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Quality by Design-A Trending Aspect for Pharmaceutical Product Development

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Research Article

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ABSTRACT

Regulatory bodies are now a days concerned with the safety, efficacy and quality of the pharmaceutical drug products. Quality is first priority of all regulatory bodies, it is at high priority for triple P factor (patient, pharmacist and physician). It serves as a linkage between pharmaceutical industries and regulatory authorities for designing, manufacturing and consistently delivering safe and efficient product.

It mainly focuses on fabricating and designing formulations and manufacturing processes to ensure predefined product quality. It is based on the ICH guidelines Q8 for pharmaceutical development, Q9 for quality risk management, Q10 for pharmaceutical quality systems. Some of the important effective elements of QbD are to define the target profile that what is the requirement of pharmacist, physician and patient (TPP-QTPP) and then measuring the criticality for achieving that target (CQA), and analyzing the risk assessment of variables associated with materials and controlling processes to produce consistent quality over time. The objective of this review is to discuss the concept of quality by design and describe its application in pharmaceutical product development.

Keywords: Quality by Design (QbD); Quality Target Product Profile (QTPP); Critical Quality Attribute (CQA); Design of Experiment (DOE); Process Analytical Technique (PAT); Design space; Control space

INTRODUCTION

Regulatory bodies and pharmaceutical industries are constantly working to enhance the quality, safety and efficacy of the products that are directly linked to patients' health. But due to manufacturing failure, cost effectiveness, finished product quality control failure, scale up issues and regulatory demand has become a major challenge for the researcher and the industries, because of these kind of failure regulatory bodies have started focusing and demand pharmaceutical product development in QbD manner so that the products will be stage wise evaluated and all the high risk materials and processes will be assessed and mitigated for successful development it has therefore reduces the chances of failure [1].

Though depending blindly on finished product quality control test as if in traditional method QbD checks product at each and every level so that the root cause analysis is easy and the success rate would be high. The concept of QbD was first advocated by USFDA and in the ICH Q8 guidance, which states that "quality cannot be tested into products, *i.e.*, quality should be built in by design".

MATERIALS AND METHODS

QbD is a systematic approach for robust product development, it is the quality system for managing a product's lifecycle and regulatory expectation intended to increase process and product understanding and thereby decrease patient risk. It begins with predefined objective and emphasizes product and process understanding using design of experiment, design space and managing its outcome to the safer range [2].

The initiation of quality has been started in 1979-P. Crosby's who believe that quality is free in 1986 Motorola develops six sigma for reducing defects and improving quality and therefore customer compliance, in 1987-FDA's first guideline on process validation has been implemented, in 1988-US DoD implements total quality management, in 1991-J. Juran has given Quality by Design: The new steps for planning quality into goods and services, finally in 2005 ICH guideline QbD related drafts appear ICH Q8-11 and at last in 2008-FDA's guidance for industry process validation a general principles and practices was given (Figure 1) [3-6].

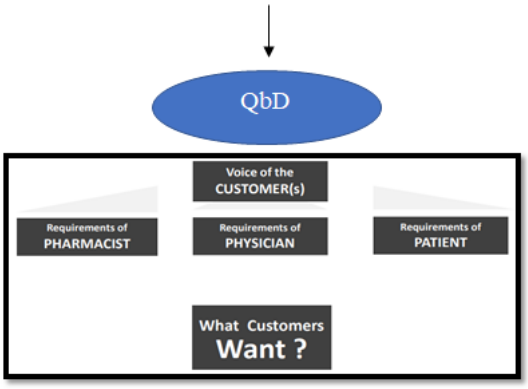
Principles of quality by design

- Risk and knowledge based decisions.
- Systematic approach for process development.
- Continuous improvement leads to "capable" processes.

ICH role in quality by design ICH implemented 4 guidelines for maintain quality of pharmaceutical product development.

- Q8: Pharmaceutical development (Nov 2005).
- Q9: Quality risk management (Nov 2005).
- Q10: Pharmaceutical quality system (June 2008).
- Q11: Development and manufacture of drug substances (May 2012).

Figure 1. Voice of consumers.



Objective of QbD

- To increase process capability and reduce product variability and defects, by enhansing product and process design, understanding, and control.
- To achieve meaningful product quality specifications based on clinical performance.
- To increase product development and manufacturing efficiencies.
- To enhance root cause analysis and post approval change management [7].
- It is applicable in both drug product and drug substances.

