DRUG DISCOVERY

Analytical quality by design used in the pharmaceutical industry: A review

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ABSTRACT

During the previous decade, the pharmaceutical industry has grown quickly as a result of its focus on product safety, quality and efficacy. By utilizing numerous scientific methods like QbD (Quality by Design) and PAT (Process Analytical Technology), various pharmaceutical companies expanded the quantity of products they were developing. The use of QbD in the creation of formulations and the API synthesis process has been covered in detail in ICH recommendations Q8 to Q11. The QbD technique for the synthesis of APIs was explicitly explained in the ICH Q11 guidelines with examples. The QbD technique is being used by generic businesses to design formulations and from the USFDA's standpoint, it is even required. As of the right moment, none of the regulatory bodies have any standards for AQbD and PAT in analytical development. The ATP-Analytical Target Profile, CQA-Critical Quality Attributes with risk assessment, MODR-Method Operable Design Region, DoE-Design of Experiments and Control Strategy with Risk Assessment, Method Validation, CMM-Continuous Method Monitoring and Continuous Improvement are the AQbD tools.

Keywords: QbD technique, ICH guidelines, Process Analytical Technology, AQbD

1. INTRODUCTION

Nowadays, Quality by Design has become quite popular in the design of analytical methods. While developing a technique, QbD's guiding principles emphasize incorporating quality throughout the whole process rather just assessing it at the end (Schweitzer et al., 2010; Raman et al., 2015; Chandramouli, 2021; Nadpara et al., 2012). According to Q8 (R2) guidelines of the ICH, QbD is defined as "a strategic approach to pharmaceutical development that starts with defined objectives and focuses on product & process expertise and process control, based on sound science and quality risk management" (ICH, 2005; Q8 (R1), 2007; ICH, 2009). ICH and WHO guidelines on the Quality risk management also support the development of method for analysis using QbD approach (Q9, 2006; Q10, 2007; ICH, 2005; ICH, 2008; WHO, 2010; ICH, 2012).

The FDA's effort, for better quality products lead to introduction of - CGMP for the 21st Century: A Risk-based Strategy (USFDA, 2003; USFDA, 2004), which was unveiled in 2002, has forced the industry to go beyond the Quality by Testing

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(QbT) principles to ensure the performance and quality of products. By adopting different concepts like QbD and PAT (USFDA, 2004; George and Howard, 2012; Munson et al., 2016; Rathore et al., 2010), the pharmaceutical industry has made significant improvements in the development of techniques to meet product quality criteria. QbD includes a few activities, such as formulation development, planning and manufacturing processes, which guarantee the product will meet predetermined requirements (Das et al., 2017). Designing a space for the method to construct, control components and manage the risks may be done using the scientific information collected throughout the method development process (Ganorkar and Gupta, 2017).

The classical QbT technique & the analytical QbD approach are contrasted in Figure 1 for general comparison. The established aims to regulate the Crucial Method Variables serve as the foundation of the Scientific AQbD methodology (CMVs) (Kumar and Sangeetha, 2020; Kadam et al., 2017). In order to obtain improved performance, ruggedness, robustness and versatility for on-going improvement, the Scientific AQbD methodology starts with the established aims to regulate the CMVs- Critical Method Variables impacting the CMAs- Critical Method Attributes (Darkunde, 2018). Similar to process QbD, analytical QbD results in a well-understood, suited for purpose and long-lasting approach that consistently provides the anticipated performance throughout the length of its existence (Bhutani et al., 2004).

