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Review Article

A Review on Implementing Quality by Design

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Abstract
Quality by Design is the modern approach for quality of pharmaceuticals. Recent pharmaceutical regulatory documents have stressed the critical significance of applying quality by design (QbD) principles for in-depth process understanding to guarantee that product quality is built in by design. Quality has been given a significance by all regulatory body for pharmaceutical goods. Quality means customer fulfillment in terms of service, products, and process. QbD is a systematic approach to product or method development that begins with predefined objectives and uses science and risk management approaches to achieve product and method understanding and finally method control. The aim of the analytical QbD is to attain quality in measurement. 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 the process to meet the product attributes. These leads to recognize the impact of raw material [Critical material attributes (CMA), Critical process parameter (CPP), on the CQA's and identification and source of variability. This paper gives idea about the Pharmaceutical Quality by Design (QbD) and describes use of Quality by Design to guarantee quality of Pharmaceutical products. The Quality by Design is described and some of its elements identified.

Key words: Quality, Design, pharmaceutical.

INTRODUCTION

The term quality means how fit the product is for the proposed use. In pharmaceutical term quality says that the product is free from any adulteration and delivers proper therapeutic benefits. Quality by Design (QbD) confirms in vitro performance of the product which further guarantees in vivo performance of the product [Raghav, G, 2014]. The aim of pharmaceutical progress is to ensure and create the quality product and its manufacturing process should be well designed and invention of quality product. Pharmaceutical industry is constantly lookingthe ways to ensure and produce safety, quality and efficacy. However, drug recalls, manufacturing failure cost, scale up issues and regulatory problem in recent past produce huge task for industry. In traditional, the product quality and performance are predominantly ensured by end product testing, with limited understanding of the process and critical process parameters. Regulatory bodies are therefore focusing on applying quality by design (QbD), a science based method that improves process understanding by reducing process differences and the enabling process-control strategies. [Woodcock, J, 2004; ICH, 2006]

Quality by design is a system for handling a products life cycle, a regulatory expectation, intended to increase process and product understanding and thereby lowers patient risk, a multifunctional exercise. QbD tools and studies comprise prior knowledge risk assessment, mechanistic model, design of experiments (DoE) and data examination and process analytical technology (PAT). Quality by design is a organized method to pharmaceutical development that begins with predefined objectives and highlights product and process understanding and process control, based on sound science and quality risk management [ICH, 2009].

Pharmaceutical companies use diverse strategies for product development: either by taking a good method such as quality testing. Quality by

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design is a strategic process for development and manufacturing. It is meant to ensure that the intended performance of a final product is asexpected – both in terms of quality and efficacy. To achieve this requires well defined objectives, and people proper risk management. Quality by design is A Quality System for managing a product's lifespan, a regulatory expectation, intended to increase process and product studying and thereby decrease patients risk. QbD was initiated in the pharmaceutical industry, the national regulatory authorities, and the academic world as a means of generatingan early understanding of the design alternatives available during the development of a new drug.

Concept and Background of QBD

Quality by Design is a concept first outlined by Joseph M. Juran in various publications. He supposed that quality could be planned. The concept of QbD was mentioned in ICH Q8 guidelines, which states that, "To identify quality cannot be tested in products, i.e. Quality should be built in to product by design." In 1970, Toyota pioneered many QbD concepts to improve their early JPQA | Volume 1 | Issue 2 | October-December, 2015 19 automobiles, since that time other industry technology, telecommunication & aeronautics taken this concept & make QbD. In 1990, Medical devices began to show that incorporated many qualities by design aspects. In mid-2002 FDA published a concept paper on cGMP for 21st century. These documents expressed a desired that companies build quality, safety, & efficacy in to their new product as early as possible. [Avellant, J, 2008; Roy, S, 2012]

Defination

Defination [ICH Q8 (R1)]

Quality by Design is a systemic approach to product development that begins with predefined and emphasizes product and processand controls based on sound science and quality risk management. [ICH, 2007]

Defination [FDA PAT Guidelines, Sept. 2004]