- To reduce the failure and improve the outcome of the product.
- Working range can be obtaining working within that would leads to no change in quality of product.
- To increase manufacturing efficiency, reduce costs and project rejections and waste.

Advantages of QbD

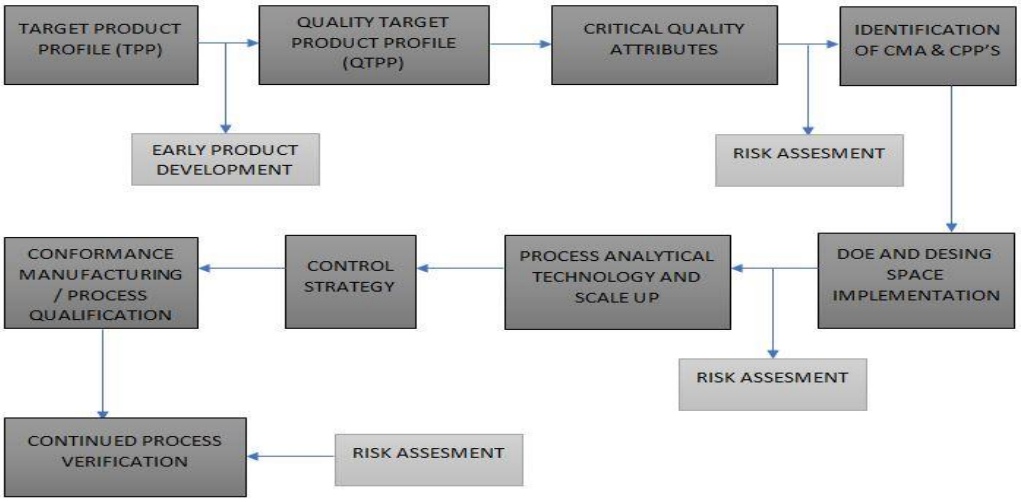
- QbD helps in providing safer, quality, and efficient drug product.
- QbD help in safer and faster drug development.
- The QbD approach sets production team up for success by providing a clear and comprehensive understanding of the parameters involved in the development process and how they work together. This deep understanding helps teams assess risk and act accordingly significantly reducing the likelihood of failure [8].
- It provides proper understanding of critical process parameter and critical material attributes and their effect on final quality of drug product.
- Using QbD helps companies achieve greater batch to batch consistency and reduces batch to batch variation.
- The QbD approach builds quality into the manufacturing process by designing, and controlling the critical parameters.
- It provides in between checkpoints for in process evaluation of the product so that the root cause analysis is easy.

Key elements of QbD9: Quality by Design is a scientific risk based holistic and proactive approach to pharmaceutical product development by improving its quality. It involves the designing and planning of a drug product and process before actual experiment (Table 1 and Figure 2) [9].

Table 1. Steps involved in QbD based product development.

Phase 1	Define phase	Defining the targets or the objective of drug product development, these targets or objective should be achieved to ensure desired quality of the drug product required for safety and efficacy.
Phase 2	Measure phase	Measuring the critical quality attributes out of Quality Attributes (QA's) because deviation or out of specification of CQA's will have definite impact on safety and efficacy of customer or patient.
Phase 3	Analyse phase	Identifying Critical Process Parameter (CPP's)and Critical Material Attributes (CMA's) and further analyzing risk factors through SIPOC, RRMA, FMEA, ANOVA
Phase 4	Improve phase	Designing design of experiment and developing and verifying design space. It can be done by first screening of experiments and then optimization of experiments.
Phase 5	Control phase	Implementation of control strategy and control critical factors with control space and continue improvement. From DoE and design space, control space for each and every CMA's and CPP's are proposed for future commercial manufacturing batches so that no out of specification or batch failure is possible.

Figure 2. Chronological order of QbD based product development.



Identifying a Quality Target Product Profile (QTPP): Defining the Quality Target Product Profile (QTPP) as it relates to quality, safety and efficacy, considering e.g., the route of administration, dosage strength, container closure system,

Therapeutic moiety release, strength, and stability. It is a prospective summary of the ideal quality characteristics of the drug product taking into account of safety and efficacy) will be defined based upon voice of patient (Table 2). Basically, it is an element for setting the target for drug product development. QTTP is worldwide used in development planning, setting up of target. Clinical strategies and commercial outcome, regulatory requirement, and risk management [10-16].