Elements	QbT approach	QbD approach
Product process development	Data intensive submission–disjointed information without 'big picture'	Knowledge rich submission- showing product knowledge and process understanding
	A specification based on batch history	A specification based on product performance requirements
	'Frozen process'–discouraging changes	Flexible process within the design space allowing continuous improvement
	Focus on reproducibility–often avoiding or ignoring variation	Focus on robustness–Understanding and controlling variations
Risk management	Compliance focus changes require prior approval	Regulatory scrutiny adjusted to the level of process understanding continuous improvement allowed within the design space
	Control strategy managed mainly by intermediate & end product testing	Risk based; control shifted up strong real-time release
	Quality decision divorced from science & risk evaluation	A decision based on process understanding & risk management
Validation	Fixed; validation on 3 initial full-scale batches, focus on reproducibility	Adjustable within the design space continuous verification within a design space; focus on control strategy & robustness
Process control	In-process testing for go/no-go offline analysis; slow response	Management of variability process control focused on critical attributes, continuous quality verification
	Quality assured by testing & inspection	Quality built into product & process by design, based on scientific understandings
Lifecycle management	Reacting to problems and OOS; post approval changes needed	Continual improvement enabled within the design space

Figure 1 Differences between QbT approach and QbD approach (Gawade et al., 2013)

2. ELEMENTS OF AQBD

Figure 2 presents all the elements of AQbD.

Analytical target profile (ATP)

The method's purpose also known as ATP can be defined "It is a statement that guides the ideal choice, design and development processes". The International Conference of Harmonization Q8 R (2) rules describe ATP as a simple instrument for method development. It consists of every performance criterion necessary for the suggested analytical application. For each of the features listed in the control approach, an ATP would be created (Gawade et al., 2013). The ATP specifies the acceptance criteria for the technique (i.e., what it must measure) and the amount of measurement that is necessary (degrees of performance parameters, which include range, sensitivity, precision, accuracy & the associated performance criterion). In AQbD, ATP is a crucial feature that allows the selection of analytical techniques to be refined more and more over time. The internal change control management system is accountable for efficient deployment of ATP to offer regulatory compliance in the pharmaceutical industry (Roy, 2012; Raman et al.,

2015). With the use of scientific information and an awareness of the analytical procedure, ATP is defined. It is necessary to do a preliminary risk assessment in order to prepare for expected technique necessities & analytical criticalities.

Figure 2 Elements of Analytical QbD

ATP for analytical methods comprises of
a) Target analytes selection
b) Analytical technique is chosen,
c) Method requirements are selected.

The performance indicators that offer the crucial data required to quantify an undetermined amount of the material by employing the method proposed are accuracy and precision. A technique must have linearity over a range of concentrations, adequate specificity, sufficient peak resolution for fine integration, repeatability of injections, etc. to be determined accurately and precise.

Critical Quality Attributes

"A physical, chemical, biological or microbiological property or feature that should be within an acceptable limit, range or distribution to achieve the intended product quality," according to ICH Q8 (8), is what is meant by CQA (Critical Quality Attributes). CQAs are parameters that affect both the product's quality and the effectiveness of the procedure that was developed.
CQA can vary depending on the analytical method used and the goal for which the approach was created.
The pH and composition of mobile phase, diluents, column choice, organic modifier and elution method are all parts of the CQA for HPLC (UV or RID).
The oven temperature and its program, the injection temperature, the flow rate of gas, the sample diluent and the concentration are the CQA for the GC method.
CQA for the assay determination procedure include plate count, extraction efficiency (percent recovery), Tailing factor and relative standard deviation of replicate injections of the reference standard.
In addition to the parameters listed above for assay determination adjacent peaks is another criterion that is crucial in impurity determination.

Polarity, solubility, pH value, charged functional groups, boiling point and solution stability are some of the physical and chemical properties of the drug substance and impurities which can also be described as CQA for analytical process development (Trivedi, 2012; Jain, 2014).

Risk Assessment

It is described as a systematic process for the examination, regulation, interactions and overview of quality risks throughout the lifecycle of the product in the ICH Q9 guideline. This phase must be finished in order to assess the method's reliability. When a methodology has been chosen, AQbD focuses on a detailed risk evaluation of the factors, such as analyst procedures, instrument design, measurement and technique characteristics, sample characteristics, sample preparation and ambient circumstances, that may cause possible method variability.