A system for designing, analyzing and controlling manufacturing through timely measurements (i.e. during processing) of critical quality and performance attributes of new and in-process materials and processes, with the goal of ensuring final product safety. The concept of "Quality by Design" (QbD) was defined as an approach which covers a better scientific understanding of critical process and product qualities, designing controls and test based on the scientific limits of understanding during the development phase and using the knowledge obtained during the life-cycle of the product to work on a constant improvement environment.[ICH, 2007; FDA]

Pharmaceutical Approach

Aspects	Traditional	QbD
Pharmaceutical Development	Empirical	Systematic, multivariate experiments.
Mfg. process	Fixed	Adjustable within design space.
Process control	Offline analysis wide or slow response.	PAT utilized for feedback and provide to real time.
Product Specification	Based on batch data.	Based on the desired product performance.
Control strategy	Mainly by intermediate product and end product testing.	Risk based, Controlled shifted upstream, real time release.
Lifecycle management	Post approval changes needed.	Continual improvement enable with in design space.

TABLE NO. 1 TRADITIONAL VS QBD APPROACH [9]

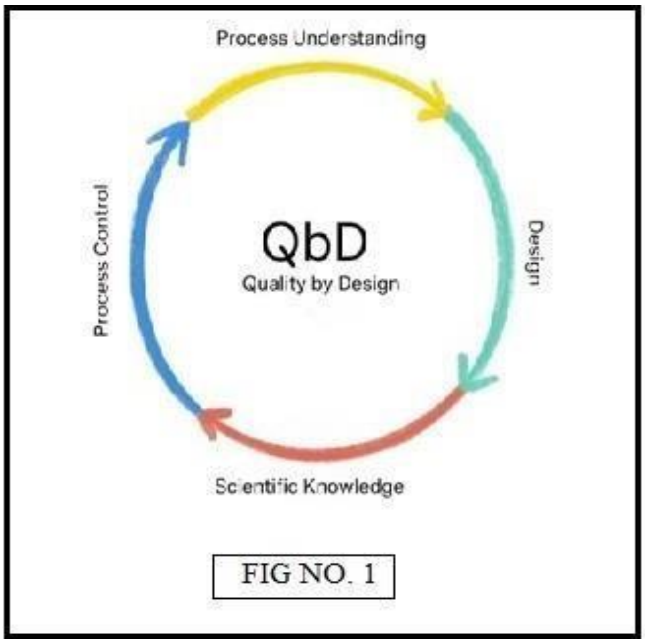

FIG NO. 1

Role of QBD

QbD guarantees that the designing of a product is made in a way to satisfy the requirements of the patients and requirements for better action.

Also with QbD implementation, the designing of the process is done in a way to meet thecritical quality attributes of the product constantly. [Nasr, M.M, 2006]

With QbD application, it becomes easy to attain the understandings of the influence ofprocess parameters and starting raw materials on the quality of the product.

Critical sources of process variability are controlled and identified by means of suitablecontrol strategies. [Nasr, M.M, 2006]

QbD guarantees the continuous monitoring of the process and also it has to bereorganized in order to maintain consistent quality over time. [Michael, T, 2015]

Benefits

Benefits of QBD to Industry

QbD is a respectable business.

Removes batch failures. [Woodcock, J, 2004]

Diminish batch deviations and overpriced investigations.

Avoid regulatory compliance issues.

Organizational studying is an investment in the upcoming days.[ICH, 2007]

QbD is a good science.

Better development decisions.

Empowerment of technical staff opportunities.

Efficient, agile and elastic system.

Build scientific information base for all products.

Better relate with industry on science issues.

Ensure constant information.

Incorporate risk management.

Decrease end product testing. [FDA; ICH, 2007]

Benefits of Implementing QbD for FDA

Improves scientific foundation for review.

Provides for better coordination across review, compliance and scrutiny.

Improves information in regulatory submissions.

Provides for better uniformity.

Improves quality of review, Uses resources to address higher risks. [Nishendu, P. N]

Provides for more flexibility in conclusion making.

Ensure decisions made on science and not on decision empirical data.

Involves various corrections in decision making.

Objectives of QbD

The main objectives of QbD is to confirm the quality products for that product and process characteristic important to desired performance must be resulting from a grouping of prior knowledge and new estimation during growth.

From this information and data process measurement and desired attributes may be created.

