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A Comprehensive Analysis of Quality by Design in Pharmaceutical Industry

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Abstract: *Quality by Design was defined as systematic technique to improvement that starts with predefined goal and emphasizes product and technique, which recommend by USFDA and ICH. Regulatory authorities are usually featuring the implementation of ICH quality guidelines which include Q8, Q9, Q10 and Q11. The differentiation between the traditional and QbD help to study the risk assessment, and technique for developing new products. There are few step involved in pharmaceutical and Analytical QbD. Various factors used for the study for QbD such as Analytical target product profile (ATPP), Risk Assessment Quality Design Space, Control Strategy, etc.CQA may be understood analysed via way of means of Understanding of the goods and technique and risk evaluation is useful for effective verbal exchange among FDA and industry, research/improvement and production, and amongst a couple of production sites inside the company.life-cycle management of analytical procedure', which begins off evolved with establishment of ATP and maintains until the approach is in use. Design of experiment involves the Q8 guidelines. DoE has been used in the rational development and optimization of analytical methods. Culture media composition, mobile phase composition, flow rate, time of incubation are examples of input factors (independent variables) that may the screened and optimized using DoE. Process analytical technology is implemented for the understanding and identification a developing a product and techniques. There are various benefits and application of QbD in pharmaceutical industry.*

Keywords: Quality by Design, ATTP, Control strategy, Life cycle management, Design Space, Design of experiment

I. INTRODUCTION

The idea of high-satisfactory with the aid of using layout became summarized with the aid of using a famous high-satisfactory professional Joseph Moses Juran; he believed that high-satisfactory may be deliberate and that maximum high-satisfactory related troubles have their foundation within side the manner which high-satisfactory became deliberate within side the first place. The standards of QbD were used to strengthen the product and method high-satisfactory in each industry. Because of want of mighty drug with protection profile, pharmaceutical industries are making an investment billions of cash within side the drug discovery and improvement method with endeavour to layout high-satisfactory product and that to with consistency in production method to supply the meant overall performance of product [1-3].

USFDA has launched specific QbD guidance for immediate and prolonged release drug products as well as biotechnological products. Regulatory authorities are usually featuring the implementation of ICH quality guidelines which include Q8, Q9, Q10 and Q11 [4].

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Figure. 1: Content of Quality by Design

The purpose of pharmaceutical improvement is to lay out a first-class product and its production technique to always supply the supposed overall performance of the product. A lot of strategies to the improvement of pharmaceutical merchandise and their next manufacture has been recommended through USFDA and the International Council Harmonization (ICH) [5]. This technique has been mounted 'Quality by Design' (QbD) and it described as- "A systematic technique to improvement that starts with predefined goal and emphasizes product and technique know-how and technique control, primarily based totally sound technological know-how and first-class hazard management"[6]. An excessive first-class drug product is a product freed from infection and reproducibly turning in the healing advantage promised at the label to the consumer. ICH Q8 defines first-class as "The suitability of both a drug substance or drug product for its supposed use. This time period consists of such attributes because the identity, strength, and purity". A regularly used definition of first-class is "Delighting the purchaser through absolutely assembly their wishes and expectations". These can also additionally encompass overall performance, appearance, availability, delivery, reliability, maintainability, fee effectiveness and price, and overall purchaser satisfaction. It is essential that first-class ought to be constructed in through layout. To gain the excessive degree of first-class there's want of Quality through Design [7, 8].

HISTORICAL BACKGROUND:

Quality by design has been seen as a new paradigm in the pharmaceutical industry, QbD is not that new. The history is given in the Table 1.

Year	Activities
1950	Operation Windows
1970	QbD introduced by Joseph M Juran
Sep 2002	QbD concept integrated by USFDA in cGMP
Sep 2004	USFDA release final report in "Pharmaceutical cGMP"
Sep 2004	USFDA Guidance for Industry: PAT – A Framework for innovative Pharmaceutical Development, Manufacturing and Quality Assurance
Nov 2005	ICH: Q9 Quality Risk Management
Jun 2008	ICH: Q10 Pharmaceutical Quality System
Nov 2009	ICH: Q8(R2) Pharmaceutical Development

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TRADITIONAL APPROACH VS. QBD APPROACH [9, 10, 11]