AQbD mandates the risk assessment before the method is transferred and all through the product life cycle as opposed to traditional quality by-testing method development, which focused on evaluating the method after transfer. Risk assessment can be done in three ways, as per ICH Q9. The three processes of risk assessment, namely the identification of risk, analysis of risk and evaluation of risk, are outlined in ICH Q9 (Q10, 2007; Mc-Connell et al., 2011; Kelley et al., 2016; Jadhav et al., 2014). Using a Fishbone Diagram, commonly known as an Ishikawa diagram, is one of the usual methods of performing a risk assessment. The risk variables are categorized into the following groups as a result:

a) Factors that are termed have High-risk, such as improper techniques of sample preparation during the process of method development, will be fixed.

b) Noise Factors: An MSA research is conducted on them. Staggered cross-nested study designs, variability plots, ANOVA and other methods can be used to accomplish this. Robustness testing is applied to these elements.

c) Experimental factors, such as equipment and operating procedures tested for toughness and a suitable range is determined.

The last step is the risk evaluation, which is carried out using matrix designs and FMEA- Failure mode and effects analysis (Kulkarni and Shrivastava, 2013).

DoE: Design of Experiments

After the possible and essential analytical method variables have been identified with the first risk assessment, DoE may be employed to validate and improve important technique variables based on their statistical significance. For each unit operation, it can be calculated alone or in combination with a range of other method elements, their correlations and their results. This approach offers a fantastic chance to test a wide range of circumstances generated by a small number of trials (Khare, 2016; Molnar et al., 2010; Raza et al., 2013). In order to find the pertinent method variables & the suitable optimal ranges for those variables, where a stable area for the fundamental method features may be formed, data studies utilising statistical methods are therefore imperative. According to the ICH Q8 guidelines, process resilience is the "capacity of a process to accept variability of materials and modifications of the process & equipment without adversely affecting quality" (ICH, 2005). The characteristics of the beginning materials have an effect on the robustness, impurity profiling, physico-chemical attributes, process capability and stability of the pharmaceutical drug substance manufacturing process. The knowledge required to define robustness parameters will be provided through process understanding by analysing various operating scenarios, scales and pieces of equipment (Ranga et al., 2013; Czitrom, 1999; Ranga et al., 2014; Shivhare and Mc-Creath, 2010). The Figure 3 shows stepwise process involved in DoE- Design of Experiments and appropriate examples are presented.

MODR (Method Operational Design Region)

To establish operating areas for routine operations, MODR is used (e.g., time of analysis, procedure and its limits). The MODR may be produced in the method development phase, in accordance with the requirements of ICH Q8 standards, respecting "design space" in development of product (Kumar and Gupta, 2015; Wagh et al., 2015), which may act as a source for trustworthy and affordable methods. Setting up the required operational conditions is made easier by understanding method performance regions. Analytes' sensitivity to analysis and key technique parameters should be assessed. The operational range (OR) of a critical method input variable, such as a CQA, is what determines whether the findings produced are consistent with the ATP's stated objectives (ICH, 2005). MODR offers the flexibility of different input process parameters to produce the anticipated method performance standards and method response without any need to resubmit it to the FDA. It is based on a process that considers risk, science and multivariate studies to evaluate the impact of various features on the success of the treatment (Chavan et al., 2015).

