VOLUME - 10, ISSUE - 06, JUNE- 2021 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper | Pharmaceutical Science

ANALYTICAL QUALITY BY DESIGN APPROACH: A NEW PARADIGM IN PHARMACEUTICAL ANALYSIS

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ABSTRACT AQbD validation of method is the newer approach for the analytical method development and validation for different ingredients (API) and market formulations. It utilizes the concept of design of experiment (DoE) and designing MODR for development of analytical method and its validation for different variety of API batches and marketed formulations without any revalidation. AQbD execute the elements of ICH validation which are required whereas it also provide information on interactions of drugs, calculating its uncertainty, risk factors, control strategy, and continuous improvement program. As compare to traditional method this approach is reliable as it requires fewer resources and provide data approach without compromising quality. AQbD approach includes risk assessment, robustness testing, and ruggedness testing for analytical methods is likely to be more effective than ICH validation requirements (Q2 (R1)). Risk assessment method compared with the limits of specification, which is one of the most important critical quality attributes decides the suitability of method. Thus AQbD approach described for ICH Q2 (R1), DoE, MODR, QbD risk assessment, critical quality attributes is explained in this article. The newer concept of AQbD approach provide the flexibility of the resources without revalidation of the analytical method in the future. The criteria for performance of method can be describe instead of method itself. Any changes to method would be covered by internal change control procedures. The performance criteria is important tool in AQbD approach.

KEYWORDS : AQbD, analytical quality by design approach, ICH guidelines, ICH validation, QbD risk based approach etc.

INTRODUCTION:

AQbD validation of method is the newer approach for the validation of analytical method over a range of different API batches and market formulations. It utilizes the concept of both DoE and MODR for designing development of analytical method and its validation for different kind of API batches and marketed formulations without any revalidation. AQbD approach provides the ICH validation elements which are required as well as it also information on interactions of drugs, measurement of its uncertainty, control strategy, and continuous improvement program. As compare to traditional method this approach is reliable as it requires fewer resources and provide data approach without compromising quality. AQbD workflow is shown in following diagram. (fig.1).

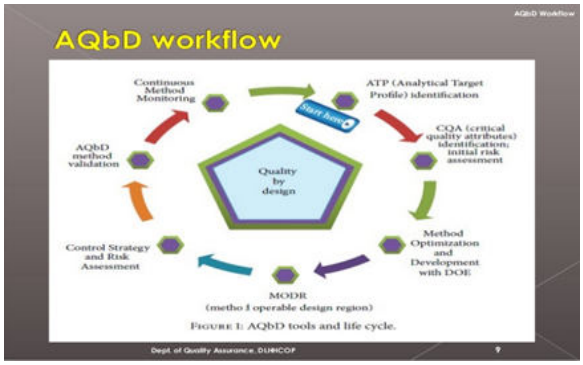

Figure no.1: AQbD tools and life cycle.

Reid et al (Phizer USA) suggested implementation of QbD in development of analytical method known as Analytical Quality by Design (AQbD). As per him there are various approaches and multiple options for development of method. Some of the examples stationary phase, columns, proportion of the mobile phase, flow rate etc. which mean we cannot depend upon single parameter and considered it "perfect", hence, another systematic approach can provide correct and accurate data of the API and marketed formulations and rapid robust method developed. The development of the method is important factor which must be suitable for its intended purpose. The method needs criteria (e.g., LOD, LOQ, sensitivity, linearity, range, accuracy, and precision), and these criteria are used to develop a method that fulfil the need of the research, (fig.2) [1].

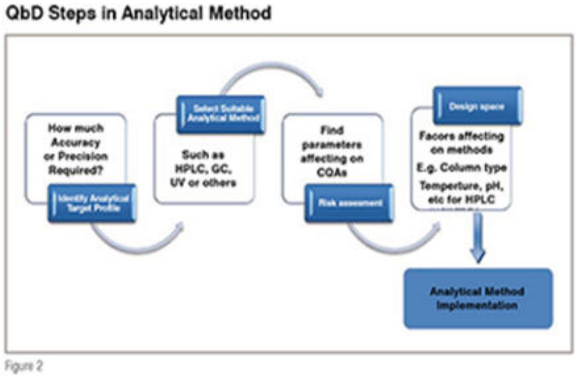

Figure no. 2: QbD steps in analytical method

Joseph M. Juran, a well-known quality expert design a concept of (QbD) which is a systematic approach that emphasizes on product, understanding of process and its control based on the concept of Echo knowledge and quality risk assessment. A traditional method may not get intended purpose during development of the method and its validation. In AQbD approach, the design and its application in various critical quality attributes are implemented with the help of Design of Experiments (DOE) and MODR that provide data analysis and designing of a model which provide assurance of quality of different drug product. AQbD parameter like MODR, risk assessment and DOE in analytical method, provide depth knowledge for study and identification of parameters that affect quality of method. Hence the objective of the current review article is to describe various steps in development of analytical method such as HPLC, HPTLC, GC-MS, and LC-MS etc. by AQbD approach. (fig.3) [2].