Traditional Analytical Method Development	QbD (Lifecycle) Analytical Method Development
Methods validated as a check-box tool as defined in International Conference on Harmonization (ICH) Q2 guidance, Validation of Analytical Procedure: Text and Methodology	Suitability of a method demonstrated against an analytical target profile, which defines the specific characteristics and criteria required by the process control strategy
Method transfer includes activities performed to transfer a method from sending unit to a receiving unit and do demonstrate equivalence between the two units	Method installation includes activities performed to ensure effective method set up in the routine operating environment and includes knowledge transfer from sending unit
The terms e.g. method verification, method, method validation and revalidation are confusing in traditional approach	In lifecycle-approach more clear terms aligned with process validation and equipment qualification terminology are used.
Method verification involves ensuring pharmacopeial methods operate under actual condition of use; revalidation is performed after changes for validation characteristics likely to be affected.	Method performance verification involves demonstrating that a method performs as intended following a change in the methods operating conditions or operating environment.

Benefits of Analytical QbD [12]

• Increased understanding and control

• Beyond traditional ICH procedure of method validation Flexibility in analysis of API, impurities in dosage forms, stability samples, and metabolites in biological samples

• Reduction in variability in analytical attributes for improving the method robustness

• To keep the values of analytical attributes within the pharmacopoeial monographs, and away from Out Of Specification (OOS) limits

• Smooth process of method transfer to the production level

• No requirement of re-validation within MODR

STEPS INVOLVED IN PHARMACEUTICAL AND ANALYTICAL QBD

QbD comprises all elements of pharmaceutical development, which will allow to design a quality product and its manufacturing process to consistently deliver the intended performance concerning its safety and efficacy. Analytical methods are considered an integral part of pharmaceutical development [13]. Thus, the application of QbD approach to analytical method development is justifiable and a recommended strategy to attain regulatory flexibility, to reduce out-of-specification results, to achieve a high degree of robustness and a cost-effective analytical method [14].

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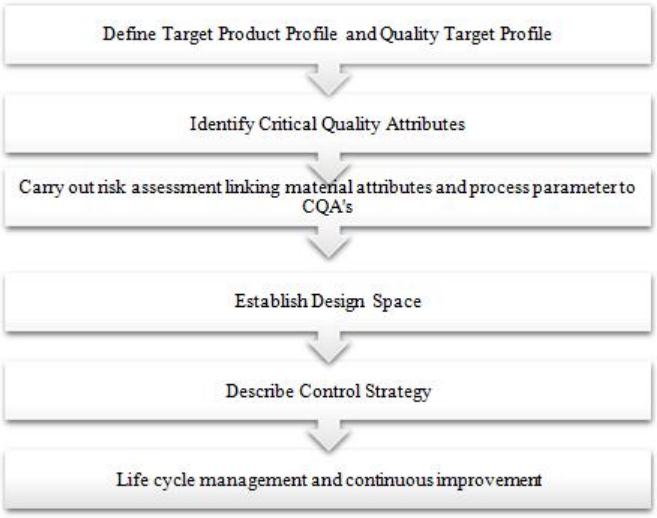

Figure. 2: Flow chart of Quality by Design

ANALYTICAL TARGET PRODUCT PROFILE (ATPP)

QbD is a scientific technique to product, process design, and development; consequently, it starts with a determination of approach aim or approach intent. During this pressure is given on the products and process understanding, ATP is a manner for brand spanking new approach development. It describes the method wishes for approach necessities that can be predicted to be measured. In usually the aim of the chromatographic approach is separation, quantification, and identity of drug substance, impurity, or degraded. Impurity is taken into account to be the critical quality attribute (CQA) [15].

The basis of any analytical technique advanced via QbD concepts is 'ATP', that is just like Quality Target Product Profile (QTPP), as described in ICH Q8 (R2). USP council of professionals outline ATP of their stimuli article as, "the requirements for the "product" of the take a look at procedure, which in this example is the reportable end result" or "the goal of the take a look at and high-satisfactory necessities, which includes the predicted degree of confidence, for the reportable end result that lets in the appropriate end to be drawn concerning the attributes of the material this is being measured". One has to take into account the subsequent factors for higher know-how of ATP. First of all, ATP isn't always restricted to technique improvement only, however have to additionally be met in the course of technique switch and additionally during lifecycle management. Also, ATP isn't always constantly limited to single technique and multiple technique/ analytical method can fulfil the identical ATP. Moreover, possible constantly compare to be had techniques to satisfy ATP. In case of compendial strategies, monograph specs and to be had overall performance information of the product may be used to establish the ATP [16].