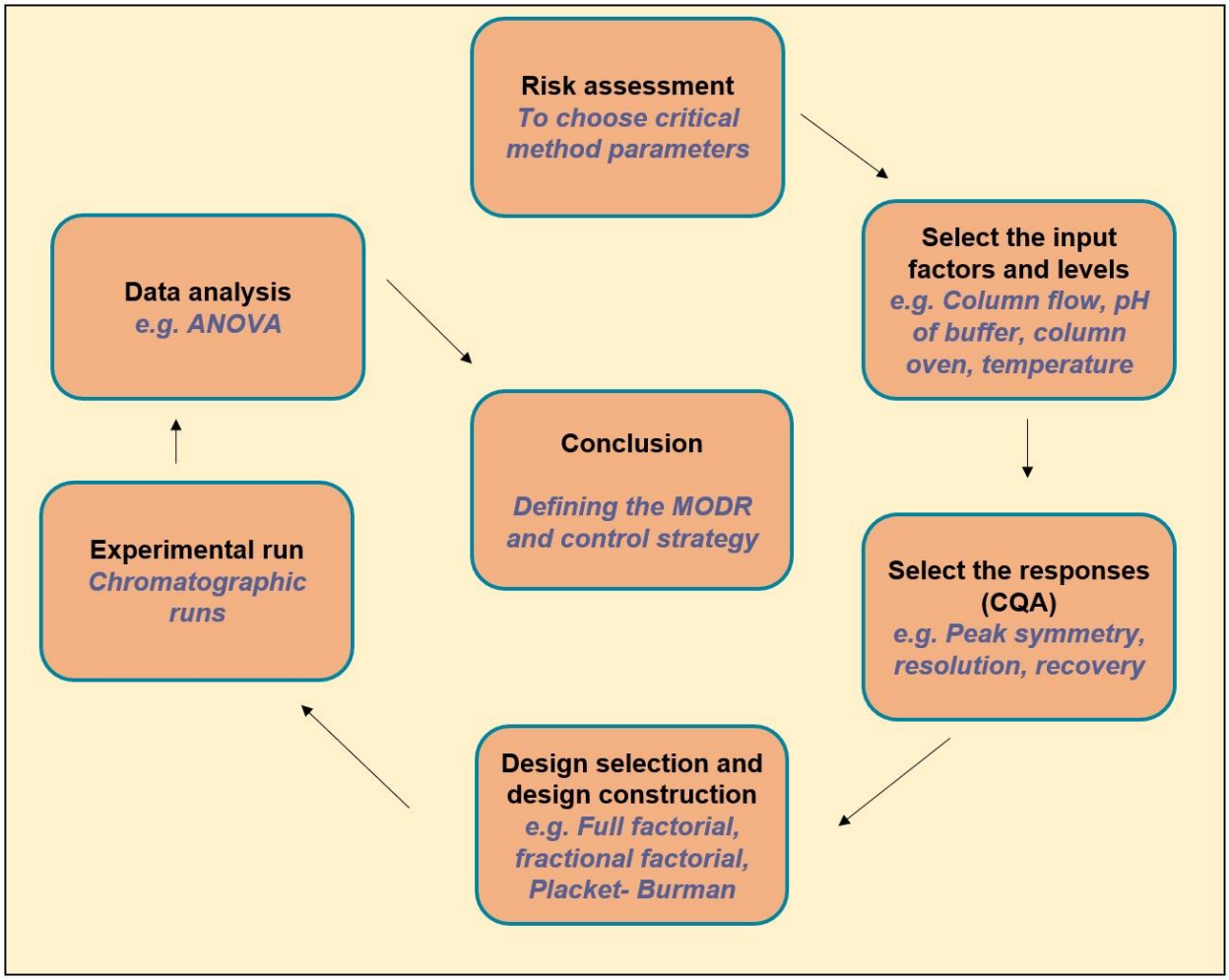

Figure 3 Outline of steps involved in Design of Experiments; CQA- Critical Quality Attribute; ANOVA- Analysis of Variance; MODR- Method Operational Design Region

Critical method parameters (CMP)

The analytical method's sensitivities are important technique parameters. CMP and CQA are causally related and CMP has an effect on the specified CQAs. Material characteristics, instrument-related CMP, instrument operational parameters and other method parameters are some of the different types of CMP. Critical method parameters are also classified using the methodology (HPLC, TLC, GC etc.) (Sangshetti et al., 2017; Davis et al., 2008). A GC method's critical method parameters could include the temperature of injector, detector temperature, type of carrier gas and split ratio, whereas the critical method parameters for an HPLC method are the mobile phase's pH, the organic modifier in the mobile phase and column oven temperature. The plate counts and tailing factor (CMP) for an HPLC procedure can be impacted by column ageing (CQA). Sonication time (CMP) during sample preparation affects the effectiveness of drug extraction (CQA). After CMP & CQA are complete, assessment of risk is carried out based on past information to choose the CMPs for additional evaluation done using experiment design (DoE).

