Available online at www.pelagiaresearchlibrary.com

Pelagia Research Library

Der Pharmacia Sinica, 2015, 6(8):18-24

Der Pharmacia Sinica
ISSN: 0976-8688
CODEN (USA): PSHIBD

Analytical method development and validation by QbD approach – A review

Sachin B. Gholve*, Rani R. Ajgunde, Omprakash G. Bhusnure and Sanjay S. Thonte

Department of Quality Assurance, Channabasweshwar Pharmacy College (Degree), Kava Road, Basweshwar Chowk, Latur, Maharashtra, India

---

ABSTRACT

Quality by Design is the modern approach for quality of pharmaceuticals. The aim of the pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product. Quality cannot be tested into products but quality should be built in by design. It is an essential part of the modern approach to pharmaceutical quality. Under this concept of QbD throughout designing and development of a product, it is essential to define desire product performance profile [Target product Profile (TPP), Target Product Quality Profile (TPQP)] and identify critical quality attributed (CQA). On the basis of this we can design the product formulation and process to meet the product attributes. This leads to recognize the impact of raw materials [critical material attributes (CMA)], critical process parameters (CPP) on the CQAs and identification and control sources of variability.

Key words: Quality by design, Analysis, Regulatory

INTRODUCTION

Quality has been given an importance by all regulatory bodies for pharmaceutical products. Quality means customer satisfaction in terms of service, product, and process. Many of these quality related activities reflect need for companies to excel in global competition [2]. Pharmaceutical QBD is a systematic, scientific, risk-based, holistic and proactive approach to pharmaceutical development that begins with predefined objectives and emphases product and processes understanding and process control. The concept of QBD was mentioned in the ICH Q8 guidance, which states that "quality cannot be tested into products, i.e., quality should be built in by design". According to ICH Q8 QBD is defined as a systematic approach to development that begins with predefined objectives and emphasis product and process understanding and process control, based on sound science and quality risk management[1]. Quality by design encompasses designing and developing formulations and manufacturing processes which ensures predefined product specifications. In 2002, the FDA announced a new initiative (cGMP for the 21st Century: A Risk based Approach). This initiative intended to modernize the FDAs regulation of pharmaceutical quality, and establish a new regulatory framework focused on QBD risk management, and quality system. The initiative challenged industry to look beyond quality by testing (QBT) for ensuring product quality and performance. An important part of QBD is to understand how process and formulation parameters affect the product characteristics and subsequent optimization of these parameters should be identified in order to monitor these parameters online in the production process[3].

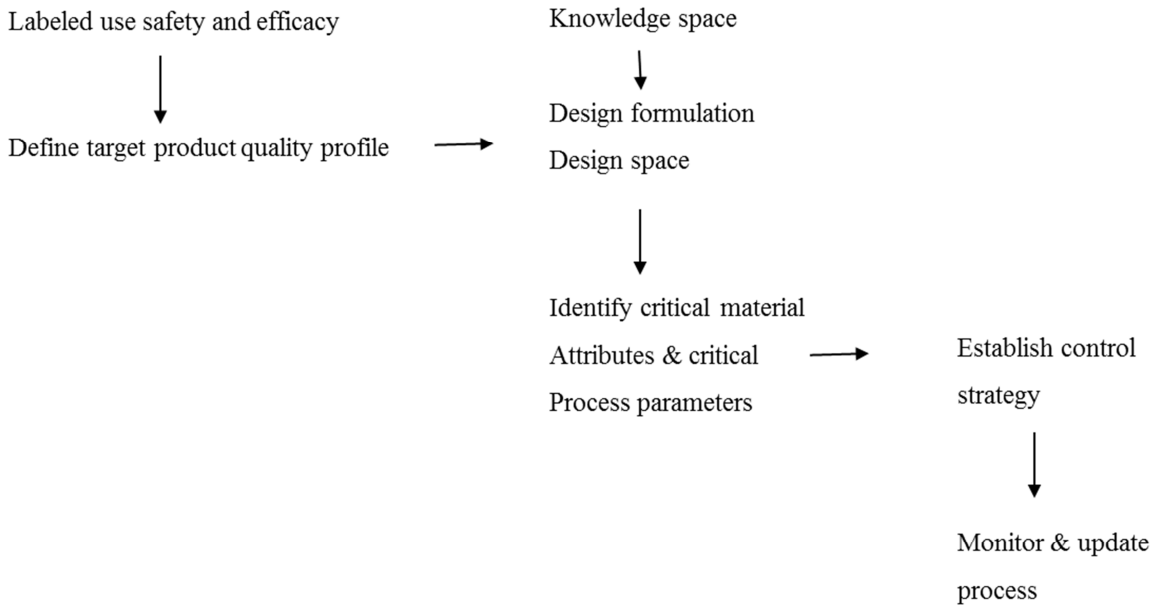
The pharmaceutical industry works hard to develop, manufacture, and bring to market new drugs and to comply with regulatory requirements to demonstrate that the drugs are safe and effective. A new approach to drug

development could increase efficiencies, provide regulatory relief and flexibility, and offer important business benefits throughout the product's life cycle[1].

