Biomedical & Pharmacology Journal, September 2023. Vol. **16**(3), p. 1669-1679

Quality by Design Approach: Progress in Pharmaceutical method Development and Validation

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https://dx.doi.org/10.13005/bpj/2745

(Received: 22 September 2022; accepted: 02 February 2023)

Pharmaceutical analysis plays a significant role in pharmaceutical formulation quality assurance and control. Due to the pharmaceutical industries' rapid expansion and the production of pharmaceuticals all over the world, there is a greater need for novel analytical procedures in this sector. Establishing the identification, purity, physical properties, and potency of medications as well as the medication's bioavailability and stability is the goal of analytical method development. A few new drug applications were recently given regulatory flexibility by the Food and Drug Administration for an analytical method based on quality by design. With Quality by design, product design and development are performed methodically. Analytical methodologies have similar opportunities for implementing Quality by design as production procedures do. It consequently enhances formulation design, development efficiency, and capacity. The underpinnings of the QbD approach have been explored in this article due to their use in the creation and validation of analytical procedures. Additionally, a summary of experimental studies reporting the application of the QbD methodology to method development is included.

Keywords: Quality by design, Method development, Validation, Design of expert, Pharmaceutical Analysis.

Pharmaceutical industrial production is one of the most carefully regulated and governed sectors by traditional regulatory agencies, as the quality of pharmaceuticals is directly tied to public health. Consequently, it is necessary to control the quality of medications. The pharmaceutical industry aims to provide products and production processes that reliably meet established requirements. The ability to meet the demands and expectations of the client in terms of service, product, and process is what is meant by quality[1]. All regulatory organizations for pharmaceutical products place a high value on quality. Customer happiness equates to quality[2].

To prove that new medications are safe and effective, the pharmaceutical industries put lot of efforts into developing, producing, and bringing them to market[3]. They also work hard to comply with regulatory regulations. Every year, more medications are released onto the market. These medications could either be entirely new or structurally modified versions of already existing ones. From the moment a drug is released onto the market to the time, it is included in

Pharmacopoeias; there is frequently a lag in time. This is brought on by potential risks associated with long-term and widespread use of these medications, reports of novel toxicities (leading to their removal from the market), the emergence of patient resistance, and rival companies' launch of superior medicines. Standards and analytical techniques for certain medications may not be included in the pharmacopoeias under these circumstances. Thus, the need to create newer analytical methods for such medications arises[4]. A new strategy for medication development might boost productivity, offer regulatory clearance and flexibility, and bring about significant economic gains throughout the product's life cycle[3].

Quality assurance and quality control of pharmaceutical formulations and bulk pharmaceuticals rely heavily on pharmaceutical analysis. The demand for novel analytical techniques in the pharmaceutical industries has increased due to the pharmaceutical industries' rapid expansion and the manufacture of drugs in different parts of the world. The biopharmaceutical and vaccine industries use analytical techniques for research and development as well as to manage the inputs and outputs of manufacturing[5]. Establishing the identification, purity, physical properties, and potency of pharmaceuticals, as well as the drug's bioavailability and stability, is the goal of analytical technique development. The improvement of analytical tools has led to recent developments in analytical methodologies. The development of better analytical methods and tools has resulted in shorter analysis times, greater precision and accuracy, and lower analysis costs. As a result, the majority of pharmaceutical companies are spending enormous sums of money to create cutting-edge analytical laboratories[4].

Product development heavily relies on the development and validation of analytical methods. In addition to guaranteeing that a drug's quality is reached as per its intended therapeutic use, each stage of the product development life cycle includes a purity check that is performed using a trustworthy analytical approach. The analytical method utilized for the production of commercial products must be quick, dependable, and accurate since the ultimate quality check results of the finished piece and other batch data influence when the product can be released to the market. Analytical techniques frequently include estimating the target substance's physical, chemical, physicochemical, and/or biological properties. Because they have many advantages over other non-chromatographic methods, chromatographic analytical techniques like High-performance liquid chromatography (HPLC), Gas chromatography (GC), and High-performance thin-layer chromatography (HPTLC), and supercritical fluid chromatography (SFC) are widely used. They need fewer samples and are sturdy and adaptable. These methods reduce the likelihood of human error by using automation.

