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Quality by Design – A Review

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Abstract

At various points along the life cycle of a pharmaceutical product, analytical procedures must be established. These tasks, if not optimised using scientific knowledge and process understanding, might result in a lengthy and expensive process. In an effort to supplement or replace the current components of risk and quality management systems, the pharmaceutical industry is always looking for new policies and features. Joseph M. Juran, a renowned authority on quality, conceived up Quality by Design (QbD) first. Analytical method development, or AQbD, is an expansion of the Quality by Design idea. The Quality by Design methodology places a focus on understanding products and processes as well as controlling those processes. It starts with predetermined objects and follows a methodical approach to development.When it comes to developing new methods and drugs, analytical quality by design is an essential component of the current paradigm. In addition to addressing implementation-related issues, the primary goal of this review article is to outline the various stages of AQbD method development. Analytical Method Validation, Control Strategy, Critical Performance Attributes (CPAs), Analytical Target Profile (ATP), and Method Operable Design Region (MODR) are all parts of the analytical method development strategy.

KEY WORDS: Analytical Quality by Design, Analytical Target Profile, Critical Performance Attributes, Method Operable Design Region...

Introduction

Following the FDA's introduction of qualityby-design (Qbd), the pharmaceutical sector began to use it as a benchmark. To be acknowledged and licenced as a medication, every substance must meet some fundamental requirements, including quality, safety, and effectiveness. A drug's quality is defined by how well it works for the purpose for which it was designed.,2. Because of its critical importance in product development, analytical procedures must be established and verified before pharmaceutical manufacture can begin. In addition to checking for purity at every step of the product development life cycle, a reliable, accurate, and precise analytical approach ensures that the medicine meets the quality standards set by its intended therapeutic application. Because of how negligent this is, a lengthy and expensive treatment could be required. In order to guarantee the method's lifetime performance, it is important to establish ruggedness and robustness early on in the development process.Analytical method failure, particularly during method transfer, is on the rise nowadays. In addition to reducing or eliminating batch failure, increasing efficiency, and cutting costs, the QbD approach to design space formation finds an appropriate method control that offers the desired space. 3

A methodical approach to development that starts with established goals and emphasises product and process knowledge and process control, based on strong science and quality risk management" is how ICH Q8 standards describe QBD."[4]

Table 1: HISTORICAL BACHGROUND of QbD[5-7]

YEAR	ACTIVITIES
1950	Operation windows
1970	QBD created by Joseph M Juran
Sept 2002	QBD concept integrated by USFDA in cGMP
Sept 2004	USFDA release final report in "Pharmaceutical cGMP"
Sept 2004	USFDA Guidance for Industry: PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Control
Nov 2009	ICH: Q8(R2) Pharmaceutical Development
Nov 2005	ICH: Q9 Quality Risk Management
June 2008	ICH: Q10 Pharmaceutical Quality System

APPLICATIONS of AQbD[8]

Analytical Research Development

The ability to transition methods from research and development to quality control depends on having a thorough grasp of each essential aspect with the Method Operable Design Region. Improving the method's resilience via reducing variability in analytical characteristics

Manufacturing Plant & Quality Control

A comprehensive model that anticipates the product's behaviour in response to changes in all CMAs and CPPs that are modifiable in the design space, in addition to additional quality by design tools.

Quality Assurance

Using Quality Risk Management throughout development, investigating variability or batch failure for root cause analysis will be simpler, faster, and more efficient. Batch failures, variances, and expensive investigations may all be eliminated.

Regulatory Affairs

It will be a breeze and take no time at all to review and approve. In addition, the established and validated design space will provide regulatory leeway for the management of changes made after approval.

What is Analytical Quality by Design? [9-10]

In order to guarantee the quality and performance of products, the industry has begun to seek alternatives to quality by testing (QbT) since the advent of AQbD. Acquired information during development may help with forming a design space and determining appropriate process controls. The output of AQbD is a solid, well-understood, and purpose-built procedure, much like process QbD. that maintains its performance characteristics throughout time. By identifying essential quality qualities and analysing their influence on final product quality, AQbD aids in the scientific knowledge of pharmaceutical process and technology. Allows for ongoing improvement till method completion, in addition to providing development with the necessary design space.By reducing deviations and scientific variances, it improves resilience and eliminates regulatory compliance concerns.

Chromatographic analytical techniques are well-known for their many benefits over non-chromatographic methods. These techniques include gas chromatography (GC), high performance thin layer chromatography (HPTLC), and super critical fluid chromatography (SFC). They can do a variety of tasks, are strong, and need few samples. By using automation, these strategies significantly reduce the likelihood of human mistake.