ANALYTICAL QUALITY BY DESIGN:

As per ICH, QBD defined as, "A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management". A QBD has different tools such as, Analytical Target Profile(ATP),Critical Quality Attributes (CQA),Risk assessment, Method Optimization and Development with DOE, MODR (Method Operable Design Region), Control Strategy and Risk assessment, Analytical QBD Method Validation and Continuous Method Monitoring[4].

Pharmaceutical QBD is a systematic, scientific, risk-based, holistic and proactive approach to pharmaceutical development that begins with predefined objectives and emphases product and processes understanding and process control. It means designing and developing formulations and manufacturing processes to ensure predefined product quality objectives. QBD identifies characteristics that are critical to quality from the perspective of patients, translates them into the attributes that the drug product should possess, and establishes how the critical process parameters can be varied to consistently produce a drug product with the desired characteristics. In order to do this the relationships between formulation and manufacturing process variables (including drug substance and excipient attributes and process parameters) and product characteristics are established and sources of variability identified. This knowledge is then used to implement a flexible and robust manufacturing process that can adapt and produce a consistent product over time[6].



A QbD development process may include:

a. Begin with a target product profile that describes the use, safety and efficacy of the product
b. Define a target product quality profile that will be used by formulators and process engineers as a quantitative surrogate for aspects of clinical safety and efficacy during product development
c. Gather relevant prior knowledge about the drug substance, potential excipients and process operations into a knowledge space. Use risk assessment to prioritize knowledge gaps for further investigation
d. Design a formulation and identify the critical material (quality) attributes of the final product that must be controlled to meet the target product quality profile
e. Design a manufacturing process to produce a final product having these critical materials attributes
f. Identify the critical process parameters and input (raw) material attributes that must be controlled to achieve these critical material attributes of the final product. Use risk assessment to prioritize process parameters and material attributes for experimental verification. Combine prior knowledge with experiments to establish a design space or other representation of process understanding

g. Establish a control strategy for the entire process that may include input material controls, process controls and monitors, design spaces around individual or multiple unit operations, and/or final product tests. The control strategy should encompass expected changes in scale and can be guided by a risk assessment.
h. Continually monitor and update the process to assure consistent quality

QbD involves the following key elements during pharmaceutical development:
1. Define target product quality profile
2. Design and develop product and manufacturing processes
3. Identify critical quality attributes, process parameters, and sources of variability
4. Control manufacturing processes to produce consistent quality over time

Identify Critical Quality Attributes, Process Parameters, and Sources of Variability:
A pharmaceutical manufacturing process is usually comprised of a series of unit operations to produce the desired product. A unit operation is a discrete activity that involves physical changes, such as mixing, milling, granulation, drying, compaction, and coating. A physical, chemical or microbiological property or characteristic of an input or output material is defined as an attribute. Process parameters include the type of equipment and equipment settings, batch size, operating conditions (e.g., time, temperature, pressure, pH, and speed), and environmental conditions such as moisture. The quality and quantity of drug substance and excipients are considered as attributes of raw materials. During process development, raw materials, process parameters and quality attributes are investigated. The purpose of these studies is to determine the critical raw material attributes, process parameters and quality attributes for each process, and to establish any possible relationships among them. Critical quality attributes (CQA) are physical, chemical, biological, or microbiological property or characteristic that must be controlled directly or indirectly to ensure the quality of the product. Critical process parameters(CPP) are process inputs that have a direct and significant influence on critical quality attribute when they are varied within regular operation range[9].

Process robustness is defined as the ability of a process to demonstrate acceptable quality and performance and tolerate variability in inputs at the same time. In process robustness studies, effects of variations in process parameters for a candidate process are evaluated. The analysis of these experiments identifies critical process parameters that could potentially affect product quality or performance, and establishes limits for the critical process parameters within which the quality of drug product is assured. Ideally, data used to identify process parameters should be derived from commercial scale processes to avoid any potential impact of scale-up.