Ensures combination of product and process knowledge gained during development. [Chetan,

V.P]

Advantages of QbD

It has several advantages:
It increases the efficacy of pharmaceutical manufacturing processes.
It decreases the high penalties and product recalls.
It gives more efficacy for regulatory oversight.
It offers an advanced assurance level of quality of drug.
It offers saving of cost.
The transparency of the sponsors can be improved with QbD which results in better understanding of the control strategies for the drug product in order to attain approval and finally commercialization.
The scale-up, authentication and commercialization can become rational, clear, and predictable with QbD implementation.
For first cycle approval, it increases opportunities.
It assists in continuous improvement and reduces the computer (CMC) supplement.
It increases the quality of Chemistry, Manufacturing and Control (CMC) and reduces theCMC review time.
Improves information in regulatory submissions.
Regulatory flexibility and Reduces product variability. [Nasr, M.M, 2006; QbD, 2013]

Steps Involved in QbD

Development of new molecular entity: Preclinical study, Nonclinical study, Clinical Study, Scale up, Submission for market Approval.
Manufacturing: Design Space, Process Analytical Technology, Real time Quality Control.
Control Strategy: Risk based decision, Continuous Improvement, Product performance [Callis, J.B. *et al.*, 1987].

Seven Steps of Quality by Design Start Up Plan

Hire an independent Quality by design skilled person.
Audit your organization and process with the skilled person conducting a gape analysis.
Hold a basic quality by design workshop with all your personal.
Review the expert's report and approval.
Draft an implementation plan, timelines and estimated budgets. [Munson, J. *et al.*, 2006]
Assign the resources (or contract out).
Retain the independent expert as your "Project Assurance" guide.

Quality by design (QbD) and well understood product and processes:
All critical sources of variability are recognized and described.
Unpredictability is measured by the process.
Product quality attributes can be accurately and reliably projected over the design space established for materials used, process parameters, environmental and other conditions.
To grow enhanced knowledge of product performance over a range of material attributes, manufacturing process selections and process parameters considering suitable use of quality risk management principle. [Callis, J.B. *et al.*, 1987; Lionberger, R.A. *et al.*, 2008]

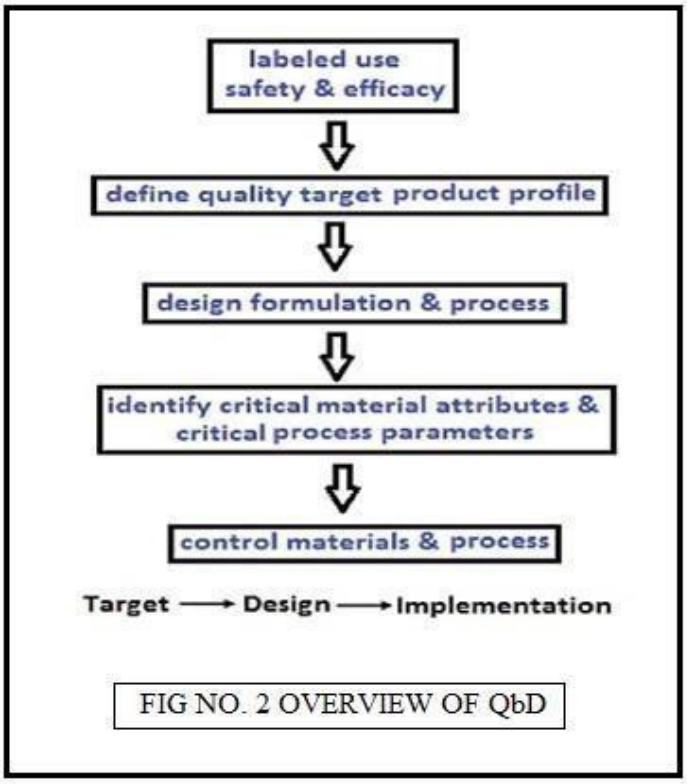

FIG NO. 2 OVERVIEW OF QbD

Key Aspects:
Quality Target Product Profile
Critical Quality Attributes
Risk Assessment
Design Space
Critical Material Attributes
Critical Process Parameters
Control Strategy

