of developing the QbD method.

In HPLC Process Development for drug Products/Substances: New Approaches to Apply Quality by Design (QbD) principles to the development process of high-pressure alternating-phase Liquid Chromatography (HPLC). Four common important parameters of HPLC (gradient time, temperature, pH of aqueous eluent, and stationary phase) are evaluated within a quality framework designed using computer modeling software and column databases. (29)

Instability studies: rapid quality-by-design (QbD) concept and development of HPLC methods to characterize the stability of complex analgesic products containing pharmaceuticals, two preservatives, and degradants are explained. The original method did not have any determination on drug-degrading and oxidative-degrading factors, as well as preservatives and other drug-degrading factors. This process optimization was performed using Fusion AE™ software following DOE guidelines. QbD-based method development is available in design space and execution space development, with details of all performance characteristics, limitations, and method robustness within the execution space.

In UHPLC: high-performance liquid chromatography with fast and high predictability, and a computer model of the design space, which demonstrates the accuracy of the prediction of retention time and high pressure (improved production) and shows that making computer-generated magic can be useful and accurate enough for UHPLC instruments.

CONCLUSION

A well-characterized method development effort aims to develop a reliable method that can be implemented with a high degree of assurance for systematically producing data that meets predefined criteria when used within defined limits. QbD can be applied in the development and evaluation of analytical data methods. AQbD tools include ATP, CQA, optimization and development of methods via DoE; MODR control strategy and risk assessment; Method validation and continuous method monitoring (CMM), and continuous improvement. AQbD requires accurate ATP and risk assessment in the use of proper equipment and proper performance of work promptly. The new QbD system provides greater constitutional changes that can be made in the future. The performance values of the system can be saved instead of the system itself. The method used can be taken as an example how to achieve the desired performance characteristics of the system.

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