However, in reality, these studies are often conducted on laboratory or pilot-scale batches. If results from the small scale batches have not been shown to be size independent, any conclusion from small scale studies may need to be verified in the actual commercial production batches. At the end, the effect of raw material attributes and critical process parameters on product quality or product variability is fully understood and established. Ideally, the interactions between materials attributes and critical process parameters should be understood so that critical process parameters can be varied to compensate for changes in raw materials[6].

Design of experiments:
Design of experiments (DOE) is a structured and organized method to determine the relationship among factors that influence outputs of a process. When DOE is applied to pharmaceutical process, factors are the raw material attributes (e.g., particle size) and process parameters (e.g., speed and time), while outputs are the critical quality attributes such as blend uniformity, tablet hardness, thickness, and friability. As each unit operation has many input and output variables as well as process parameters, it is impossible to experimentally investigate all of them. Scientists have to use prior knowledge and risk management to identify key input and output variables and process parameters to be investigated by DOE. DOE results can help identify optimal conditions, the critical factors that most influence CQAs and those that do not, as well as details such as the existence of interactions and synergies between factors. Based on the acceptable range of CQAs, the design space of CPPs can be determined. When considering scale-up, however, additional experimental work may be required to confirm that the model generated at the small scale is predictive at the large scale. This is because some critical process parameters are scale dependent while others do not. The operating range of scale dependent critical process parameters will have to change because of scale-up. Prior knowledge can play a very significant role in this regard as most pharmaceutical companies use the same technologies and excipients on a regular basis. Pharmaceutical scientists can often take advantage of past experience to define critical material properties, processing parameters and their operating ranges[1].

Risk Assessment:
Risk assessment is a science-based process used in quality risk management and it can identify the material attributes and method parameters (ATP). Risk assessment can be performed from initial stage of method development to continuous method monitoring. Analytical scientist identifies the risk at the earlier stage and minimize with QbD approach. A risk assessment is helpful for effective communication between FDA and industry, research/development and manufacturing and among multiple manufacturing sites within company.

ICH guideline Q9 gives description of risk management and various terminologies associated with it, like Risk Acceptance, Risk Analysis, Risk Assessment, Risk Communication, Risk Control, Risk Evaluation, Risk Identification, and Risk Management. Quality management policies should mention procedures and practices to the tasks of assessing, controlling, communicating and reviewing risk[5].

MODR (Method Operable Design Region):
Method operable design region (MODR) is used for establishment of a multidimensional space based on method factors and settings MODR can provide suitable method performance. It is also used to establish meaningful method controls such as system suitability, RRT, RRF etc... Further method verification exercises can be employed to establish ATP conformance and ultimately define the method operable design region[5].

1)Quality Target Product Profile (QTPP):
QTPP is a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product. More recently an expanded use of the TPP in development planning, clinical and commercial decision making, regulatory agency interactions, and risk management has started to evolve. The TPP can play a central role in the entire drug discovery and development process such as:
1. Effective optimization of a drug candidate
2. Decision-making within an organization
3. Design of clinical research strategies, and
4. Constructive communication with regulatory authorities.

The TPQP guides formulation scientists to establish formulation strategies and keep the formulation effort focused and efficient. For example, a typical QTPP of an immediate release solid oral dosage form would include:

Tablet Characteristics
- Identity
- Assay and Uniformity
- Purity/Impurity
- Stability, and
- Dissolution

2)Design Product and Manufacturing Process:
A. Product design and development
In order to design and develop a robust generic product that has the desirable TPQP, a product development scientist must give serious consideration to the biopharmaceutical properties of the drug substance. These biopharmaceutical properties include physical, chemical, and biological properties. Physical properties include physical description (particle size, shape, and distribution), polymorphism, aqueous solubility as function of pH, hygroscopicity, and melting points. Pharmaceutical solid polymorphism, for example, has received much attention recently. Its impact on product quality and performance has been discussed in recent review articles. Chemical properties include pKa, chemical stability in solid state and in solution as well as photolytic and oxidative stability while biological properties include partition coefficient, membrane permeability, and/or oral bioavailability. Biopharmaceutical properties should be assessed for every form for which there is an interest in development and every form that can potentially be created during processing (e.g., hydrates, anhydrates) or in vivo (e.g., less soluble salts, polymorphic forms, hydrates). The investigation of these properties is termed Preformulation in pharmaceutical science[9].

The goal of Preformulation studies is to determine the appropriate salt and polymorphic form of drug substance evaluate and understand its critical properties, and generate a thorough understanding of the material's stability under various processing and in vivo conditions, leading to an optimal drug delivery system. Pharmaceutical

Preformulation studies need to be conducted routinely to appropriately align dosage form components and processing with drug substance and performance criteria[6].