The development of an analytical procedure that precisely serves the intended function is the analytical chemist's top priority. There are currently two methods used for developing analytical methods in analytical chemistry. The former relies on trial and error and analyses one factor at a time (OFAT), in which a single parameter is optimized for the anticipated response while all other parameters are held constant. This procedure consistently results in the method's narrow robust behaviour for the instrumental variables used throughout the method development phase. Because of this, developing analytical methods with the OFAT approach involves a significant chance of method failure and constantly necessitates the development of alternate methods or revalidation protocols, which drives up the cost of the technique[1].

Quality by design approach

Dr. Joseph M. Juran, a quality pioneer, is credited with creating the idea of quality by design (QbD). According to Dr. Juran, quality should be built into a product from the start, and most quality crises and issues originate from poor product design[6]. The QBD is described as "A systematic approach to development that begins with established objectives and stresses product and process understanding and process control, based on strong science and quality risk management"[7] in accordance with the International Conference on Harmonization Quality guideline 8 (ICH Q8) criteria. To improve robust production processes, facilitate product quality, and create products in accordance with "six sigma," the concept of "quality by design" (QbD) has been developed in the pharmaceutical business[8].

According to several experts, the prospects for applying QbD to analytical methods are

comparable to those for production processes[9]. The AQbD (analytical QBD) assists in the development of a trustworthy and reasonably priced analytical method that is relevant across the lifecycle of the product in order to enhance the regulatory leeway in the analytical approach. It refers to the ability to modify a method's parameters anywhere in its design space, also known as the method operable design region (MODR)[10,11].

Objectives of Quality by design

Pharmaceutical QbD is a methodical approach to development that emphasizes both process and product comprehension and control based on solid science and quality risk management[6,12]. The following objectives of pharmaceutical QbD may be present:

1. Establishing clinical performance-based meaningful product quality specifications
2. To increase process capability and minimize product variability and faults by improving product / process design, understanding, and control.
3. To boost productivity in product development and production
4. To improve postapproval change management and root cause analysis

Robustly developed products and processes are necessary for achieving this goal. The identification and management of issues affecting the quality of the drug product can also be facilitated by increased product and process expertise. The procedure should be improved after receiving regulatory approval to decrease product variability, flaws, rejections, and recalls.

Product design and development are done systematically with QbD. As a result, it improves formulation design, development speed, and capabilities. Additionally, it moves resources from an upstream proactive mode to a downstream corrective way. It enhances the manufacturer's capacity to pinpoint the underlying reasons behind manufacturing failures. Therefore, improving manufacturing and product development efficiency is pharmaceutical QbD's third goal.

Key Elements of Quality by design

In a pharmaceutical QbD strategy for product innovation, a claimant identifies qualities that are crucial to quality, changes them into the critical quality attributes (CQAs) of the drug product, and identifies the association between formulation/manufacturing factors and CQAs to ensure the patient will receive a medication product with these CQAs. The elements that make up QbD are as follows:

1. A quality target product profile (QTPP) that lists the drug product's crucial quality attributes (CQAs)[6,13].

To support drug labelling and drug development efforts, TPP describes the necessary profile or attributes of a drug product. TPP lists the intended application, target, pace of administration, and other key product characteristics, together with quality designing for a drug product[14].

The phrase "TQPP" for product quality may be a logical extension of "TPP." The QTPP is a crucial document that enables the rationalization and evolution of the data that is not inheritable throughout the drug's lifespan. To affirm the targeted quality, a prospective outline of the attributes of quality for a drug product that will be reached while taking into account the safety and effectiveness of the targeted product is provided. Indefinite-quantity, type, strength, instrumentation closure system, identity, indefinite-quantity type, purity, and stability are all included in TQPP[15].

The QTPP is a possible list of the characteristics of a drug product that should be met in order to ensure that it is of the desired quality, in addition to the safety and efficacy of the medicinal product. The QTPP serves as the design framework for creating the product[6,12].