Table 2: DIFFERENCE BETWEEN REGULATORY PERSPECTIVE OF QbD and AQbD[11]

Product Quality by Design (QbD)	Analytical Quality by Design (AQbD)
Quality Target Profile **(QTPP)** Definition	Analytical Target Profile (**ATP**) Definition
Critical Quality Attributes **(CQA)**	Critical Performance Attributes **(CPA)**
Risk Assessment of Critical Material Attributes and Critical Processing Parameters	Risk Assessment of Critical Method Attributes and Critical Method Parameters
Designing of Experiments and Development of Design Space**(DS)**	Designing of Experiments and Development of Method Operable Design Region **(MODR)**
Manufacturing Process Validation	Analytical Method Validation
Implementation of Control Strategy	Implementation of Control Strategy
Continual Process Improvement	Continual Method Improvement

ELEMENTS OF AQbD[12]

Fig. 1 Elements of QbD

ANALYTICAL TARGET PROFILE (ATP):

The ICH Q8 R(2) guidelines state that ATP is the first stage in developing a technique by considering systematic variability, inherent variability, and system appropriateness. No matter how detailed the analytical requirements are, there will almost certainly be several modifications to the technique while it is being developed. These changes might be caused by unintended deviations, continuous improvement efforts, or changes in operating conditions.The first step in developing a method is identifying and selecting the target analytes, which may be either products or contaminants, that will have an impact on the technique's performance. Potential targets include active pharmaceutical ingredients (APIs) and contaminants, analytical method, analyst, laboratory setting, apparatus, and procedure..[13]

Precision, accuracy, range, sensitivity, and the related performance criterion are examples of performance level attributes that are defined in the ATP. The acceptance criteria are the things that the technique needs to test.

Some of the most typical ATPs for an instrument like an LCMS/MS include things like noise, column temperature, heat block temperature, buffer pH, flow rate, and so on. .[14-15]

CPA (Critical Performance Attributes)

According to ICH Q8 (8), a critical quality attribute (CQA) or critical product attribute (CPA) is a physical, chemical, biological, or

microbiological feature or characteristic that has to fall within a certain range in order for the product to meet the quality standards set forth.

Analysis of the method's success is dependent on the analyst's ability to isolate its most important parameters. Project to project, the CPAs will look different. Parameters pertaining to the analyte, the instrument, and the operating circumstances make up the three main categories of critical method parameters (CMPs). Standardisation, reagents, mobile phase composition, pH and flow of mobile phase, column temperature, detector selection, and sampling are some of the typical CPAs for chromatographic investigations. For the parameters mentioned above, the correct quality attributes (responses) would be robustness, resolution, retention duration, tailing factor, detection limit. When developing analytical methods, CQA takes into account the drug's physical and chemical characteristics as well as any contaminants, including polarity, charged functional groups, solubility, pH value, boiling point, and solution stability.[17]

Risk Assessment

"It is systematic process for the assessment, control, communication and review of risks to the quality across the method development," said the ICHQ9 guideline. In order to establish a degree of certainty about the method's reliability, this stage is crucial. Analyst techniques, instrument setup, measurement and method parameters, sample properties, sample preparation, environmental factors, and CPA and ATP identification are some of the variables that AQbD emphasises in a thorough risk assessment of potential method variability.

Risk identification, analysis, and evaluation are the three phases that make up a risk assessment, as stated in ICH Q9.Every step of a method's lifecycle, from conceptualisation to ongoing evaluation, may benefit from a thorough risk assessment. [18-19]

Risk identification

Diagram of the Ishikawa Fishbone

By classifying the components according to their origin, the Ishikawa Fishbone diagram may reveal the potential dangers and their effects on the method's efficiency. Additionally, SIPOC may detect it by looking for a possible disconnect between the following: (S= supplier, I input, P= high level process, O= output, C= customer).[20]

Risk Analysis

Relative Risk Matrix Analysis and Failure Modes Effects Analysis are two methodologies that may be used to analyse potential risks.

Analysing Risk in a Matrix Format Sorting the chosen ATPs into low, medium, and high risk categories on the CPA is the first step in calculating the relative risk matrix. Method of instrument operation, reagent properties, cycle duration, etc., might all pose dangers. No more research is necessary since the dangers are minor and may be widely accepted. Unacceptable and requiring further research to mitigate, medium and high risk variables get the lion's share of the spotlight.

Analysing the Effects of Failure Modes.