Quality Target Product Profile (QTPP)
According to ICH Q8 (R2), QTTP is "Prospective summary of the quality characteristics of a drug product that ideally will be achieved to guarantee the desired quality, taking into account safety and efficacy of the drug product". Basically it is a tool for setting the strategy for drug development. Recently QTTP is widely used in development planning, clinical and commercial decision making, regulatory agency interactions, and risk management.It is the quality characteristics that the drug product should possess in order to reproducibly deliver the therapeutic benefit promised in the label. The QTTP guides formulation scientists to establish formulation strategies and keep the formulation effort focused and efficient. QTPPis related to identity, assay, dosage form, purity, stability in the label.For example, a typical QTPP of an immediate release solid oral dosage form would include:

Tablet Characters
Identity
Assay and Uniformity
Stability
Dissolution

It is significant to acknowledge that QTPP should only contain patient releted product performance elements. For example, tablet density or hardness may be included as a specification for process monitoring but may not be included in QTPP. Also, if particle size is critical to the dissolution of a solid oral product, then the QTPP should include dissolution but not the particle size [Lawrence, X.Y. *et al.*, 2009; Patil, A.S. *et al.*, 2013].

QTPP is a quantitative substitute for parts of logical wellbeing and viability that can be utilized to plan and enhance a formulation and assembling process. It ought to incorporate quantitative focuses for contamination, strength and item unique performance necessities. QTPP isn't determination since it incorporates tests, for ex-

ample, bioequivalence or consistency that are not done in bunch to cluster release. QTPP ought to just incorporate patient related item to show [Lawrence, X. Y. *et al*., 2008]. The Quality Target item profile is a term that is a normal expansion of TPP for item quality. It guides researchers to set up plan methodologies and keep detailing is efficient. QTPP is identified with personality, test, dose structure, virtue, solidness in the mark. [Avellant, J. *et al*., 2018]

Critical Quality Attributes

CQA is the following stage of QbD.Once TPQA has been finded, the next step is to determine the related CQAs. A CQA is characterized as a Physical, Chemical, organic or microbiological property or trademark that should be within an proper limit, range or distributed to gaurantee the desired product quality. Recognition of CQA is done through risk evaluation according to ICH guideline Q9. Previous product knowledge, such as the accumulated laboratory, non-clinical and clinical experience with a specific product quality characteristic, is the key in creating these risk assessments such knowledge may also include relevant data from same molecules and data from literature reference. Taken together, this information gives a rationale for relating the CQA to product safety and efficacy [Kumar, V.P. *et al*., 2015]. Factorsthat have direct effect on the quality and safety of the products are first sorted out, and its potential impact on method development is studied. CQA will be understood analyzed by understanding of the drug products and method. If drug product contains the contamination which may have direct impact on quality and safety of drug product it is being considered the critical quality attribute for the HPLC method development of that particular drug compound. According to Schweitzer et al safety and efficacy can be achieved by demonstration measurable control of quality attributes i.e. products specification, intermediate specification, process control [ICH, 2006].

CQA for the GC method is the temperature of the oven and its program, injectiontemperature, gas flow rate, sample diluent and concentration.
CQA for the HPLC method is mobile phase buffer, pH of the mobile phase, column selection, organic modifier, and elution method.
CQA for HPTLC method is TLC plants, mobile phase, Injection concentration and volume, time taken for plate development, a reagent for color development and detection. [Rozet, E. *et al*., 2013; Reddy, K.R. *et al*., 2017]

Risk Assessment

Risk assessment is a science based strategy used in quality risk management and it can distinguish the material attributes and method parameters (ATP). Risk assessment can be performed from begining of method development to continuoue method monitoring. Analytical scientist recognizes the risk at the previous stage and reduce with QbD approach.A risk assessment is used for successful communication in between FDA and industry, research/development and manufacturing and among multiple manufacturing sites within company. ICH guideline Q9 gives clarification of risk management and various terminologies associated with it, like Risk Acceptance, Risk Analysis, RiskAssessment, 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 [Raman, N.V.V.S.S].