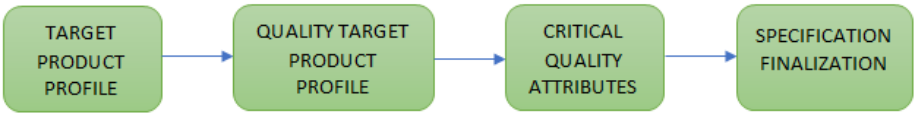
Table 2. These are examples of final quality targets that the product should always have in order to satisfy customer compliance. Some of the elements of QTPP.

QTPP elements	Target		
	Solid	Liquid	Parenteral
Dosage form	Uncoated, coated, scored	Solution, suspension, emulsion	Injection
Dosage design	Immediate release, modified release etc.	Immediate release formula	Immediate release formula
Route of administration	Oral	Oral, topical	Parenteral
Dosage strength	X mg	X mg/ml	X mg/ml
Drug product quality attribute	Must meet the same compendia or other applicable reference standard (identity, assay, purity, quality)		
Packaging	HDPE, blister, strip to protect from heat moisture, light and microbial attack to achieve target shelf life.	HDPE plastic container Al closure to protect from heat moisture, light and microbial attack.	USP type I glass vial with neoprene rubber closure and Al seal to protect product from heat, moisture, oxygen, light and microbial attack
Pharmaco-kinetics	Should meet fasting and fed bioequivalence limit (80-125) when compared to reference product.	Solution bioequivalence study can be waived of in case of solution, suspension should follow bioequivalence limit (80-125) with reference product, emulsion rate of penetration, rate of drug release and extent of absorption should be comparable with reference product.	Bioequivalence study can be waived as it is directly administered into systemic circulation and release of the drug substance from product solution is self-evident.
Stability and shelf life	At least 24 moth of shelf life is required equivalent or better than reference product.	At least 12 month of shelf life is required at room temperature or better than reference and 28 days of in-use shelf life at room temperature in case of emulsion	At least 6 months of long term shelf life is required at proposed condition and 28 days of in use shelf life is required for multidose
Patient acceptance and patient compliance	Should have suitable colour, flavour, and can be easily administered or applied.	Should have suitable colour, flavour, and can be easily administered or applied.	Can be easily administered similar with reference product to achieve desired patient compliance.

The main thing to acknowledge is that QTPP should only include target or target reflecting quality, not the critical parameter for determination of specification [17].

Critical Quality Attribute (CQA's): "A property or characteristic that when controlled within a defined limit, range, or distribution ensures the desired product quality (Figure 3)."

Figure 3. Steps involve in product development.



CQA's are the physical, chemical, biological or microbiological property that should be within an appropriate limit, range or specification in order to ensure the desired product quality [18].
It is important to identify the quality attributes that are critical, *i.e.*, those defining purity, potency and surrogate for efficacy (Figure 4 and Table 3). It is based on the impact of quality attribute on the safety, efficacy and quality of the product. If the drug product contains a polymorphism that is having direct impact on dissolution and bioavailability then it should be specified so as to provide proper bioavailability and efficacy [19].

- Potential CQAs are derived from the QTPP and guide product and process development.
- CQAs are identified by quality risk management and experimentation to determine the effect of variation on product quality.

Figure 4. Impact of CQAs.

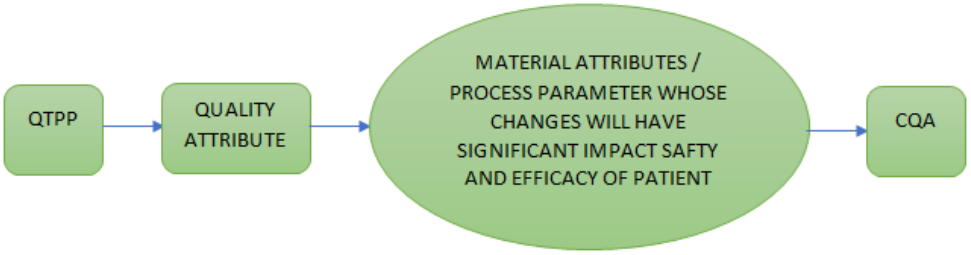
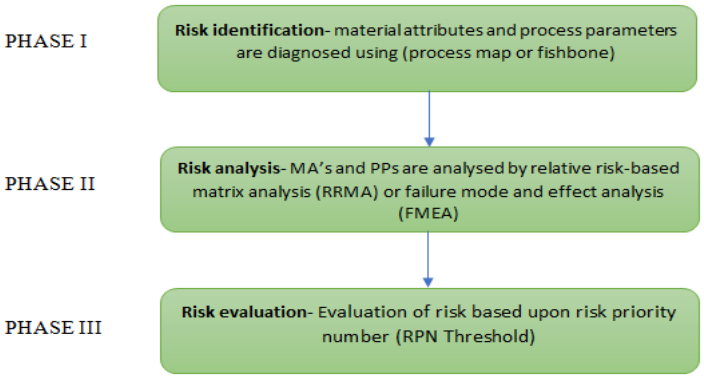