Here we have an alternative method of risk analysis.The procedure involves assigning each risk a severity, incidence, and detection-based numerical value from 1 to 5, which, when multiplied, yields the Risk Priority Number. After that, we'll draw a bar graph with RPN on the y-axis and the method's characteristics and factors on the x-axis. Each element is ranked from most important to least important using a Pareto chart, with high-risk variables being labelled as "Critical" according to RPNs. Out of all the hazards, the method attributes with an RPN greater than 25 should be considered the most critical material attributes of the API and should be optimised or managed accordingly.

Method Operable Design Region

MODR is an experimental strategy that systematically changes input factors to find out what changes the output responses significantly. It also finds out what factors are related to each other so that all the possible factors can be evaluated quickly and methodically.

While developing a method, it is possible to identify a source for a reliable and economical method by establishing a method operable design region (MODR).It is the crucial method input variable's operational range that reliably yields outcomes that meet the ATP's objectives. Without having to resubmit to the FDA, MODR allows for flexibility in a number of input method parameters, which in turn offer the desired performance requirements and reaction of the method. Following its definition, the necessary controls for the method may be

implemented, and the process of verifying and validating the method can begin.

If there are more than four elements, screening designs must be used to identify which ones are significant before optimisation strategies can be used. When there are less than four factors, optimisation designs may be used directly.[21-22]

Selection of Designs :

a) **Screening**

Qualitative input factors may be eliminated by screening. For the optimisation studies, it specifies which crucial method parameters (CMP) are important to take into account. Use a plackett burmann or fractional factorial design when you want to screen a lot of variables. The fractional factorial design is an option when there are more than four but less than six variables, while the Plackett Burmann design is an option when there are more than six elements.

b) ***Optimization***

Multiple optimisation strategies are available, including factorial, response surface, and mixed designs. Full factorial designs are appropriate for evaluating both the main effects and the interactions between variables when there are more than two but less than five factors. Response surface designs are used when there are no more than two or four elements and the objective is to optimise identified individual important factors. Mixture designs are used when optimising the ratio of important components in a mixture is the aim, and factors are components of a mixture. Two designs for the response surface—the box behnken and the central composite—and two for the mixture—the basic lattice and the confined mixture—are available. For each Experimental Run, dependent responses (CPAs) are tested for each possible combination of variables once the experimental design has been chosen. It is necessary to provide all answers after model assessment in order to optimise all factors numerically and graphically.

Selection of model:

The predicted response behavior's shape should inform the model's selection after all experimental runs. A model is a mathematical link between variables and response. Scheffe, cubic, linear, or quadratic are all possible forms. It is important to do a comprehensive analysis of variance (ANOVA) while selecting a model in order to assess the relevance of each model using the Goodness of Fit and Lack of Fit statistics. Here, we'll look at the adjusted and anticipated R2 values as well as the f and p values and accuracy values.

Interpretation of model graphs:

A)1D interaction: it displays the linear impact of altering the level of a single factor; model graphs will provide a clear image of the response's behaviour at multiple levels of factors at once via the projected response equation with separate coefficients.

A two-dimensional contour shows how two separate variables influence a single answer.c) three-dimensional surface: it shows how a four-dimensional cube works.

The Design Space should be validated by conducting at least three confirmatory experimental runs within the specified design space range after its development. In order to compare the observed results from these test runs

with the predicted results from the model prediction equation, a correlation coefficient (R2) of at least 0.9 will be used.[23]

Control Strategy

The performance of the technique and the quality of the product are guaranteed by a set of controls for CMAs and CMVs that are generated from the present extensive method development that is taking place during the lab scale developmental stage. An all-encompassing plan for ensuring quality using what is known about the process and the product as of now is the control strategy.To make sure the procedure stays under control, this step also involves collecting data, analysing it, and eventually replicating optimised trials.[24]

Product life cycle by continual improvement The process will be kept under control by taking the necessary steps to fix, foresee, and avoid future issues in the event that any unanticipated technique variability is identified.[25]

CONCLUSION

If you want to make sure a system or process regularly functions as expected, you need an accurate data analysis tool to do the job. One method that really encourages scientists to study a process or system in depth is using QbD. Several regulatory rules worldwide now require process optimisation using QbD. The

knowledge gained by developing and transferring methods is the end result of AQbD. Method Optimisation and Development with DoE, MODR, Control Strategy with Risk Assessment, Method Validation, and Continuous Improvement are all AQbD tools. ATP and CPA are also part of the toolkit. The pharmaceutical industry has seen a rise in the use of QbD in areas such as biopharmaceuticals, analytical methods, drug development, formulations, and formulations.

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