Also, inside ATP, approach overall performance characteristics are commonly validation parameters, e.g., selectivity, precision, accuracy, linearity, limit of detection, limit of quantification, etc. These needs to be measured to assure that the technique is able to generating end results, which are appropriate for its intended purpose. The specification limit for every overall performance feature have to be met to the assurance of technique quality, e.g., with inside the case of accuracy observe for an associated substance technique, limit may be set at 90-110% and limit of quantification as now no longer much less than 0.05% [17].

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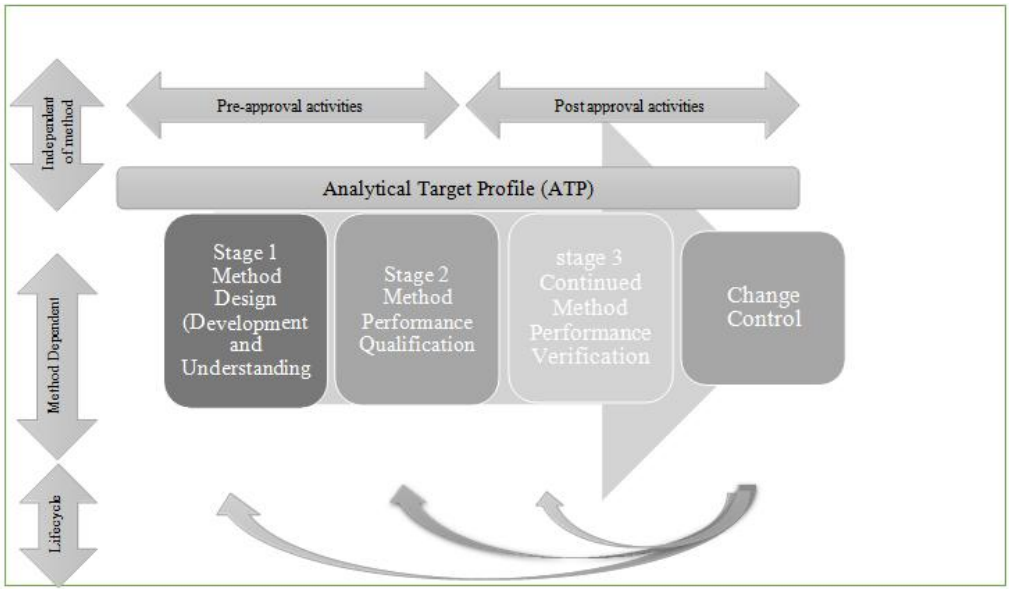

Figure 3: Life Cycle Management of Analytical Method.

CRITICAL QUALITY ATTRIBUTES

Factors that without delay has an impact at the excellent and protections of the goods are first taken care of out, and its ability effect on technique improvement is studied. CQA may be understood analysed via way of means of Understanding of the goods and technique. If drug product includes the impurity which can also additionally have direct effect on excellent and protection of drug product it's far being taken into consideration the essential excellent characteristic for the HPLC technique improvement of that precise drug compound. According to Schweitzer et al protection and efficacy may be performed via way of means of demonstration measurable manipulate of excellent attributes i.e. merchandise specification, intermediate specification, technique manipulate [18, 19].

Identification of CQA may be executed primarily based totally on earlier information and/or pleasant danger management (QRM). Prior information might also additionally be attained with the aid of using literature review, production experience, technology transfer, balance reports, uncooked fabric checking out data, unfavourable event record and recalls. Quality risk management, on the alternative hand, applies various equipment to identify and prioritize capability CQA [20].