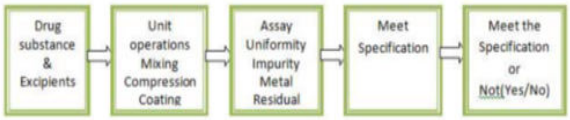

Figure no. 3: Flow-chart for Product Quality by End Product Testing

The AQbD Approach for development of method consist of the different steps such as define method to be developed, perform design experiment, analysis of results and choice of final method and experiment risk assessment test for analysis of robustness and ruggedness . The main objective of AQbD is to perform quality experiment and its measurement. In this review article we will give a deep study and implementation of various concepts of AQbD, Quality by Design' (QbD) is defined as- "A systematic approach to development that begins with predefined objective and emphasizes product and process understanding and process control, based sound science and quality risk management". The history of AQbD is presented in table no.1 [3].

Table no. 1: History of AQbD approach.

Year	Activities
1950	Operation windows was design
1970	Joseph M Juran created QBD
Sep 2002	USFDA integrated concept of QBD in cGMP
Sep 2004	USFDA release final report in "Pharmaceutical cGMP"
Sep 2004	USFDA Guidance for Industry: PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance
Nov 2009	ICH: Q8(R2) for Pharmaceutical Development
Nov 2005	ICH: Q9 for Quality Risk Management
Jun 2008	ICH: Q10 for Pharmaceutical Quality System

The advantages of AQbD method are as follows:

- Transfer success is very high when transferred method from research laboratory to QC department of the industries.
- A robust method is developed which provide greater confidence in case of physical and chemical changes in conditions.
- A well understood method is developed.
- It eliminates the post-approval changes by designing space concept which leads to fund higher cost for any of the firm.
- Continuous improvement provide a space for future research in whole life cycle.
- With regulatory authorities provides better compliance.

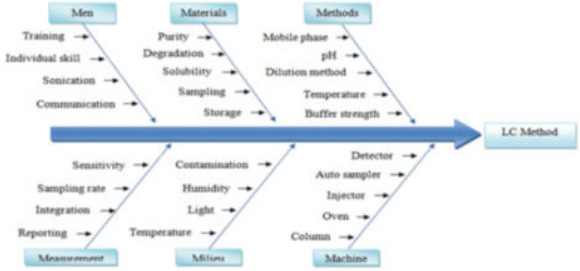

Figure no. 4: Fish bone diagram of AQbD approach

Regulatory perspective of AQbD approach

A comparison of the regulatory perspective of AQbD is shown in following table no. 2. [4].

Table no.2: A comparison of Regulatory perspective i.e, QbD of product and QbD of analytical method

QbD. Steps	QbD of product	QbD of analytical meyhod
Step 1	QTPP	ATP
Step 2	CQA	CQA
Step 3	Risk assessment	Risk assessment
Step 4	Design space	MODR
Step 5	Control strategy	Control strategy
Step 6	Life cycle management	Life cycle management

Implementation of AQbD

The implementation of AQbD approach work on one factor at a time (OFAT), where only a variable is suitable for the result to be expected.

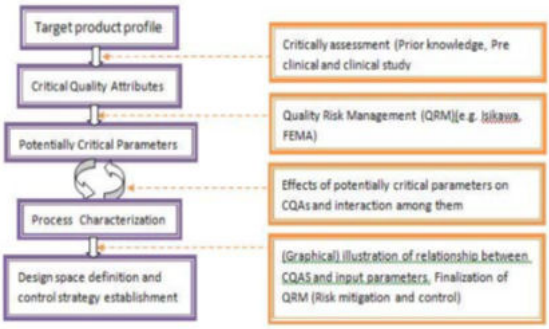

Figure no. 5: Comparison of OFAT and AQbD in Development of analytical method.