Risk can be usually defined as the combination of the probability of occurrence of any harm and the severity of that harm. The assessment of risk helps in developing the quality of process or method, in determining how the input variable affects a process or method. By carrying out the risk assessment, the CQA can be recognized which may affect the final quality of the product. It also helps in communicating effectively in between FDA and research/development unit, whole company and manufacturing unit as a whole and among various manufacturing sites within the industry. The various principles involved in quality risk assessment include. [Rathore, A.S. *et al*., 2010]

Risk assessment is a combined responsibility of business development unit, quality unit, regulatory affairs unit, engineering unit, sales and marketing, production operations, statistics unit, legal and clinical departments.

Assessment of risk based on scientific information in order to confirm patient protection. Some methods of risk management as men-

tioned in the ICH guideline Q9 contain; Fault Tree Analysis (FTA), Failure Mode, Effects and Criticality Analysis (FMECA), Hazard Operability Analysis (HAZOP), Hazard Analysis and Critical Control Points (HACCP), Risk ranking and filtering, Preliminary Hazard Analysis (PHA), Failure Mode Effects Analysis (FMEA) and Supporting statistical tools [Goel, R. *et al*., 2014].

When CQA has been studied, the subsequent step is to clarify the relevant risk assessment. Once the technique is recognized, analytical QbD focuses on the assessment of the risk associated with variability includes analyst method, instrument configuration, measurement and method parameters, sample characteristics, Sample preparations, and environmental conditions. [Bhusnure, O.G. *et al*., 2015]

According to ICH Q9 guidelines, risk assessment is a systematic process for the assessment, control, communication and review of risk to the quality across the product lifecycle. Risk identification, risk analysis, and risk evaluation are the three-step of risk assessment. [Gupta, K, 2016] The first step of risk assessment is very important to identify and prioritize potential risk. These risks include methods of operation of the instrument, characteristics of reagent and cycle time. It is the most desirable to determine a contingent method in case the primary method fails. Flow chart and check list are used to describe the risk factor. The next step of risk assessment is risk valuation. Fishbone diagram is used to perform risk assessment, also called Ishikawa. According to this approaches the risk factor is divided into three categories- high- risk factor, noise factor and experimental factor. [Pande, P.P. *et al*., 2017]

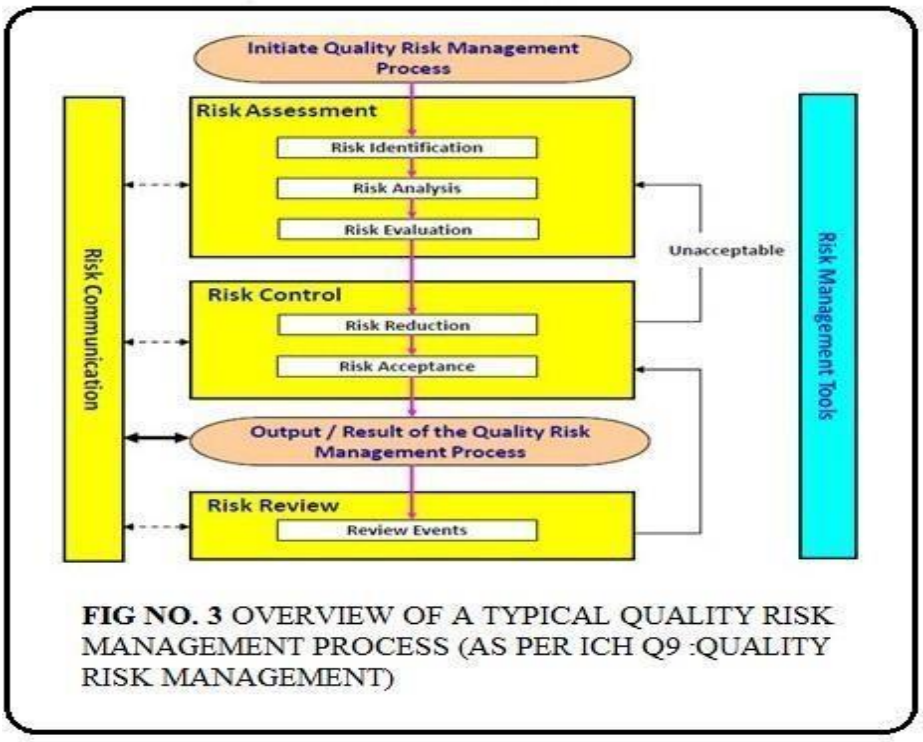

FIG NO. 3 OVERVIEW OF A TYPICAL QUALITY RISK MANAGEMENT PROCESS (AS PER ICH Q9 :QUALITY RISK MANAGEMENT)