To ensure the required product quality, a CQA should be within appropriate limits. Clinical safety and efficacy, manufacturing attribute, and parameter boundaries approach edge of failure are examples of quality attributes[16].

1. A drug product's quality may or may not be essential. The severity of the patient's harm determines how critical of an attribute it is. The criticality of an attribute is unaffected by the probability of occurrence, detectability, or controllability[6,12].
2. Product design and understanding, including the identification of critical material attributes (CMAs)

Clinical research confirms that the product's design impacts whether it can satisfy patients' needs. Stability studies, which corroborate this, show that product design also affects whether a product can retain its performance throughout its shelf life. This kind of product insight might have avoided some historical stability breakdowns.

Creating a high-quality product that can deliver the necessary QTPP over the duration of its shelf life is the primary goal of product design and understanding. Designing a product can take many different directions because it is so open-ended. The following are crucial components of product design and comprehension:

• The drug substance's physical, chemical, and biological characterization (s))

• Determining and selecting the excipient kind and grade, as well as being aware of the inherent excipient variability

• Connections between drugs and excipients

• Formulation optimization and CMA identification for both excipients and the medicinal substance

CMAs differ from CQAs in that they are used for input materials such excipients and drug ingredients. CQAs, on the other hand, apply to output materials like completed drug products and product intermediates[17].

3. Process design and comprehension include identifying critical process parameters (CPPs) and having a solid grasp of scale-up principles that connect CMAs and CPPs to CQAs.

When all significant causes of variation are recognized and explained, variability is controlled by the process, and product quality attributes can be predicted with reasonable accuracy, a process is often regarded as being well understood. The input operating parameters like mixing time, stirring speed, etc., of unit operation are called process parameters. A process parameter should be monitored or managed to guarantee that the process yields the desired quality when variability affects a crucial quality feature.

The formation of a control plan with three tiers of controls, as follows, is the result of the knowledge gathered from properly structured development studies:

The CQAs of the output materials are continuously monitored at Level 1 using automatic engineering control. The most adaptable level of control is this one. Pharmaceutical control at level 2 includes adjustable material attributes, process parameters within the defined design area, and fewer end-product tests. The typical level of control employed in the pharmaceutical sector is Level 3.This control method is based on rigorous end-product testing, closely controlled material properties, and process-related parameters. Any significant change in these necessitates regulatory control due to the incomplete categorization of the causes of variability and the lack of knowledge regarding CMAs and CPPs' effect on the CQAs for medicinal products. The formulation of acceptance criteria, the necessity for further controls, and the debate about acceptable variability consume a significant amount of industry and regulatory resources. A hybrid strategy that combines levels 1 and 2 can be applied. A control strategy is described by ICH Q8 (R2) as a planned set of controls that are drawn from current product and process knowledge and ensure process efficiency and product quality.

Process capability and ongoing development

Process capacity measures the intrinsic variability of a stable process under statistical control with regard to the established acceptance criteria. Through continuous improvement programmes that focus on removing sources of significant variance from the process operation conditions and raw material quality, process capability can be used to measure process improvement. When significant deviations are detected, remedial and preventive actions must be implemented; this can be done by regularly checking process data for Cpk and other statistical process control metrics.

Table 1. Parallels between QbD for Process and Product, and AQbD

QbD	AQbD
Involves quality target product profile (QTPP)	Involves analytical target profile (ATP)
CQAs related to patients requirement or product development	CQAs related to analytical method development
Consider design space	Consider method operable design region(MODR)
Consist of processperformance qualification (PPQ)	Method validation

Table 2. Summary of research work on optimization of analytical methods using the AQBD approach

