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QUALITY BY DESIGN: A NOVEL APPROACH FOR THE DEVELOPMENT OF QUALITY PHARMACEUTICALS

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ABSTRACT

Customer satisfaction and loyalty are indicators of quality. Because of the public's increased awareness of product quality, it has become a top priority for most businesses. In this review, various aspects of product quality design will be discussed. QbD is a development methodology which begins with predetermined goals & stress on product and process quality formulated on prior experience and effective control of risks. The target product profile, critical quality characteristics, risk control, creating a design room, and control methodology are all important aspects of QbD. QbD describes how composition & production process attributes affect production efficiency. With the help of some case studies, this approach is explained in the present review. QbD is an efficient tool, and with mandatory regulatory requirement to ensure that pharmaceutical products are of high quality.

Keywords: Quality, critical quality Attributes, Risk assessment, predetermined goals

INTRODUCTION:

Quality, along with protection and effectiveness, is one of the most important requirements for any molecule to be qualified and approved as a drug **[1]**. Consumer's fulfilment with reference to utility, outcome, and the activity is what quality entails. Several of these quality-associated pursuit reviews a company's requirement to shine in international competitiveness. Pharmaceutical business has an urgent need to improve its operational performance and overall product quality as global competition intensifies and impacts as the information technology grows **[2]**. The customer expects perfection in terms of quality, dependability, economics, and appropriate enforcement. Consumer's fulfilment can be

attained by two approaches: attribute and price and zero flaws in the produce. The product must include attributes such as fulfilment, reliability, durability, convenience, and usability, and it must be free of flaws. Quality must be strengthened into the product and also in the resources through deliberate arrangement in order to avoid future failures **[3]**. The focus has recently shifted from testing to building "quality" in order to ensure continuity of performance of pharmaceutical products and systems **[1]**. To guarantee that drug products meet safety and efficacy criteria, processes must adhere to current good manufacturing practises. In the pharmaceutical business, this need has traditionally been addressed by undertaking authentication of processes in three different parts. It has been acknowledged that this method is not likely to describe accurately the situation. Raw materials, operators, shifts, and reactor vessels are all potential sources of uncertainty in normal Manufacturing, hence they are unlikely to be covered. The Food and Drug Administration has reported this subject as a statutory difficulty, stating that now there will be an "emphasis on process validation rather than process comprehension." Quality by Design aims to change this approach **[4]**.

Dr. Joseph M. Juran, a quality visionary, was the foremost to introduce the scheme of QbD. Dr. Juran believed that quality must be developed into a finished product, & that product development process is to blame for the majority of quality-related difficulties. The US FDA strongly supports a risk-based approach that incorporates QbD in drug production, manufacturing, & regulation **[2]**. QbD has got the approval by statutory bodies (FDA & EMA) following the publishing of a number of (ICH) guidelines Q8, Q9, Q10, and Q11. The ICH Q8 guideline, describes. As a method of defining the process's initial targets, QbD encourages visibility, monitoring, and risk management for the final product's quality. As a result, Quality by design allows for the manufacture of secure and high-quality pharmaceuticals **[1, 3]**. Because it demands a full understanding of the product and its manufacturing process, QbD involves an upfront commitment of time and money in the discovery and development of a product. Quality by Design pushes for quality to be included into the development process and product, as opposed to the traditional Quality by Testing (QbT) approach, in which quality is mostly tested in the completed product **[2]**. Raw material, the relationship between a process and its fundamental quality characteristics (CQAs), and the link between CQAs and clinical qualities are all part of the product and process knowledge base for QbD **[5]**. The FDA initiated an up-to-date

programme in 2002 cGMP for Twenty-First Century: A Risk-Based Approach. This will be aimed to modernise the FDA's pharmaceutical quality regulation and create a new regulatory structure focusing on QbD risk management and quality systems. The initiative urged businesses to think beyond consistency through testing (QbT) when it came to ensuring product quality and efficiency. This idea encourages industry's apprehension of the product and manufacturing process begins with production, which is essentially building consistency into the product rather than testing it **[6]**.