Design Space

It is multidimensional grouping and interaction of input variables (e.g. material attributes) and method parameters that are incontestable to supply assurance of quality. Moving out of the planning area is taken into account to be an amendment and would usually initiate a restrictive post-approval amendment method. The planning area is projected by the individual and is subject to restrictive assessment and approval. For the scientist, style, the area could be a Y (Quality Attributes) = F (Process Parameters Material Attributes) – a function or a relationship between (critical) method parameters and

(critical) quality attributes/material attributes [FDA].

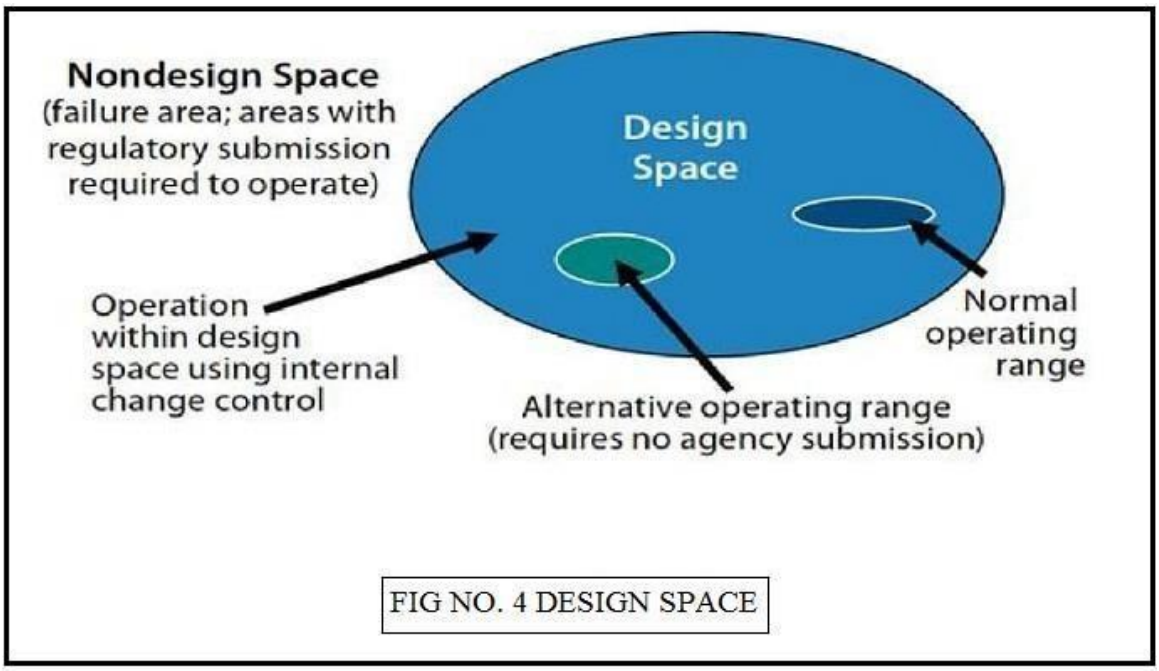

FIG NO. 4 DESIGN SPACE

Critical Material Attributes

CMA parameter is important, once a true modification in parameter will cause the product to fail to fulfill the QTPP. Thus, whether or not a parameter is important or not depends on the however giant of an amendment one is willing to think about this as well as different properties or characteristics of associate input material. CMAs ought to be inside associate applicable limit, range, or distribution to make sure the required quality of that drug substance, excipient, or in-process material [FDA, 1995].

Critical Process Parameters

CPP is outlined as any measurable input (input material attributes or operational parameter) or output (process state variable or output material attribute) of a method step that has got to be controlled to attain the required product quality and method uniformity. During this read, each item would be a method parameter. Parameters are monitored before or in processes.