RISK ASSESSMENT QUALITY

It is generally understood that risk is described because of the aggregate of the possibility of prevalence of damage and the severity of that damage. Risk evaluation facilitates to growth pleasant of approach or process. Also, it's far determinant for the impact of input variables on approach or processes. From risk evaluation, one can understand crucial attributes which are going to have an effect on the final quality of the product[21]. A risk evaluation is useful for effective verbal exchange among FDA and industry, research/improvement and production, and amongst a couple of production sites inside the company[22,23]. There can be danger and uncertainty invalidation of bio-analytical approach even though the hints for validation are given with the aid of using numerous regulatory bodies there can be a variant in the interpretation of these hints and as a result in experimental approach designing which leads to undeserving approach improvement for the meant purpose. Risk control for excipients to determine shelf existence may be accomplished through statistical parameter [24, 25].

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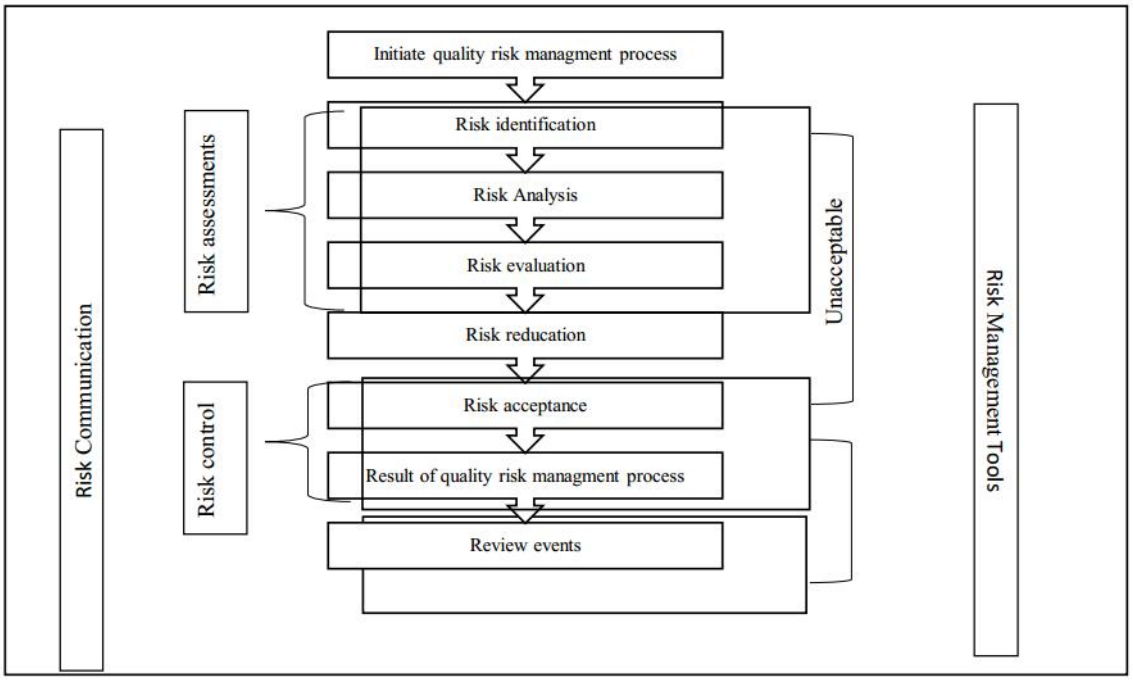

Figure. 4: Flow chart of the working of risk assessment tools

Principles of quality risk management are: [26]

• Scientific information is primarily based totally assessment of the chance to nice which ultimately links to the safety of the patient.

• Adequate attempts have to be taken; formality and documentation of the nice chance control process have to be executed with the extent of chance involved.

The pharmaceutical industry and regulators can evaluate and manage risks by using well-known risk management tools and/ or internal procedures such as,

• Basic risk management facilitation methods (flowcharts, check sheets etc.)
• Failure Mode Effects Analysis (FMEA)
• Failure Mode, Effects and Criticality Analysis (FMECA)
• Fault Tree Analysis (FTA)
• Hazard Analysis and Critical Control Points (HACCP)
• Preliminary Hazard Analysis (PHA)
• Risk ranking and filtering

DESIGN SPACE [27]

A Design Space is described as, "Multidimensional mixture and interplay of enter variables (e.g. cloth attributes and system parameters) which have been validated to offer guarantee of quality". A layout area can also additionally construct for a single unit operation, a couple of unit operations, or for the complete system. According to FDA guideline, defining layout area is non-obligatory for the reason that product and system knowledge may be installed without a proper layout area, by no means the less, above technique can help to higher knowledge and achieve normal manage of a system.