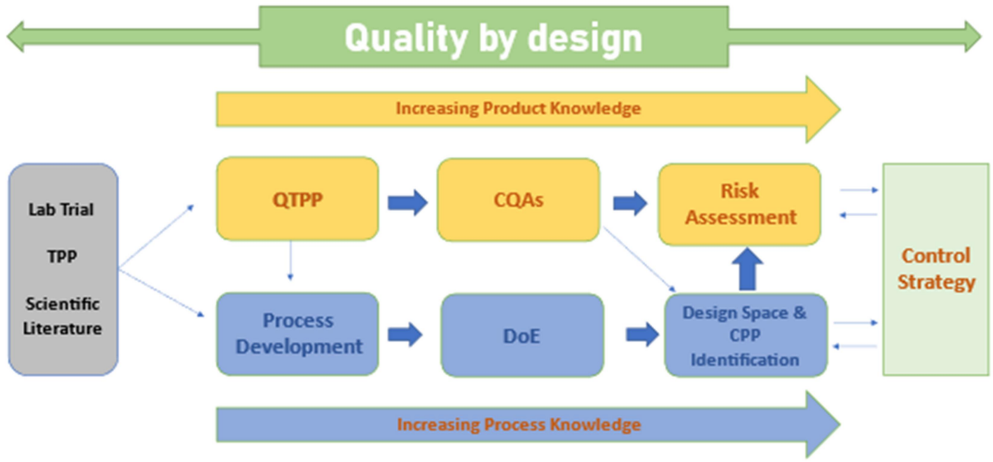

Figure 1: QbD process with its elements

Accordingly, the first and most important task during QbD implementation is to prioritise the "select a few" from all the possible "so many" attributes affecting the specific pharma process or product **[7]**. To describe those characteristics, the following parameters are defined: QTPP, CQAs, CMAs, and CPPs. Some QbD elements could be:

- Defining the TPP
- Creating the design and the production processes
- Determining the most important quality characteristics, process variables, & variability's sources
- Manipulating production line to ensure consistency over the time.

In the pharmaceutical industry, QbD makes cost-efficiency and manufacturing process simplicity a reality **[9]**.

As per ICH Q8 guideline QbD is a "A Holistic methodology to growth that starts with predetermined goals & emphasis is on the product and operation awareness, process monitoring, & quality risk management based on scientific evidence " complements with the FDA's recent medication quality system concept of "quality cannot be tested into things; it should be built into things" **[13]**.

Nonetheless, successful QbD adoption in pharmaceutical formulation and process design relies heavily on a thorough monitoring of the variabilities sources & manufacturing process, and Process Analytical Technology (PAT) is an indispensable element in the QbD model. As a vital metric, risk assessment (RA) is the key component of development that is driven by QbD. It is possible to have an initial and/or final RA. It can be practised and improved upon, but it is always required. RA data can be important during the development phase, even if the technique varies. RA can help to save a substantial amount of time and money across the research. According to the ICH definition, "a holistic approach for organising methodology for organising data to help a risk decision." It comprises distinguishing threats along with analysing and assessing the risks that come with them. Risk assessment and management knowledge pertaining to the product's manufacturing, storage, and distribution, as well as how to effectively minimise any dangers, is predefined and implemented into the product **[16, 32]**.

Regulatory bodies as an example the EMA, US-FDA, & CNMPA favour marketing authorization applications that incorporate QbD because they allow more flexibility in the manufacturing process, lower development costs, and minimise regulatory burden **[16]**. According to Suresh and Basu **[18]** the medication development process accounts for roughly 30-35 percent of R&D costs and around 4-5 years of the product's complete life cycle from conception to launch **[18]**. Understanding formulation features and process parameters in the R&D phase, as well as quantitative prediction of their impact on drug product CQAs and a holistic process viewpoint, are all capabilities that can have a significant impact on pharmaceutical product and process development. In this context, QbD is seen as the key to achieving quantitative knowledge and, as a result, a decrease in R&D time and expenses **[2]**. QbD has applications in large-scale conventional manufacturing as well as research and development. According to studies, the cost of goods sold (COGS) for brand-name pharmaceuticals accounts for around 27-30% of the entire cost of the product, whereas the cost of goods sold (COGS) for generic drug makers accounts for nearly twice as much, despite the fact that non branded drug manufacturers have significantly less Research and development, promotion, & price of sales. As a result, while QbD is important regardless of whether a drug is branded or generic, it may be more important in decreasing waste and maximising profit margins for generics **[2]**. The QbD

approach is very well suited for the development of biosimilars. The quality attributes and requirements stated in advance by the originator reference standard (RP) can assist in focusing the process and lowering the chance of profile deviation. The QbD process can also be simplified and made more realistic when identifying the quality target product (QTPP) and important quality attributes because the RP has already identified the product qualities (CQA) **[25]**.