Control Strategy

Control strategy is defined as "A planned set of controls, derived from current product and process understanding that assures process performance and product quality" [FDA, 2004].

Analytical Target Profile (ATP)

QbD is starting with an analytical goal profile, that is a linear to QTPP. Analytical goal profile defines the goal of the analytical technique improvement procedure, referring to the effects of the approach to obtain QTPP. ATP describes the method requirements that are expected to be the size. The analytical target profile is specifying with the assist of information and medical motive of the analytical system. The ATP defines to what level the measurement is needed (i.E. Functioning degree traits, such as precision, accuracy, variety, and sensitivity) and what the approach has to degree (i.E. Popularity standards). [Peraman, R. *et al*., 2015] Generally, ATP for analytical procedure consists of a variety of goal analytic (API and impurities), selection of analytical technique (HPLC, HPTLC, gasoline chromatography, ion chromatography, and so forth.) and approach requirements (assay and impurity profile).AQbD is started with an analytical target profile or ATP, which is an analogue to QTPP. ATP defines the goal of the analytical method development process, relating the results of the method to achieve QTPP. Recently Ph RMA and EFPIA furnished the definition of ATP: "ATP is a assertion that defines the technique's purpose that's used to pressure technique selection, layout, and development activities."

ATP is a key parameter in AQbD that allows extra continuous development of analytical strategies and their desire, as soon as the regulatory government approve the ATP declaration. In pharmaceutical industry, internal change manage management machine is chargeable for effective implementation of ATP to provide regulatory flexibility [ASME, 2001; CITAC, 2007]

Target Product Profile (TPP)

Under this title goal is crucial word. Target is not anything but a result that we strive to reap. So, on this we goal the drug profile or goal product which guarantees desired fine, protection & efficacy. [Lawrence, X. Y. *et al*., 2008] TPP is defined as, "A potential summary of the best characteristics of drug product that preferably can be accomplished to ensure the preferred pleasant, taking in to account protection & efficacy of drug product."(ICH Q8)

Target product profile should includes,
Dosage form
Route of administration
Dosage strength
Pharmacokinetics
Stability

The TPP is a patient & labeling focused principles, as it identifies the preferred overall performance traits of the product, associated with the patient's need & it's miles prepared according to the key phase inside the drug labeling. [ICH, 2014] Pharmaceutical agencies will use the desired labeling facts to construct a target product profile.The TPP is then used to layout the medical trials, protection & ADME studies in addition to to layout the drug product, i.E. The QTPP.

Design of Experiment

The method of figuring out the most perfect composition and operating conditions is referred to as optimization. The time period optimizes literally manner to carry some thing as close to perfection as possible. A variety of variables are involved within the layout and improvement of prescription drugs. The variables that may be managed by means of the producer are known as independent variables/factors and those independent variables have the potential to steer the characteristics of the analytical technique and outputs. Levels are the values of the elements. The properties exhibited by way of completed products are termed as reaction variables or based variables. Any alternate in independent variables ends in a corresponding alternate inside the dependent variables. [Raman, N.V.V.S.S. *et al*., 2015]

Design of experiments (DOE) is a structured and prepared approach to determine the connection amongst elements that impact outputs of a manner. When DOE is implemented to pharmaceutical manner, factors are the raw cloth attributes (e.G., particle length) and system parameters (e.G., speed and time), whilst outputs are the important satisfactory attributes which include combination uniformity, tablet hardness, thickness, and friability. As every unit operation has many enter and output variables in addition to manner parameters, it's far impossible to experimentally check out all of them. Scientists should use prior knowledge and risk control to become aware of key enter and output variables and procedure parameters to be investigated by DOE. DOE outcomes can assist pick out most advantageous conditions, the vital elements that most affect CQAs and people that do not, as well as information whichincludes the lifestyles of interactions and synergies between factors. Based at the suitable variety of CQAs, the layout area of CPPs can be decided. When thinking about scale-up, however, additional experimental work may be required to confirm that the version generatedat the small scale is predictive at the large scale. This is because a few vital technique parameters are scale structured even as others do no longer. The operating variety of scale based vital system parameters will must alternate because of scale-up. Prior information can play a very widespread position in this regard as most pharmaceutical companies use the equal technology and excipients on a normal foundation. Pharmaceutical scientists can frequently take advantage of beyond experience to define essential material properties, processing parameters and their working tiers [Bhagyesh, T, 2012].