Table 3. Determination of critical quality attributes.

Substance quality attributes	Product quality attributes	Is this a CQA's?
Particle size	Identification	Yes
Solid state	Assay	
Organic impurity	Impurity	
Inorganic impurity	Uniformity of Dosage (UOD)	
Residual solvent class	Disintegration/Dissolution	
Water content	Water content	
Assay	Residual solvent	
Hygroscopicity	Microbial limit	

Risk assessment: Identification of critical material attributes and critical process parameters. Risk assessment is an important element used in quality risk management that can aid in identifying which critical material attributes and critical process parameters potentially have a significant impact on product CQAs. Risk assessment is typically performed early in the pharmaceutical development process and is repeated as more information becomes available and greater knowledge is obtained [20].
The evaluation of the quality risk should be based on the both scientific knowledge as well as therapeutic benefit to the patient. Independent formulation variable and independent process variable likely to have impact on in process or finished product CQA's can be analyzed based upon preliminary experiments or prototype fabrication.
It can be further divided into 3 phases (Figure 5).

Figure 5. Phases of risk assessment.



Identification of critical process parameter: Process parameter which have a significant impact on critical quality attribute, whose variation will directly impact the quality of the finished product. CPPs are responsible for ensuring the CQAs and it is identified from a list of potential CPPs using risk assessment.
It is a measurable input material attribute or output material attribute of a process step that should be controlled to achieve the desired product quality as well as process uniformity.
Further CPP's can be classified into 2 types

- **Critical parameter:** A realistic variation in parameter can cause the product to fail to achieve CQA's and QTPP.
- **Non-critical parameter:** No failure in QTPP determined the within the potential operating space and no interactions with other parameters in the established suitable range (Table 4).

Table 4. Some of the critical process parameter during tablet formulation.

S. No	Manufacturing process step	Input processing parameter	Output quality attributes
1	Co-sifting	Screen size mill type sifting speed	Particle size distribution flow ability powder bulk density
2	Wet granulation	Impeller speed chopper speed dry mixing time kneading time binder addition/spraying time amperage reading	Granule PSD flow ability
3	Drying	Inlet air volume inlet air temperature fill volume filter type/shaking time	Granule PSD loss on drying
4	Sizing	Mill type clade orientation oscillation speed screen size	Granule PSD flow ability granule assay granule uniformity
5	Blending	Blender type Fill volume order of addition rotation speed and time	Blend assay blend uniformity BD/TD flow ability compressibility index
6	Compression	Turret speed feed frame paddle speed feeder fill depth precompression force main compression force ejection force hopper design	Appearance, dimension, weight variation hardness, assay, related substance related solvent disintegration dissolution
7	Coating	Inlet air volume inlet temperature exhaust air volume exhaust temperature time spray pattern spray rate atomization air pressure	

Qualitative risk base matrix analysis: Can be further divide into 3 categories (Tables 5 and 6).

Table 5. Qualitative risk base matrix analysis.

Low risk	Broadly acceptable risk
Medium risk	Risk may be acceptable, may or may not impact product quality.
High risk	Risk is unacceptable, will have significant impact on quality

Table 6. Quantitative risk Failure Mode Effect Analysis (FMEA).

Probability	Severity	Detectability	Score
Very unlikely	Minor	Always detected	1
Relatively less	Low	Regularly detected	2
Occasional	Moderate	Likely not detected	3
Repeatedly high	High	Normally not detected	4
Almost inevitable	Hazardous	Absolute uncertainty	5
Risk priority number more than 25 seeks critical attention prevent from further product failure.			