Table 1: Traditional vs QbD approach

Aspects	Traditional Approach	QbD Approach
METHOD DEVELOPEMENT	**Material, product, process parameters measured based on standard guidelines (e.g., ICH Q6)**	**Material attributes measured on risk assessment and multivariate strategy**
METHOD VALIDATION	**Based on required validation characteristics in ICH Q2**	**Starts with the end in mind (i.e., a predefined analytical target profile) and identifies and considers all possible variables that affect product performance**
METHOD TRANSFER	**Only a few procedures are used in this one -time experiment**	**Considered as a change control process where variables likely to change as a consequence of operating method**
METHOD OPERATIONS	**To determine how effectively the method is working, it relies on general system-suitability criteria**	**A reliable method based on system appropriateness tests generated from a rigorous risk assessment**
LIFE-CYCLE MANAGEMENT	**The cost of regulatory action limits the introduction of method adjustments or upgrades**	**Changes, such as the adoption of more appropriate technology, are undertaken without the need for proper regulatory approval as long as the analytical target profile is fulfilled**

Vaccines have played a major role in the prevention of infectious diseases and continue to do so and the progress of human well -being throughout history. Due to the complicated nature of biopharmaceuticals, vaccines come with longer time frames of growth and more severe regulatory criteria based on the procedure at the plant and the characterization of the product. QbD's application to biopharmaceutical development is complicated, and industry concerns that these notions will add time and resources to the process are common. However, studies have shown that QbD has a strong commercial motive, exhibiting the ability to streamline process development if used effectively. Biological processes and product quality are intimately linked in all items **[26]**. Furthermore, PAT tools used in various manufacturing processes in the QbD system are summarised in order to provide insight into the continuous manufacturing process **[27]**.

QBD'S GUIDING PRINCIPLES ARE AS FOLLOWS:

QbD is a rational mindset of doing things well the first time, anticipating the intricacies of full procedural aspects. As a result, the complete QbD exercise aims to

reveal scientific minutiae that would otherwise go unnoticed through the systematic product design and manufacturing process(es) **[7]**. The Federal Government has suggested and embraced "Quality Risk Management (QRM)" as a major technique to not only give a holistic awareness of the patient set of risks with each step of product development, but also to facilitate risk reduction. Nonetheless, "Design of Experiments (DoE)," which utilises appropriate usage of various experimental designs, has been one of the main instruments in the QbD for generating optimised goods and processes. The emergence of systematised QbD-based paradigms has provided a fresh viewpoint on drug formulation development and subsequent patient care in the pharmaceutical product development arena.

HISTORY AND BACKGROUND:

Despite having been seen as a new paradigm in the pharmaceutical industry, QbD is not that new. In the 1950s, quality by design (QbD) is a concept first developed by the quality pioneer Dr. Joseph M. Juran, who created the QbD as a term in the 1970s and popularized it in the 1990s with several publications. The US Food and Drug Administration (FDA) took the initial steps in incorporating the QbD idea under current good manufacturing practices (cGMPs) in 2002, and the FDA published its final report on 'Pharmaceutical cGMPs for the 21st Century: a Risk-Based Approach' guideline in 2004, with the goal of modernising pharmaceutical development and process performance monitoring **[6]**. Process Analytical Technology (PAT) has been a technique for developing, assessing, and managing manufacturing techniques based on knowledge of science and elements that affect the final quality of the product **[10]**. A few years later, the ICH Q8 was released, thereby codifying the QbD concept as a systemic method to drug development that originates with established purpose and stresses product and process knowledge and process monitoring, according to strong research and quality risk assessment" **[14]**. Several tens of publications have been published since 2007 proposing to use QbD to generate tailored Nano medicines. A considerable portion of them come from Asia (with India accounting for the bulk at 48 percent) and the United States (33 percent), indicating a much more established implementation of QbD in those locations. In Europe (11%) and Africa (8%) the QbD analysis is less established. In 62 percent of the studies reviewed, QbD is only used to address formulation issues, 29 percent addressed both formulation and manufacturing issues, and only 9% are solely dedicated to identifying essential components in the

development process's production steps **[14]**.