B. Process design and development:

The selection of type of process depends upon the product design and the properties of the Materials. For example, tablet manufacturing typically involves one of two methods: direct compression or granulation. Direct compression is the most straightforward, easiest to control, and least expensive tablet manufacturing process. It uses two primary unit operations, mixing and compression, to produce the finished tablet. Direct compression is used when ingredients can be blended, positioned onto a tablet press, and made into a high quality tablet without any of the ingredients having to be changed. When powders are very fine, fluffy, will not stay blended, or will not compress, then they may be granulated. Granulation is the process of collecting particles together by creating bonds between them. Bonds are formed by compression or by using a binding agent. Wet granulation, the process of adding a liquid solution to powders, is one of the most common ways to granulate. The dry granulation process is used to form granules without using a liquid solution. Forming granules without moisture requires compacting and densifying the powders. Dry granulation can be conducted on a tablet press using slugging tooling, or more typically on a roller compactor.

Pharmaceutical development scientists have just begun making use of computer-aided process design (CAPD) and process simulation to support process development and optimization of manufacturing. Process simulation has been successfully used in the chemical and oil industries since the early 1960s to expedite development and optimize the design and operation of integrated processes. Similar benefits can be expected from the application of CAPD and simulation in the pharmaceutical industries. Currently, CAPD and process simulation are largely used in drug substance manufacturing. The utility of CAPD and process simulation in drug product design is limited. This is largely because the pharmaceutical industry has traditionally put emphasis on new drug discovery and development, and the complexity of drug product manufacturing operations are not well recognized. With the emphasis of QbD by the FDA and industry and drug product cost pressures, this trend is expected to change. The use of CAPD and process simulation should result in more robust processes developed faster and at a lower cost, resulting in higher qualityproducts[6].

PHARMACEUTICAL QUALITY BY TESTING:

Product quality is ensured by raw material testing, drug substance manufacturing, a fixed drug product manufacturing process, in-process material testing, and end product testing. The quality of raw materials including drug substance and excipients is monitored by testing. If they meet the manufacturer's proposed and FDA approved specifications or other standards such as USP for drug substance or excipients, they can be used for the manufacturing of the products. Because of uncertainty as to whether the drug substance specification alone is sufficient to ensure quality, the drug substance manufacturing process is also tightly controlled. A change to the drug substance manufacturing process may require the drug product manufacturer to file supplements with the FDA. Finished drug products are tested for quality by assessing whether they meet the manufacturer's proposed and FDA approved specifications 4 .If not, they are discarded[1].

Table No. 1: Traditional Vs QbD approach to pharmaceutical development

Traditional approach	Quality by Design approach
Product specifications: Primary means of control based on batch data available	**Product specifications:** Based on desired product performance and overall quality-control strategy
Quality control: Mainly by testing of intermediates and end products	**Quality control:** Risk management-based control strategy for well-understood products and processes
Life cycle management: Reactive	**Life cycle management:** Based on continuous improvement.

ANALYTICAL QbD METHOD VALIDATION:

AQbD method validation approach is that the validation of analytical method over a range of different API batches. It uses both DoE and MODR knowledge for designing method validation for all kind of API manufacturing changes without revalidation. The approach provides the required ICH validation elements as well as information on interactions, measurement uncertainty, control strategy, and continuous improvement. This approach requires fewer resources than the traditional validation approach without compromising quality[6].

Continuous Method Monitoring (CMM) and Continual Improvement:
Life cycle management is a control strategy used for implementation of design space in commercial stage. CMM is final step in A QbD life cycle it is an continuous process of sharing knowledge gained during development and implementation of design space. This includes results of risk assessments, assumptions based on prior knowledge, statistical design considerations and bridge between the design space, MODR, control strategy, CQA, and ATP. Once a method validation completed, method can be used for routine purpose and continuous method performance can be monitored. This can be performed by using control charts or tracking system suitability data, method related investigations etc. CMM allows the analyst to proactively identify and address any out-of-trend performance[6].

Applications of Quality by Design: [5-6]
Quality by design (QbD)–a comprehensive systematic approach to pharmaceutical development and manufacturing
Advancement in the pharmaceutical development and manufacturing by QbD can be explained against traditional approach.