Method Control Strategy

Creation of a control strategy is crucial to ensuring that the method consistently achieves the objectives outlined in ATP. In essence, it is a designed set of controls meant to reduce process variability. The approach depends on the data. The control strategy is built on data produced during method development and method verification. An element that has been deemed dangerous has to be under control. More weight is placed on high-risk variables. An established method control plan can be made if the risk is modest and manageable. This approach usually involves an appropriate system suitability check, which is periodically checked by exerting control over it to make sure the method provides the necessary method qualities. It is interesting to note that the AQbD control approach is identical to the conventional control strategy. Administration of Life cycle when going through each of the AQbD components for a specific analytical method developed, the validation of method, verification and the transfer are the crucial phases

that guarantee the method is fit for its intended use. The phrase "lifecycle management of analytical method" describes the entire operation, which begins with the creation of ATP and lasts until the procedures are being used. Performance qualification, like precision testing at the site of regular use, is centred on the ensuing ATP confirmation (Piriou et al., 2012; Zhang and Mao, 2016). The assurance that the technique is under control throughout its lifespan is provided by the continuous verification activities.

Validation of AQbD Methods

Analytical methods are validated using distinct API batches using the method validation technique. To create method validation for every type of API manufacturing change without the need for revalidation, it uses both the DoE and MODR knowledge. The method offers data on the interactions, measurement uncertainty, control strategy and continual enhancement in addition to the necessary ICH validation elements (Gholve et al., 2015; Gandhi and Roy, 2016). Compared to the conventional validation strategy, this method uses fewer resources without sacrificing quality. Figure 4 shows the general differences involved in between the Quality by testing and Analytical Quality by design approach.