OBJECTIVES IN PHARMACEUTICAL INDUSTRY: [6]

Pharmaceutical QbD is a comprehensive way to the development that starts with clear objectives & emphasises product and process comprehension and assurance, as well as quality risk analysis. The following are examples of pharmaceutical QbD objectives:

1. Based on scientific results, build better manufacturing quality standards.
2. Focus on improving product and process design, awareness, and control to increase efficiency while reducing product variability and deformities.
3. To increase the productivity of product growth and engineering
4. Upon confirmation, strengthen root cause evaluation and process improvement.

All such goals are frequently met under QbD by tying quality of the product to expected clinical performance and then developing a strong formulation and manufacturing process to consistently supply the preferred quality of the product. The FDA has made significant progress toward its main objective: performance-based standards for quality. The 2nd goal of QbD is to improve product performance and reduce product deviation, which frequently leads to product flaws, denials, and recalls. QbD represents a comprehensive framework to product design and development. As a result, production capacities, pace, and reviewed performance all have been enhanced. Thirdly, it adjusts resources from a reactionary downstream mode to an upstream progressive approach. It boosts the producer's ability to recognise the underlying factors of production Errors. As just a consequence, the 3rd goal of QbD is to enhance the efficiency of product manufacturing. After approval, the ultimate goal of QbD is to improve underlying causes and systems integration. Without a strong understanding of the product and process, the ability to effectively scale-up and conduct root cause analysis is just a few, necessitating the development of various data sets on the planned larger scale. The FDA's notification lay the groundwork for post-approval changes **[16, 17]**. The FDA has issued guidelines to streamline the statutory filing process for low-risk post-approval chemical, manufacturing, and manufacturing adjustments.

PHARMACEUTICAL QbD DESIGN AND TOOLS [7]

The QbD-based approach is used in a five-step methodology for medicinal product development.

STEP I: DETERMINING THE DRUG PRODUCT'S OBJECTIVE (S) AND ATTRIBUTES

The quality target product profile (QTPP) is a list of future quality attributes of the delivery systems product that should be ideally achieved to ensure the intended quality, while also taking into account the drug's safety and effectiveness. Structural, biochemical, physiological, or microbial qualities of a product which must be within a specified range, or distribution to be able to achieve the product quality that is desired are known as critical attributes. Drug substance quality attributes, excipients CQAs, packaging material CQAs, and other types of CQAs are all related with drug goods. The amount of harm a patient could conceivably suffer as a result of a product failure is used to identify prime CQAs from the QTPP. Once the QTPP is determined, the CQAs that idealistically symbolise the objective(s) are designated for the goal.

STEP II: CHOOSING THE MOST IMPORTANT VARIABLES FOR OPTIMIZATION INPUT

Material and process attributes are two different types of input variables connected with a product or process that have a direct impact on the drug product's CQAs. Non-critical Process Parameters (non-CPPs), Unclassified Process Parameters (UPPs), and Critical Process Parameters (CPPs) are examples of PPs. The "prominent few" inputs variables, referred to as Critical Material Attributes & Process Parameters, are identified from the "possible so many" using early risk assessment and QRM methodologies. Factor screening is the common name for this procedure. Commonly used evaluation methodologies include the Comparison Matrix (CM), Risk Estimation Matrix (REM), Failure Mode Effect Analysis (FMEA), and Hazard Operability Analysis (HAZOP).

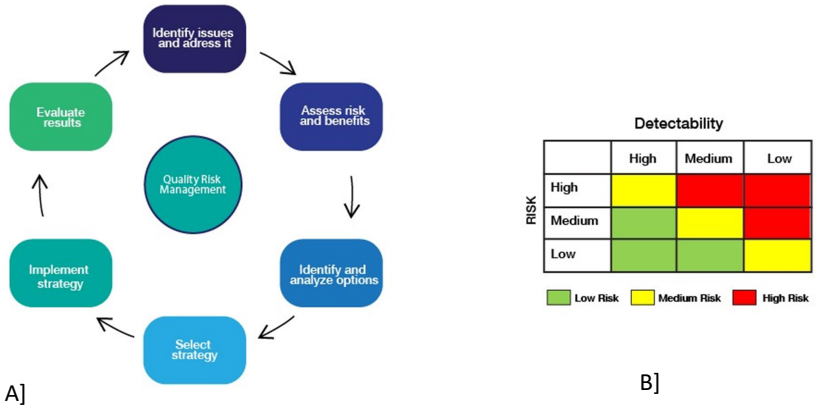

Figure 2: A] A high-quality risk management strategy B] Risk estimation matrix

STEP III: EXPERIMENTATION & ANALYSIS WITH A DESIGN:

The technique for the surface response is a critical component of a whole Quality by design process for optimising product and/or process attributes identified through RA and screening studies. The use of prototypes assists in the visualization of responses based on the examined objective(s), CQAs being investigated, and CMA levels at high, medium, or low levels. The most significant experimental designs used during design-based development of a product for response surface methodology are depicted in **Figure 3**. The most frequent high resolution second-order designs used for drug product optimization include Factorial, Box-Behnken, central Composite, Optimum, and Mixed designs. The drug delivery scientists are guided by a design matrix, which is a matrix of experimental runs produced by the design of an experimental choice. The medication formula is generated quantitatively based on the design matrix, & the selected outcome parameters which are thoroughly analysed.

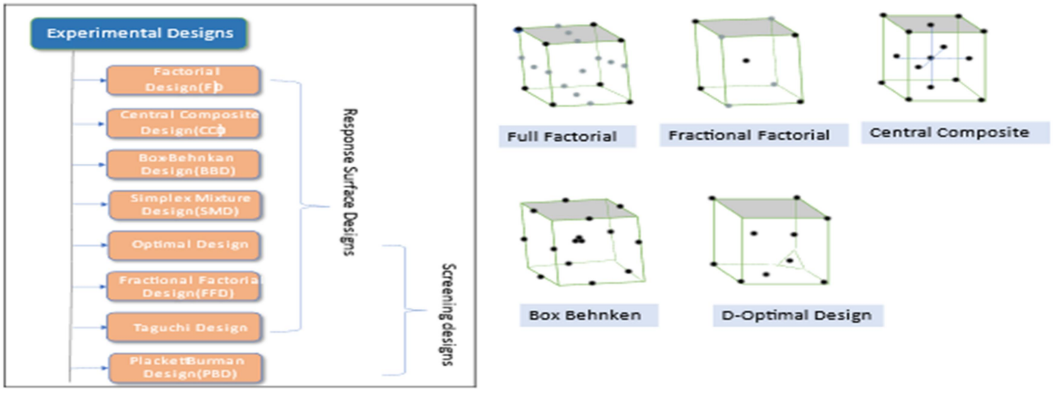

Figure 3: Pictographic representation of experimental designs employed during QbD

STEP IV: MODELLING & VALIDATION OF QBD METHODOLOGY

Modelling is done by choosing appropriate mathematical models such as linear, quadratic, and cubic models to build 2D and 3D response surfaces that connects the critical attributes with the process/material attributes in order to find underlying interaction(s). Some of the primary multivariate chemometric approaches used for modelization are Multiple Linear Regression Analysis (MLRA), Partial Least Squares (PLS) analysis, and Principal Component Analysis (PCA). The design and control spaces include the optimum formulation. The ideal solution with quality assurance is determined by a multifaceted conjunction of both the type of variables. In accordance with ICH Q8, design space is defined as a "Quality was demonstrated by a multifaceted mix and interplay of material Accepted Manuscript features and/or

process factors." **[2]** The capacity to calculate the impact of a process variation on product quality aids in the reorganization of critical process variables. When a design space is established, it is possible to anticipate challenges and achieve greater process control **[2]**. The process design space can be used to define a control space. It enables us to comprehend operations in such a way that the product's quality may be assured based on the adaptability of well-known variables, manufacturing procedure which allows improved command over multidimensional methods of production **[2]**.

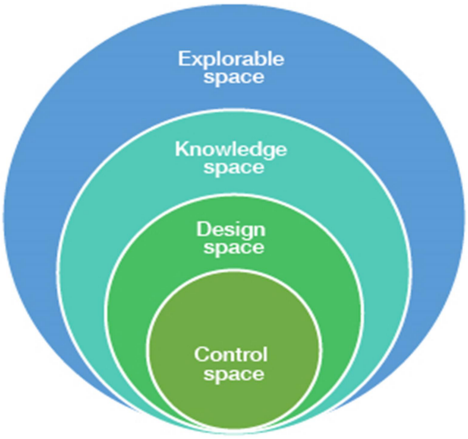

Figure 4: pictographic representation of Process design space and control space

Operating space is outlined as the optimal combination of statistically derived attributes that are simple to handle any natural adaptability in both process and quality variables. When it comes to non-branded, the space for operation must be contained within the control space, making possible for the testing a product of reference with a similar set of characteristics, while for the novel drugs, the operating space should be contained inside the design space, in compliance with legal requirements.