The comparison between the traditional method, product development quality by design and analytical quality by design approach is shown in figure no. 5. [5].

ICH guidelines (Q8, Q9, Q10): The basics of QbD

ICH has provided the various guidelines as the foundation of QbD such as Guidelines Q8 for Pharmaceutical Development, Q9 for Quality Risk Management, Q10 for Quality systems are foundation of QbD (Figure: 6) [6].

Figure no. 6: The Foundation of QbD

Quality by Design relative to ICH is the foundation of QbD approach. In QbD a concept is aligned for the development of method. The study of method was design by design space concept. A robust process was then developed. The criteria of QbD was achieved by DOE- design of experiments, followed by quality management.

Table no. 3: Analytical method in pharmaceutical testing and control strategy

Sr. No	Pharmaceutical testing	Control strategy
1	testing of API	Product QTPP and CQA design. The study of effects of variability on process and method development.
2	In-process testing	product variation was minimize by measuring real time (at-, on-, or in-line) Active control on process
3	Stability testing	stability failures can be minimize by predicting models
4	Release testing	Critical Quality attributes (design space) and specification of the quality control strategy such as (quality, safety, efficacy, and performance)

Steps in quality by design approach

1) ATP (Analytical Target Profile):

In AQbD, Analytical Target Profile (ATP) is same to Quality Target Product Profile (QTPP) element in QbD. A method is developed for ATP which is describe in the ICH Q8 R (2) guidelines. Selecting ATP is an important tool. It mostly describes the requirements of the method which is to be developed. Selection of ATP consists of the choice of variables in method selection which include quality target profile (product, impurities, API and formulations), selection of analytical technique, and specifications of the product. Risk assessment is done for requirements of method and analytical conditions. ATP for analytical method consist of following steps. (fig.7)

Figure no. 7: Steps of quality by design approach.

a) Selection of analytical target profile (API and impurities),
b) Assortment of analytical methods (HPLC, HPTLC, GC-MS, LC-MS etc.)
c) Selection of development of method.

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

ICH Q8 (8) defines "CQA 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". The Analytical Method Performance Characteristics affect the quality of the final product. This is analogous to QTPP in product QbD. These are also known as critical Quality attributes (CQA). ICH Q8 R2 describes CQA as "A CQA is 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'. Predefining these parameters is important, so that the method developed can meet the goal of ATP.

It is very important to find out critical quality attributes in AQbD, i.e. those defining purity, assay and potency etc. The critical quality attribute/ parameter is based upon the safety, efficacy & quality of the product. CPP & CQAs are inter related with each other: Identification of attribute or parameters that can be used as clinical safety & efficacy of CPP (Figure 2).

CQA for analytical methods comprises of analytical method attributes and its parameters. CQA can diverge from different analytical technique [7].
a) HPLC (UV) CQA are mobile phase, pH of mobile phase, diluent, column, flow rate, organic modifier, and elution technique etc.
b) CQA for GC methods are temperature of oven, temperature of injection, flow rate of gas, sample diluent, and concentration of sample etc.
c) CQA for HPTLC are plate, volume of mobile phase, concentration, development time for plate, reagent for color development, and detection methods are the CQA for HPTLC.

CQA for analytical method development are physical and chemical properties of the drug substances, API, marketed formulations and impurities such as solubility, polarity, dissolution, pH value, boiling point, and solution stability. The method development parameters such as specificity, accuracy, precision, linearity, range, and quantitation limits for impurities etc. should be analyzed so that the method is suitable for demonstrating critical quality attribute in the manufacturing process and stability testing of the analytical target profile.

3) Design Of Experiment:

ICH Q8 guidelines for 'Design Space 'in Product Development QbD is modeled for Method Operable Design Region (MODR) in Method Development Phase to give a robust analytical method. Method design is done to ensure availability of materials and take into account various experimental conditions, regional and geographic. Additionally, instrument feasibility is checked and an Experimental Design is prepared. Critical quality attributes provides MODR which is the operation for the critical method input of various variable (similar to CQAs) that provides results which are consistent to the objective of the ATP. MODR also permits the flexibility range in various input variables method parameters which in turn provide the expected method performance criteria and method response without the need of resubmission to FDA [8].