To ensure product first-rate, in the lifestyles of interacting critical system parameters, a "design space" is one technique. The "design area" is "the multidimensional combination and interac-

tion of input variables (e.G., fabric attributes) and method parameters which have been tested to offer warranty of satisfactory" [Lionberger, R.A. *et al.*, 2008; FDA, 2010]. FDA acquiescence of a layout space is a path acquiring the capacity to feature contained by way of that design area without additional approval from the regulatory our bodies [FDA; 1995; Nasr, M.M, 2006]. There are numerous steps covered in layoutarea, and those are:

Identify the unclassified parameters then.
Applying design of experiments using the unspecified parameters by means of the further fixed unclassified parameters.
Selection of selected parameters. [FDA]

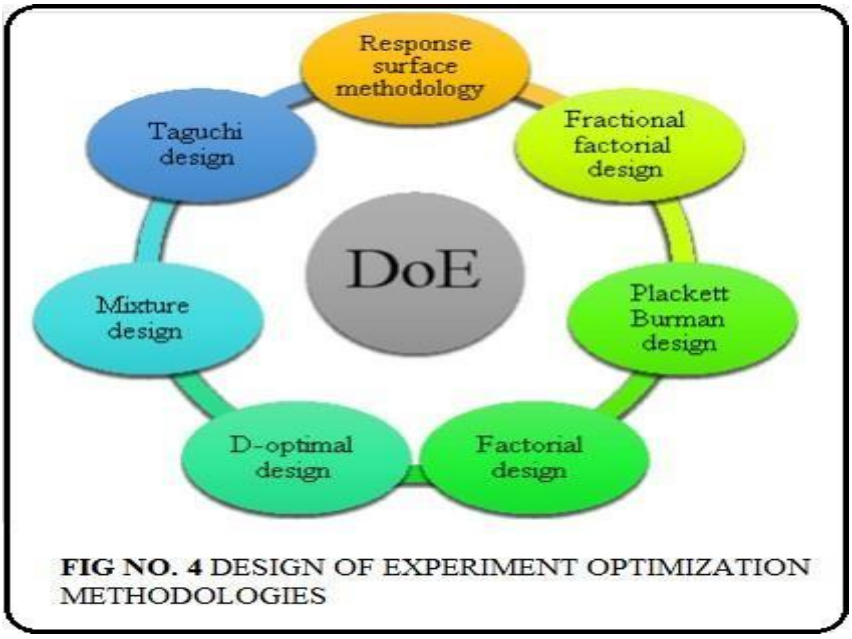

FIG NO. 4 DESIGN OF EXPERIMENT OPTIMIZATION METHODOLOGIES

Applications of QbD

In analytical method development:
Chromatographic techniques like HPLC (For stability studies, method development, and determination of impurities in pharmaceutical)
Karl Fisher titration for determination of moisture content
To Biopharmaceutical processes
Dissolution studies and Analysis of genotoxic impurity
Hyphenated technique like LC-MS
Advanced techniques like mass spectroscopy, UHPLC, capillary electrophoresis

CONCLUSION

Quality by Design is an critical part of contemporary technique pharmaceutical quality. Thisis a concept which could and is changing the traditional technique, and is firmly taking roots inside the enterprise. Identification of important fabric attributes that offers a hyperlink of the product first-class to the producing technique. Implementing QbD concept in product improvement offer pleasant drug treatments to sufferers, manufacturing enhancements to Manufacturers with extensively reduced batch disasters and drug regulatory bodies can have greater self belief inside the sturdy excellent of merchandise. QbD calls for the right ATP and chance assessment and usage of proper equipment and performing the perfect amount of work inside proper time lines. The potential product CQAs which might be derived from QTPP and prior knowledge must be used as a manual for the improvement and manufactureof the products. Further, first-class chance management can help to evaluate the quantity of variation of the CQAs which can affect the fine and overall performance of the product. QbD is the destiny of product and system improvement, and as such ends in non-stop development and innovation in products and tactics.

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