Table No. 2: Pharmaceutical aspects: Traditional vs. QbD

Aspects	Traditional	QBD
Pharmaceutical Development	Empirical	Systematic; Multivariate experiments
Manufacturing Process	Fixed	Adjustable within design space; opportunities for innovation
Process Control	In process testing for go/on-go; offline analysis wide or slow response	PAT utilized for feedback and feed forward at real Time
Product Specification	Primary means of quality control; based on batch data	Part of the overall control strategy, based on the desired product performance
Control Strategy	Mainly by intermediate product and end product testing	Risk based; controlled shifted up stream, real time release
Lifecycle Management	Reactive time problem and OOS; Post approval changes needed	Continual improvement enabled within design space

BENEFITS OF IMPLEMENTING QbD FOR FDA:
- Enhances scientific foundation for review
- Provides for better coordination across review, compliance and inspection
- Improves information in regulatory submissions
- Provides for better consistency
- Improves quality of review (establishing a QMS for CMC)
- Provides for more flexibility in decision making
- Ensures decisions made on science and not on empirical information
- Involves various disciplines in decision making
- Uses resources to address higher risks

BENEFITS TO INDUSTRY:
- Ensures better design of products with less problems in manufacturing
- Reduces number of manufacturing supplements required for post market changes –rely on process and risk understanding and risk mitigation
- Allows for implementation of new technology to improve manufacturing without regulatory scrutiny
- Allows for possible reduction in overall costs of manufacturing –less waste
- Ensures less hassle during review –reduced deficiencies –quicker approvals
- Improves interaction with FDA –deal on a science level instead of on a process level
- Allows for continuous improvements in products and manufacturing process

CONCLUSION

Analytical method development and validation by QbD plays a key role in the pharmaceutical industry for ensuring the product quality. The outcome of AQbD is the understanding from product development to commercial production. Scientist can easily identify the risk initially so that quality can be increased. AQbD tools are ATP, CQA, Method Optimization and Development with DoE, MODR, and Control Strategy with Risk assessment, Method validation and Continuous Method Monitoring (CMM) and continuous improvement. QbD requires the

right ATP and risk assessment and usage of right tools and performing the appropriate quantity of work within proper time lines.

REFERENCES

[1] Bhagyesh Trivedi. *International Journal of Pharmacy and Pharmaceutical Sciences*, **2012**; 4(1): 17-29.
[2] Jaiprakash N. Sangshetti, Mrinmayee Deshpande, Zahid Zaheer, Devanand B. Shinde, Rohidas Arote. *Arabian Journal of Chemistry*, **2014**; 1-14.
[3] Amit S. Patil, Anil M. Pethe. *IJPQA*, **2013**; 4(2); 13-19.
[4] Nishendu P. Nadpara, Rakshit V. Thumar, Vidhi N. Kalola, Parula B. Patel. *International Journal of Pharmaceutical Sciences Review and Research,Rev. Res.*, **2012**; 17(2); 20-28.
[5] N.V.V.S.S. Raman, Useni Reddy Mallu and Hanimi Reddy Bapatu. Analytical quality by design (AQbD) approach to test method development and validation in drug substance manufacturing.
[6] Lawrence X. Yu. *Pharmaceutical Research*, **2008**; 25(4): 781-791.
[7] Oona McPolin. Validation of analytical method for pharmaceutical analysis, Mourne training services, **2009**.
[8] Mayank Nagar, Kamal Singh Panwar, V. S. Chopra, InduBala, PiyushTrivedi. Scholars Research Library *Der Pharmacia Letter*, **2010**; 2(2): 111-130.
[9] Sandipan Roy. *International Journal of Pharmaceutical and BiomedicalResearch*, **2012**; 3(2): 100-108.
[10] Nwoko valentine eziokwu. *Journal of Global Trends in Pharmaceutical Sciences*, **2013**; 4(4): 1257-1262.
[11] Food and Drug Administration CDER. Guidance for industry, Q8 pharmaceuticaldevelopment; **2006**.
[12] Yu Lx. *Pharmaceutical research*, **2008**; 25(4): 781-791.
[13] Woodcock J. *Am. Pharm. Rev*,**2004**: 1–3.
[14] Lawrence X, Raw A, Lionberger R, Rajagopalan R, Lee L, Holcombe F, Patel R, Fang F, Sayeed V, Schwartz P, Adams P, and Buehler G. U.S. *J. Generic Med*, **2007**; 4:239–248
[15] Nasr M. Risk-based CMC review paradigm. Advisory committee for pharmaceuticalScience meeting; **2004**.
[16] Food and Drug Administration CDER. Guidance for industry: Immediate release solid oral dosage forms scale-up and post approval changes: Chemistry, manufacturing, and controls,in vitro dissolution testing, and in vivo bioequivalence documentation; **1995**.
[17] Food and Drug Administration CDER. Guidance for industry: Modified release solid oral dosage forms scale-up and post approval changes: Chemistry, manufacturing, and controls, invitro dissolution testing, and in vivo bioequivalence documentation; **1997**.