Process parameters based process used in quality risk management that can aid in identifying which material attributes and process parameters potentially have an effect on product CQAs. Risk assessment is typically performed early in the pharmaceutical development process and is repeated as more information becomes available and greater knowledge is obtained.

Design space: Multidimensional combination of and interaction of input variables (material attributes) and process parameters that have been demonstrated to provide quality assurance. (Multidimensional combination of factors) is developed, where all the desired responses simultaneously met.

Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. It provides assurance of quality of the product.

Design space can be established by the implementation of design of experiment. It is the systematic series of experiments in which purposeful changes are made to input factors for screening and optimization of CMA's and CPPs with respect to CQA's (Figures 6 and 7). Methods for presenting design space included graphs (surface response curves and contour plots), linear combination of parameter ranges, equations, and models.

Figure 6. Steps for design of experiment.

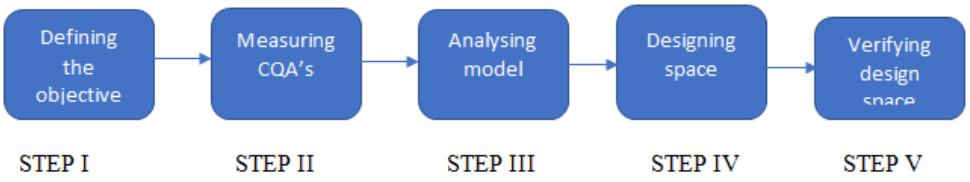
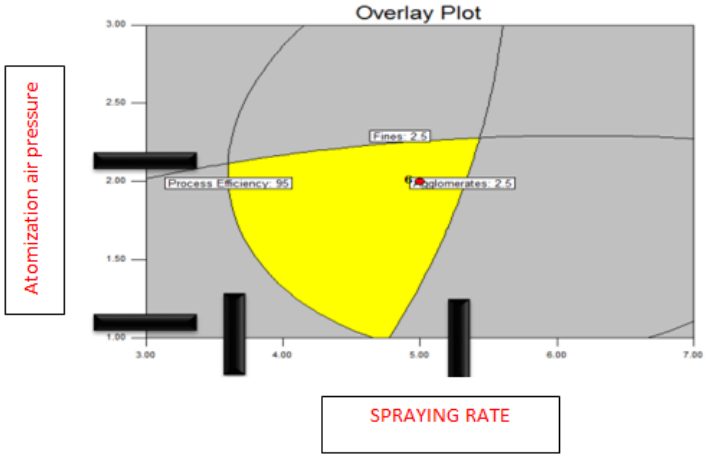


Figure 7. Design space for fluidized bed granulator.



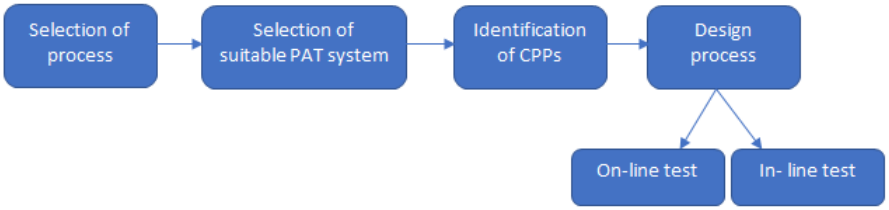
RESULTS AND DISCUSSION

Development of process analytical technique: Process Analytical Technology (PAT) has been defined by the Food and Drug Administration (FDA) "as a method to design, analyses, and control pharmaceutical manufacturing processes through the measurement of Critical Process Parameters (CPP) which affect Critical Quality Attributes (CQA). The framework has two components: (a) A set of scientific principles and tools supporting innovation. (b) A strategy for regulatory implementation that will accommodate innovation.
PAT is the system for designing, analyzing, and controlling manufacturing through timely measurements of CQAs and CMAs with the goal of ensuring finished product quality through 3 phases (Table 7 and Figure 8).

Table 7. Phases of process analytical technique.

Design	CMAs and CPPs are optimised with respect to CQAs at lab scale developmental level with at line/off line analyzer.
Analysis	Exhibit scale data are analyzed by inline/online analyzers and compared with at line/offline data.
Control	According to the ranges specified in control strategy, controller are used at manufacturing scale for continuously attaining acceptable ranges of CMAs / CPPs to achieve desired in process/finished process CQAs.