STEP V: VALIDATION, SCALING-UP, AND PRODUCTION OF QBD

Validation of the QbD techniques is an important phase in predicting the prognostic potential of the polynomial models under consideration. A variety of products and processes characteristics are chosen from the area of experimentation and evaluation according to to the typical working conditions established in order to achieve the optimal product and process conditions, often known as controls or confirmatory runs. The outcomes of these controls are then correlated to the prime examples of theoretical frameworks employed during (FbD) projected ones using linear correlation plots and residual plots to look for any typical patterns such

as ascending or descending lines, cycles, and so on. The product or process is scaled up to verify QbD results in an industrial setting using a pilot plant, exhibit, and production scale to establish reproducibility and robustness. For "continuous improvement" in achieving superior completed product quality, a holistic and varied "control strategy" is methodically proposed.

TOOLS OF QbD:

1. RISK ASSESSMENT:

"A drug products manufacturing and use, as well as its components, would inevitably involve some level of risk" in accordance with ICH Q9. The initiative, formalism, and paper work of a good risk management process should all be commensurate to the level of risk, and the appraisal of the quality at risk should be founded on scientific understanding and eventually lead to the safety of patients **[6]**. Prior to research and development, risk assessment is used to detect formulation and method variables that could have a high risk of affecting the therapeutic products consistency. It aids in prioritising which investigations should be carried out and is frequently motivated by information gaps or uncertainty **[6]**.

The following is a partial list of common risk assessment instruments provided by ICH Q9:

- Methods for facilitating risk management at a basic level.
- Analyse the fault tree, risk assessment, initial consultation of hazard
- Analyse the risks, monitor points of critical importance, and analyse the consequences of failure modes.
- Analyse the mode of failure, repercussions, and critical ability.
- Danger operability analysis.
- Statistical software to assist.

Adapting these instruments/software's in the areas of specifications relating to drug substance and drug product quality may be Suitable.

2. DESIGN OF EXPERIMENTS (DOE):

Understanding products and processes is an essential part of quality by design. DoE is an exceptional resource that enables pharmaceutical experts to adjust parameters in a methodical manner in accordance with the defined plan, in addition to mechanistic models, to better achieve these objectives.

In the case of conflicting objectives, DoE techniques give the "best answer" and requires less trials to attain an optimal formulation. It provides a thorough understanding of the formulation scheme and can solve a dilemma in a far more straightforward manner. Furthermore, the screening methods used in DoE assist in identifying important and minor factors.

Now days, techniques for DoE enhancement are developing into a common practice worldwide, not obnoxiously in the design and evolution of a range of novel dosage forms, but also for amending the prevailing ones. When DoE is applied to formulation or process expansion, input variables include the material attributes (e.g., particle size) of raw material or excipients and process parameters (e.g., press speed or spray rate), while outputs are the critical quality attributes of the inprocess materials or final drug product (e.g., entrapment efficiency, particle size or particle size distribution of the particulate or vesicular carrier system, drug contender. DoE can assist to determine optimal circumstances, Material attributes, Process Parameters, and, ultimately, the design space. In recent papers, Food and drug administration experts have demonstrated the application of DoE in product and process design **[6]**.

3. PROCESS ANALYTICAL TECHNOLOGY (PAT):

The use of PAT could be a part of the control approach. The usage of PAT is identified in ICH Q8 (R2) to ensure that the process stays inside a defined design area. Continuous monitoring of CPPs, CMAs, or CQAs is possible using PAT.so that go/no-go decisions may be made and the process can be demonstrated in the design space. In-process testing, also known as CMAs or CQAs, online measurements are possible in accordance with Process Analytical Technology. End product testing is less effective than PAT applications. PAT can control the situation actively for CMAs and/or CPPs, as well as prompt modification of operational parameters, in a more robust process, if a change in the surrounding or materials that are contributing have a negative impact on the quality of a therapeutic product is identified **[6]**.