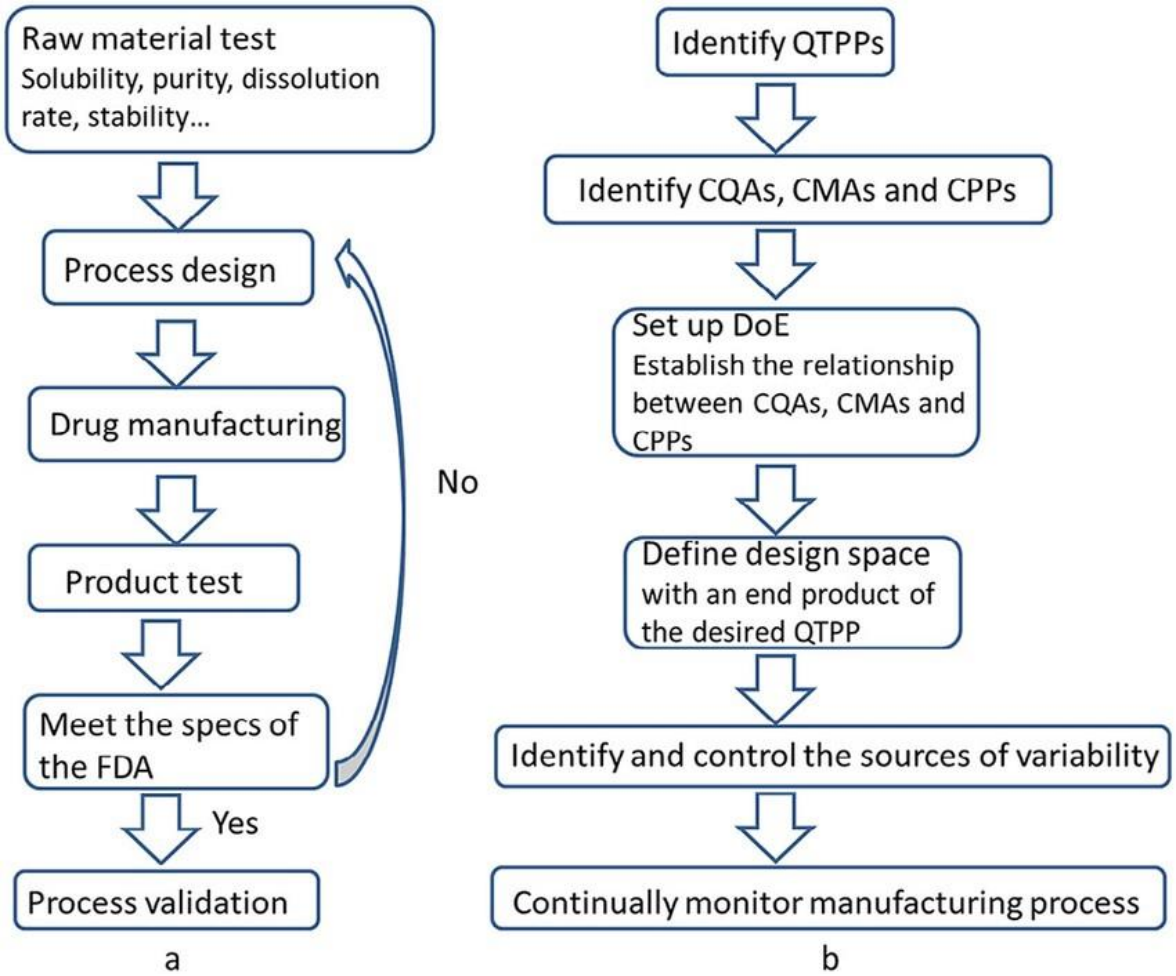

Figure 4 Stepwise differences between (a) QbT- Quality by Testing & (b) QbD- Quality by Design; QTPP: Quality target product profile; CQA: Critical quality attributes; CMA: Critical material attributes; CPP: Critical process parameters; DoE: Design of experiments) (Zhang and Mao, 2016)

Continual Method Monitoring (CMM)

Life cycle management is a control strategy for the commercial stage execution of the design space. CMM, which is a continuous method of exchanging knowledge acquired during the design and use of the design space, is the final stage in the AQbD life cycle. This includes the results of risk studies, assumptions based on information currently available, issues with statistical design and a relationship between the design space, MODR, control strategy, CQA and ATP. After a method validation is finished, it can be utilized regularly and its performance can be tracked continuously method-related research and other tools can be used to accomplish this. The analyst can proactively spot & handle any OOT performance thanks to CMM (Araújo et al., 2021; Bhise et al.,

2019). This may be done using a variety of techniques, including control charts, tracking system appropriateness data, process-related research and more.

3. CONCLUSION

The pharmaceutical industry relies heavily on Analytical QbD to guarantee both reliability of the method and the quality of the final product. Understanding technique development and applying the approach to massive commercial production are the results of AQbD. The AQbD tools are the ATP, CQA, MODR and Control Strategy with Risk Assessment, Method Validation and Continuous Improvement. The inputs, which represent prospective influences and the outputs, which represent crucial analytical answers, are investigated to ascertain the links during method development. Important analytical factors are identified during the process development using a method like that stated in ICH Q8 and Q9. The AQbD strategy actively participates in detecting potential risks and afterward works on reducing those risks to improve product quality. Consequently, when taken as a whole, all the components of AQbD offer a greater knowledge of the method's performance and enable on-going method improvement.

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Informed consent

Not applicable.

Ethical approval

Not applicable.

Conflicts of interests

The authors declare that there are no conflicts of interests.

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Data and materials availability

All data associated with this study are present in the paper.

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