Drug	Analytical technique	Mobile phase	Experimental design	Independent variables	Dependent variables	Reference
Abiraterone acetate	RP-HPLC Method	CAN/phosphate buffer (20:80 %v/v)	Box-Behnken	Mobile phase composition, pH, and flow rate	Retention time and peak area	[23]
Amiodarone hydrochloride	HPLC	ACN/MeOH/buffer (4.6/3.4/2)	QBD approach	Mobile phase pH, % organic phase, and column temperature	—	[24]
Zolmitriptan, naratriptan, dihydroergotamine, ketotifen, and pizotifen	RP-HPLC	—	24 Factorial design	ACN% in the mobile phase, mobile-phase pH, nature of the buffer, and column temperature	Resolution and Run time	[25]
Artesunate and Amodiaquine impurities	Green HPLC method	Ethanol and 10mM acetic acid	pH, temperature, and gradient slope	3-level full factorial design	—	[26]
Atorvastatin	RP-HPLC	Acetonitrile: water (50: 50)	Box–Behnken statistical design	Mobile phase (acetonitrile: water), flow rate (Rt), and UV wavelength	Area of the chromatogram (AUC), retention time (Rt, min), and tailingfactor (%)	[27]
Ceftazidime	RP-HPLC	ACN to acetic acid (75:25)	Face-centred cubic design	Mobile phase ratio(ACN) and flow rate	Peak area (PA), retention time (Rt), theoretical plate count (TPC),and tailing factor (TF)	[28]
Ceftriaxone Sodium	RP-HPLC	Acetonitrile to water (0.01% triethylamine with pH 6.5) (70:30, v/v),	Central composite design	Mobile phase composition and pH	Retention time, theoretical plate, and peak asymmetry	[29]
Daclatasvir	HPLC, LC-MS/MS, UPLC	55% buffer and 45% ACN	Central composite design	pH and temperature	Resolution of impurity (c-h) and drug	[30]
Efavirenz	HPLC	Methanol, 10 mM ammonium acetate buffer (70:30 v/v),	3^2 full factorial design	Flow rate and pH of the buffer	Retention time (y1) and peak area	[31]
Eltrombopag olamineand its degradation products	Stability-indicating RP-HPLC/ RP-UPLC	0.1 % trifluoroacetic acid (TFA) and acetonitrile	2^4 factorial design	Column temperature, flow rate, the organic ratio in mobile phase, and the concentration of TFA	Resolution	[32]
Etofenamate	RP-HPLC	Methanol and 0.2% triethylamine in water at 85:15	Central composite design	pH of aqueous phase, percentage of the aqueous phase, and flow rate	Retention time	[33]
Ferulic acid	RP-HPLC	ACN: water	2^7 Taguchi design,	Mobile phase ratio	Peak area (PA), retention	[34]

		(47:53 % v/v	face-centred composite design	(X1) and flow rate	time (RT), tailing factor	
Ketoprofen	Stability-indicating RP-HPLC	Phosphate buffer–methanol (50: 50v/v)	Central composite design	Mobile phase ratio and pH of mobile phase	Theoretical plates and peak tailing	[35]
Nevirapine	Reversed-phase HPLC bioanalytical method	68:9:23% v/v elution of methanol, acetonitrile, and water	Box–Behnken design	Mobile phase ratio, pH, and flow rate	Peak area, retention time, theoretical plates, and peak tailing	[36]
Olmesartan medoxomil	Stability-Indicating HPLC	Acetonitrile and water (40 : 60 v/v)	Face-centred cubic design	Mobile phase ratio and flow rate	Peak area, retention time, theoretical plates and peak tailing	[37]
Rufinamide	RP – HPLC bioanalytical method	Buffer :ACN at 84.7:15.3% v/v	Box Behnken design	pH and proportion of the buffer and wavelength of detection	Peak area and theoretical plate number	[38]
Sorafenib tosylate	RP-HPLC	ACN and water 65:35 v/v	Taguchi orthogonal arrays and Face centred cubic design	Mobile phase ratio and flow rate	Peak area, theoretical plates, retention time (Rt) and peak tailing	[39]
Tamoxifen Citrate	—	ACN and phosphate buffer (pH 3.5) 52:48 v/v	Taguchi design and Box-Behnken design	Mobile phase ratio, Buffer pH and oven temp	Peak area, retention time, theoretical plates, and peak tailing	[40]
Telmisartan and Hydrochlorothiazide	RP-HPLC	Mobile phase-A 0.02 M potassium dihydrogen phosphate (pH of 3.5) and mobile phase-B- a mixture of Milli-Q water and acetonitrile (100: 900 v/v) respectively	Three-Level Factorial design	Flow rate, column Temperature and buffer pH	Resolution between drug and impurity	[41]
Fusidic acid (FA)	RP-HPLC	Methanol: acetonitrile (5: 95, v/v)	Taguchi designand Central Composite Design	The ratio of solvents %w/w) and (Water %w/w)	Theoretical Plates, assay (%) and tailing factor	[42]
Valsartan	RP-HPLC	Methanol, ACN, water, and buffers	Box–Behnken design	Mobile phase pH, flow rate, and % organic modifier	Peak area, retention time, theoretical plate count, and peak tailing (PT)	[43]
15 fixed-dose combinations (FDCs) of anti-hypertensive drugs	RP-HPLC	ACN-water (pH 6.2; 42:58 %, v/v).	Box-Behnken design	—	—	[44]
Rotigotine	RP-HPLC	ACN proportion: 54% v/v	Plackett-Burman design and Box-Behnken design	ACN proportion, pH of the buffer, and flow rate	The number of theoretical plates and retention time	[45]
Efavirenz	RP-HPLC	mobile phase: CAN 51.17%v/v	Plackett-Burman design and Box-Behnken design	ACN proportion, pH of the phosphate buffer, and mobile phase flow rate	Retention time and number of theoretical plates	[46]
Bosutinib	Stability-Indicating RP-HPLC Method	ACN-1.0% triethylamine (v/v) in water	Central composite design	Critical method attributes	Critical analytical attributes	[47]