SOFTWARES IN QbD:

The benefits of QbD approaches are numerous, and their acceptance is high. However, putting such sensible techniques into practise frequently necessitates a tremendous degree of mathematical and statistical complexity. The former computational glitches have been substantially reduced and streamlined thanks to the availability of powerful and affordable hardware, as well as the full QbD software.

LIMITATIONS CONFRONTING QBD WITH FDA PERSPECTIVE [36]

- a range of products
- Putting new ideas/methodologies into practise (QbD, Design space, Quality risk management)
- Various regulatory procedures (NDA, ANDA.BLA)
- Expectations for QbD-based applications that meet customary criteria

FORMULATION	QbD DESIGN	PARAMETERS	REFERENCE
Tablets	Two factorial designs	Independent variables: concentration of super disintegrant, drug: total polymer ratio disintegration time	8
Hard gelatine capsules	-	CQA-Disintegration time, loss on drying, sulphated ash, weight specifications	10
Proliposomes	Face centred central composite design, risk assessment studies, multiple regression analysis	CMAs: Amount of carrier, lipid: drug ratio CQAs: percentage drug release, entrapment efficiency, vesicle size of liposomes	11
Polymeric nanoparticles	BB design, PB design	CQAs: entrapment efficiency, average particle size, zeta potential	12
Microsponges	FMECA, One factor response surface method	CMAs: amount of acetone, Ethyl cellulose, tween 80, span 80, and water ratio in primary emulsion	15
Solid emulsifying formulations	FMECA	CMAs: ranscutol HP, tween 80, maisine	18
Nanoparticles	DoE	CQAs: Particle size, entrapment efficiency, Sonication time and amplitude	35
Process Control			
Process	**QbD design**	**Parameters**	**Reference**
Dissolution	Multivariate analysis	Type of dissolution apparatus, volume, ethanol content, pH	19
Spray Drying	DoE	Process Parameters: Nozzle gas flow rate, inlet air temperature, feed flow rate	20
Tablet Coating	Combined optimal design	Disintegration time, hardness	21
CHROMATOGRAPHIC TECHNIQUES			
Purpose	**QbD design**	**Parameters**	**Reference**
Method development/ optimization strategy for HPLC	PB design	Assay/impurity testing of pharmaceuticals	22
Development and validation of rapid UHPLC	QbD approach with the aid of fusion AE	Gradient time, Mobile phases	23
Development of HILIC	AQbD and Rechtschaffen design	CPPs: Duration of linear gradient, temperature	23
Screening of column used for RP-HPLC and ULC	Systemic approach	-	24
HPLC method development for drug products/substances	BB design	Interaction, main and quadratic effects on the responses, tailing factor, peak solutions.	28
Biological Applications			
Process	**QbD design**	**Parameters**	**Reference**
Vaccine Development	Risk and experimental based strategy	High product impact or potential strain sensitivity	29
Development of botanical drug products	Risk assessment methods	Ethanol consumptions, concentrate density, setting temperature	30
Synthesis of polyacrylamide corn fibre gum	-	Concentration of initiator and acrylamide	31
Dissolution and solubility enhancement	BB design	CPPs: Amount of HPMC, Polymeric surfactants, preparation techniques, mobile phase, buffer pH	34

Figure 5: Software's used in QbD

CONCLUSION

QbD is a basic assumption of the ICH Q8, Q9, and Q10 ideas that can be critical in the development phase. The article clarifies the usage of a product profile, risk assessment, the determination of critical material qualities, the idea of critical process parameters, the implementation of a control plan, and the method's ongoing monitoring and updating. It also discusses how to apply QbD theories and processes to the manufacturing of pharmaceutical products and processes. Quality by Design (QbD) principles and tools, contribute significantly to the advancement of process knowledge and establishing control techniques in formulation and method innovation.

LIST OF ABBREVATIONS:

QbD- Quality by design

CQA- Critical quality attributes

FDA- Food and drug administration

CMA- Critical material attributes

USFDA- United nations food and drug administration

CPPs- Control process parameters

EMA- European medical agency

ICH- International conference on harmonization

CGMP- Current good manufacturing practices

RA- Risk assessment

QTPP- Quality target product profile

NMPA- National medical products administration

CONSENT

It is not applicable

ETHICAL APPROVAL

It is not applicable

CONFLICT OF INTEREST

There is absolutely no conflict of interest

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