Figure 8. Working of process analytical technique.



Implementation of control strategy

As per ICH guideline Q10 control strategy can be defined as planned set of controls, derived from current product material and process understanding, that assures process performance and product quality. For finalizing of control strategy (planned set of controls), each and individual CMA's and CPPs are reviewed with respect to their past, present and future prospective.
The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in process controls, finished product specifications, and the associated methods and frequency of monitoring and control (Tables 8 and 9 and Figure 9).

Table 8. Levels of control strategy.

Past	Present	Future
Ranges studied at lab scale or R&D scale	Range studied at pilot scale/exhibit scale	Ranges proposed for commercial scale.

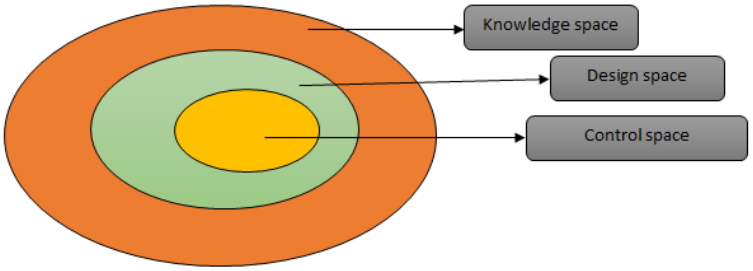
In order to ensure batch to batch uniformity in evaluation parameter and quality and performance of the finished drug product during commercialization process.

Table 9. Some of examples explaining control strategies.

Control strategy for critical material attributes					
Factor	**CMAs**	**Range at lab scale**	**Range at pilot or exhibit**	**Proposal for commercial batches**	**Control strategy**
Active pharmaceutical ingredient					
Particle size distribution	D10 D50 D90	NMT 5 µm NMT 10 µm NMT 15 µm	NMT 5 µm NMT 10 µm NMT 15 µm	NMT 5 µm NMT 10 µm NMT 15 µm	To ensure batch to batch uniformity in BU, CU, dissolution, bioavailability
Inactive ingredient critical material attribute					

Magnesium stearate	Level specific surface areal	0.5-1.5 w/w 10-15 m^2/g	0.75-1.25 w/w 10-15 m^2/g	0.80-1.20 w/w 10-15 m^2/g	To ensure proper lubrication and smooth compression and ejection force.
Critical process parameter for fluidized bed granulator					
Fluidized Bed Granulator (FBG)	Spray rate	4.0-8.0 g/min	3.5–6.0 g/min	4.0-5.0 g/min	To ensure batch to batch uniformity in, PSD, BD to provide better flow ability, disintegration as well as moisture content of granules.
	Atomisation air pressure	1-3 bar	1.5-3.5 bar	2-4 bar	
Critical process parameter for tablet compression machine					
Compression machine	Compression force	2.0-6.0 kN	3.0-5.0 kN	3.5-4.5 kN	Uniformity hardness, weight and disintegration to ensure friability, cu, dissolution
	Turret speed	10-40 rpm	10-30 rpm	15-25 rpm	

Figure 9. Quality by design for product development.



CONCLUSION

QbD is emerging to an important element providing significance for quality improvement. The objective of quality by design method in pharmaceutical product development is to formulate a reliable method that gives assurance of the ultimate quality and efficacy of the product and minimizes batch to batch variation or inconsistency and to reduce errors.

Implementation of quality by design at materials and processing method will provide a quality based effective and robust product. Production improvements to Manufacturers with significantly reduced batch failures and regulatory bodies will have greater confidence in the robust quality of products.

QbD is emerging into a promising scientific tool in quality affirmation in pharmaceutical industry. Which provides a safe operating range that assures or provide confidence for batch to batch consistency, quality, safety and efficacy and mitigate the lengthy step of scale up post approval changes? QbD successfully provide a layout or the path from initial defining objective and finally successfully commercializing the product.

Conflict of interest

The authors have no conflicts of interest regarding this review article.

Author contributions

Mr. Anwar khan, Mr Rizwanul hasan, Mrs Rupa Gupta was involved in the collecting, organizing of the data, reviewing, and editing of the manuscript. Dr. Sabir alam and Dr Mohini chaurasia was involved in the study analysis, drafting, reviewing article, and Mr Mohsin ali khan was involve in editing the manuscript.

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