Regulatory Perspective of QbD

Regulatory bodies now strongly emphasize QbD alone rather than only "Quality by Testing" or "Quality by Chance". Analytical procedures are a crucial component of the control plan concerning the pharmaceutical quality system (ICH Q 10 recommendations). Analytical QbD will be implemented in the manufacturing process to guarantee predetermined performance and product quality as a control technique[7].

ICH guidelines and QBD

The ICH guidelines provide clear definitions of QbD principles: Q8 (R1): pharmaceutical development, Q9: quality risk management, and Q10: pharmaceutical quality system.

Stages in QBD vs AQBD

Analytical QbD implementation follows a similar method to that of product QbD. Initially, the target measurement for implementing AQbD is dependent on the product file in the form of the ATP (analytical target profile) and CQA (ATP is the analogue of QTPP in product design).A comparison between QBD and AQBD is given in Table 1.

Implementation AQBD

Analytical Target Profile (ATP)

ATP specifies the objective of the development of analytical methods. The definition of ATP, recently offered by PhRMA and EFPIA, is as follows: "ATP is a declaration that describes the method's goal and is used to guide method selection, design, and development activities." Following regulatory authorities' approval of the ATP statement, ATP is a crucial AQbD characteristic that enables increased improvement of analytical techniques and their selection. While the examples above are mostly focused on directly measurably and changeable technique parameters, the ATP should ideally cover all important aspects of method performance.[20,21]

Analytical Method Performance Characteristics

These are specified to satisfy the requirements of the analytical target profile. For chromatographic separations, USP and ICH have published numerous validation factors and are regarded as method performance characteristics. Accuracy, specificity, linearity, precision, detection limit, and quantification limit are these parameters. Robustness and range.

Selection of Analytical Techniques

The chosen analytical methodology must meet the validation requirements of ICH[8] as well as the required method performance specified in Adenosine triphosphate (ATP).

Risk Assessment

The parameters that affect the ATP are identified by risk assessment as the essential method variables. Following the identification of the technique, AQbD concentrates on developing the method and includes a thorough evaluation of the risks related to variability, such as analytical techniques, instrument settings, measurement and methodology parameters, sample properties, sample preparation, and ambient factors. The ICH Q9 guideline must be followed in the risk assessment strategy: Risks to the quality over the product lifecycle are assessed, controlled, communicated, and reviewed using a systematic approach[22].

Design of Experiments

Method operable design region (MODR) can be formed in the method development phase, which could serve as a source for reliable and affordable methods, in compliance with the requirement of ICH Q8 recommendations, regarding "design space" in product development. DoE implementation during the method development phase necessitates a deep comprehension of input variable selection and output reaction. The following are the components of DoE in the AQbD technique.