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In this regard, you may observe the one-aspect-at-time (OFAT) method, which varies simplest one element or variable at a time even as retaining others constantly. However, the design of the experiment (DoE) technique that varies numerous enter variables concurrently is extra efficient when reading or extra factors. Factorial designs (complete or fractional) and the reaction floor methodology (RSM) are feature gear for this sort of application. The key advantages of the use of the DOE method are summarized as follows

a) Exhaustive records from a minimum number of experiments
b) Study results for my part via way of means of simultaneously various all working parameters
c) Can account for variability in experiments, manner, materials, or operators
d) Able to provide understanding about the interplay among numerous variables
e) Determine applicable stages of critical process parameters contributing to identity of a design space.

CONTROL STRATEGY

A deliberate set of control(s) for all feasible variation(s) assures that ATP requirement could be met during analytical technique switch in addition to recurring use. This can be attained with non-stop tracking of CMAs or system suitability parameters. Control approach is not constantly a one-time exercising this is finished most effective during technique development; however it may get modified with special levels of method lifecycle [28]. Development of a Control Strategy requires a structured process, involving a multi-disciplinary team of experts, linking pharmaceutical development to the manufacturing process, and engineering controls of process equipment [29].

Although the primary driver for development of a control strategy will be assurance of product safety, efficacy and quality, the Control Strategy may also ensure the meeting of other business objectives such as operator health and safety, protection of the environment, manufacturability, and supplies related issues, efficiency, and profitability. Development of a Control Strategy for a product will therefore be a structured activity involving a multidisciplinary team of experts. This team may include representatives from formulation development, drug substance development, process development, analytical development, QC, QA, Regulatory Affairs, manufacturing, engineering, and specialists in Process Analytical Technology (PAT) and chemo-metrics.

A Control Strategy and a product release strategy are not the same, but demonstration of adherence to the Control Strategy would support the product or batch release strategy [30, 31].

LIFE CYCLE MANAGEMENT [32]

Even after going via all of the factors of QbD for a specific analytical lifecycle management of analytical procedure', which begins off evolved with establishment of ATP and maintains until the approach is in use. The resultant affirmation with recognize to ATP is the principle recognition for overall performance qualification, e.g., precision look at on the web website online of recurring use. Continual verification involves activities, which give the guarantee that the approach is under control at some stage in its lifecycle.

Applications of Quality by Design

Application to Analytical QbD [33]

1. Development of robust method.
2. Understand, reduce and control sources of variability.
3. Applicable all through the life cycle of the method.
4. Regulatory flexibility Movements within "Analytical Design Space" aren't taken into consideration an alternative in method.

Application to Industry [34]

1. Ensures better design of products with much less problems in production.

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2. Reduces wide variety of producing dietary supplements required for post market changes – depend on technique and risk understanding and danger mitigation.
3. Allows for implementation of latest era to enhance production without regulatory scrutiny.
4. Allows for viable reduction in standard expenses of producing –much less waste.
5. Ensures much less problem throughout review –decreased deficiencies –faster approvals.
6. Allows for continuous improvements in products and production method.

FAILURE MODE AND EFFECTS ANALYSIS (FMEA):

Failure mode and effects analysis (FMEA): regularly written with "failure modes" in plural) is the technique of reviewing as many components, assemblies, and subsystems as viable to pick out ability failure modes in a system and their reasons and results. For every component, the failure modes and their ensuing outcomes at the relaxation of the device are recorded in a selected FMEA worksheet. There are several versions of such worksheets. An FMEA can be a qualitative analysis, but may be located on a quantitative basis even as mathematical failure fee models are blended with a statistical failure mode ratio database. It changed into one of the first rather structured, systematic strategies for failure analysis. It changed into evolved with the aid of using reliability engineers with inside the overdue 1950s to observe issues that could rise up from malfunctions of military systems. An FMEA is regularly step one of a system reliability observe [35].