4) Method Qualification:

ICHQ2 (R1) guidelines are followed for method qualification. Risk assessment can be done to develop method which is the subsequent step in method qualification. Method qualification generally occurs before method transfer to the industry which is done only once in order to provide quality assurance that a totally reliable and reproducible method has been developed. Method qualification is to be conducted under normal operating conditions to provide the accurate data. The design qualification of an operation typically includes installation qualification (IQ), operation qualification (OQ) and process qualification (PQ). As per regulatory guidance in addition to method validation, method verification can be performed through MODR by assessment of accuracy and precision at different method parameters within the analytical separation space (from MODR). Multipoint verification within MODR ensures the greatest probability of the ability of the method to meet the requirement specified in ATP [9].

5) Control Strategy:

It was very important to establish a control strategy while ensuring that the finished product meets the goals described in analytical target profile (ATP). Mostly it is design to control aimed at minimizing the variability in the process. The control strategy is fully dependent on data. The basis of the control strategy is the data generated during method development and method verification. A factor identified for risk assessment has to be controlled. An attention has to be paid to the high risk factors. System suitability test can be performed and verified time to time by having control strategy. It is noticed that the control strategy of AQbD is same as that of the traditional control strategy. [10]

6) Quality Risk Management:

Quality Risk Management (ICH Q9) is "a systematic process for the assessment, control, communication and review of risks to the quality… across the … lifecycle". Risk assessments are a very important part of the Analytical quality by design process. It shows smooth progress of method recognition and its steps parameters that could brunt method performance and conformation to the ATP. Risk assessments are often iterative throughout the development of a method, and are generally performed at the last of method development, with product changes (e.g., formulation or process, route of administration etc.) and as a precursor to method transfer. These RAs emphasizes on potential differences (e.g., laboratory practices, environment, testing cycle times, reagents sources). During the selection of technique and development of method stages various major differences such as (e.g., availability of equipment) should be recognized and factored. [11]

7) Continuous Assessment:

Life Cycle Management is a form of continuous assessment that is necessary to be conducted so that the analytical method remains compliant with the goal described ATP. It begins with articulation of ATP and continues throughout life cycle of the analytical operation. Any abnormal and Out Of Trend (OOT) results are to be tracked and necessary changes are to be made to maintain the integrity of the Analytical Method. Information from risk assessment and statistics from DOE used as the basis of understanding and further changes can be done if required. This reiterates the importance of creation and maintenance of knowledge space. Control charts and tools to record system sustainability data are employed in life cycle management. [12]

Regulatory Considerations for Current and Future

Recently a joint collaboration announced by the FDA and EMA that began in January 2013. The major aim of this collaboration are (1) development of analytical techniques (e.g., HPLC, HPTLC, GC-MS etc.) of QbD approach; (2) define different protocols for transfer of method; (3) develop method for MODR and its verification on transfer to the industry; and (4) define the various parameters for review for analysis of analytical methods of QbD. [13]

Recommendations

using AQbD developed analytical methods for various drugs that to be reevaluated timely to fulfil any requirements or any improvement in development of method, and various risk factors. Robustness of the method with different range which has to be justified by verification and scientific study in to minimize failure of method in its transfer and reduction of OOS and OOT. [14]

PAT and AQbD

Development of AQbD is greatly suggested by the effective implementation of process analytical technology (PAT) system. According to the FDA guidance, "the desired state of pharmaceutical manufacturing is that product quality and performance are ensured through the design of effective and efficient manufacturing processes" where continuous and life time quality assurance was recommended. Thus PAT is depend upon two major constituents: (a) the study of scientific and technical principles includes process manufacturing; (b) identification of the parameters that affect quality of product. First the study of properties of the API is done, then identification of processing variables which define the properties of the drug. The variables that are essential for requirement of multivariate approach are identified. Now, the progress of pharmaceutical industries to established specific process study and design analytical process control strategies that have effective PAT approach. [15]

CONCLUSION:

AQbD- have an important role in the pharma industry for assuring quality of the product. The output of Analytical Quality by Design approach is the study the product development to commercial production. AQbD tools are QTPP, CQA, MODR, Optimization of Method and Development of Design of Experiment, and Risk Assessment and Control Strategy, validation of Method, and continuous improvement. AQbD provide the correct QTPP and risk assessment and implementation of these parameters and the quality of work can be performed accordingly within proper time lines. AQbD approach can only succeed if there is commitment in the pharmaceutical industry.

Acknowlegement:

This work was supported by the Priyadarshini J. L. College of Pharmacy, Nagpur, India. The authors are thankful for providing necessary facilities to carry out the research work.

Conflict of interest:

No conflict of interest.

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