Screening

Screening allows for the exclusion of qualitative input characteristics. It lists the different critical method parameters (CMP) that should be considered during the optimization studies. The CMP that has to be regulated or subjected to DOE approaches in MODR optimization should be separated as a result of the screening studies.

Optimization

Quantitative metrics for critical methods in variables (i.e., CMP) can be introduced at this point either directly from risk assessment or through screening. It provides a basis for comprehending the scientific connection between the quantities of input variables (CMP) and responses at the output, which will significantly impact the approach's effectiveness and ATP.

Selection of DOE Tools

Numerous methods can be employed throughout the optimization to derive a statistical correlation (model). The quantity of input variables, acquaintance with regulated parameters, and scientific knowledge of the relationship between outcome and variable (if any) must all be taken into account while selecting the tool for DoE.

Surface Response Plots

Counter (2D) or Surface response plot (3D) represents the impact of input variables on output variables. Numbers like "1, 0, and +1, in both axes, represent the coded level of variables used in DOE.

Model Validation

Before choosing from a contour or graph, the results of an actual experimental run must verify the expected values for the desired technique response. The model must then undergo regression analysis in order to be statistically validated.

Application of AQBD for method development and validation

Numerous papers using the DOE methodology for developing analytical methods have already been published. For the testing of various bulk pharmaceuticals or active pharmaceutical ingredients, methods for HPLC, UPLC analysis, etc., are developed with high accuracy and precision. These QBD-steered approaches have also been used to determine the number of pharmaceuticals in various dosage forms, including tablets, capsules, and vesicular drug delivery systems, such as liposomes, cubosomes, exosomes, ethosomes, etc. Most research teams today use pharmacological models to validate their in vivo results. As a result, the validity of in vitro results is uncertain in the absence of in vivo research. In these situations, estimating the drug concentration in plasma samples or any other bodily fluids is desirable. This problem requires a suitable analytical technique with a higher sensitivity for detecting the minute-to-minute concentrations in fluids. The AQBD methodology primarily produces the analytical method's robust performance.

Testing the stability profile of pharmacological compounds is an intriguing need of the analytical approach. The safety and effectiveness of the therapeutic product are impacted by the chemical stability of pharmaceutical molecules, which is a significant problem. A drug product may encounter several situations during storage times that could cause the product to degrade over time. In these situations, it is preferred to use analytical techniques to detect the degradation products. Understanding a molecule's stability facilitates the choice of an appropriate formulation and packaging and the provision of proper storage conditions and shelf life, all of which are necessary for regulatory paperwork. The market withdrawal of medications is prevented by an accurate stability indication assay or identification of the degradation products of drugs or formulations.

Before submitting a registration dossier, stability tests of novel drug moieties are now required. Long-term (12 months) and accelerated stability investigations are also included in the stability studies (6 months). However, intermediate studies (6 months) can be carried out under more hospitable circumstances than those employed in rapid studies. Therefore, it would take considerably longer to analyze degradation products using separation, identification, and quantification methods. Forced degradation studies help produce degradants in a much shorter time than stability experiments, often a few weeks. To establish a stability-indicating approach that can later be used for examining samples produced by accelerated and long-term stability tests, forced degradation samples can be used[22]. Some of the exciting Research works involving the use of the QBD approach for HPLC method development are summarized in Table 2.

CONCLUSION

In the pharmaceutical sector, AQbD is crucial for assuring method consistency and non-variability in outcomes. In order to improve quality, scientists can quickly identify the threads. The performance of analytical methods for currently available pharmaceuticals must be periodically reviewed to rectify any gaps and risk factors utilizing AQbD.

ACKNOWLEDGEMENT

The authors are thankful to the management of Vels Institute of Science,

Technology and Advanced Studies (VISTAS), Pallavaram, Chennai-600 117, Tamil Nadu, India for providing Digital Library facility for completing this work successfully.

Conflict of Interest

The authors declare that there are no Conflicts of Interests among us.

Funding Support

None.

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