Major advantages derived from a nicely carried out FMECA attempts are as follows: [36]

1) It presents a documented technique for choosing a design with a excessive opportunity of a success operation and safety.
2) A documented uniform technique of assessing capacity failure mechanisms, failure modes and their effect on device operation, ensuing in a listing of failure modes ranked consistent with the seriousness in their system effect and chance of occurrence.
3) Early identity of single failure points (SFPS) and device interface problems, which can be crucial to assignment achievement and safety. They additionally offer a technique of verifying that switching among redundant factors isn't always jeopardized with the aid of using postulated single failures.
4) A powerful technique for comparing the impact of proposed modifications to the layout and operational processes on assignment achievement and safety.
5) A foundation for in-flight troubleshooting methods and for finding overall performance tracking and fault-detection devices.
6) Criteria for early making plans of tests.

DESIGN OF EXPERIMENT (DoE) [37]

DoE is a structured and organized strategy for establishing mathematical models (y = f (xi)) to determine the links between input factors (xi – independent variables) and one or more output responses (y – dependent variables). The controlled input factors are systematically varied in the DoE approach to determine their effects on the output responses, allowing for the identification of the most important input factors, the identification of input factor settings that lead to optimized output responses, and the elucidation of input factor interactions.

STEP INVOLVED IN DOE [38]

Defining the Problem: It is essential to define the experimental process' objectives. Preparing a list of specific concerns to be addressed by the experiment is typically beneficial. It's also crucial to keep all of the experiment's goals in mind.

Cause-and-Effect Relationship: The cause-and-effect diagrams are important for establishing the data collected during the pre-experimental design phase. Because the impact of interest or the response variable is drawn along the spine of the diagram and the potential causes or design considerations are structured in a series of ribs, the cause-and-effect

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diagram is also known as a fishbone diagram. The information and prospective design factors are organized using the traditional causes of measurement, materials, people, environment, methods, and machines.

Factor Screening: When a system or process is brand new, it's critical to pinpoint the critical components that have the greatest impact on the desired response(s). In most pharmaceutical products or processes, there are a plethora of variables at play, and the experimenters are unfamiliar with the system. As a result, if we want to get the best performance out of the system, we should screen it first.

Selection of the Factor Ranges: When considering the factors that may influence the performance of a formulation system, the experimenter usually discovers that these factors can be classified as either potential design factors or nuisance factors. The specific ranges are assigned to the factors for executing the experimental designs. The selection of factor levels or ranges is very crucial in order to observe the meaningful impact of the factors on the response variables. The range for a factor can be identified on the basis of prior experimental knowledge or experience.

Selection of the response variable: In selecting the response variable(s), the experimenter should be certain that this variable really provides useful information about the process under study. Most often, the average or standard deviation (or both) of the measured characteristic will be the response variable. The experimenters must decide how each response will be measured, and address issues to achieve accuracy in the measured response variable.

Factor Optimization: When a system or process is brand new, it's critical to pinpoint the critical components that have the greatest impact on the desired response(s). In most pharmaceutical products or processes, there are a plethora of variables at play, and the experimenters are unfamiliar with the system. As a result, if we want to get the best performance out of the system, we should screen it first.

Experimental Performing: It's critical to keep a close eye on the experiment while it's being carried out to verify that everything is done correctly. Experimental validity is generally destroyed by errors in the experimental process at this stage. On several runs, the people performing the experiment failed to set the variables to the right levels, which is one of Application of DoE in Pharmaceutical Product and Process Optimization 51 the most common mistakes I've seen. Before each run, someone should be appointed to double-check factor settings.

Applications of design of experiments in QbD and AQbD

1. DoE used for screening and optimization purposes of pharmaceutical products and their manufacturing processes may be found in the literature.
2. DoE has been used in the rational development and optimization of analytical methods.
3. Studied output responses (dependent variables) included particle size, entrapment efficiency, dissolution rate, among other.
4. QbD allow to identify the critical material attributes (CMAs) and critical process parameters (CPPs) (independent variables) affecting the critical quality attributes (CQAs) (dependent variables) and, therefore, the quality target product profile (QTPP) [39, 40].

II. CONCULSION

The article conclude that Quality by design as per ICH guidelines Q8,Q9, Q10, all the factors that impact on QbD such as Control strategy, analytical target product profile, Critical Quality attributes and lifecycle management. After coming mathematical errors the failure mode and design of experiment help to resolve them. The major advantages of QbD is help to analysis the product as much as in low cost which effects on better formulation and development, and all essential application was studies through this article.

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CONFLICT OF INTEREST

The authors hereby want to declare that there is no conflict of interest.

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