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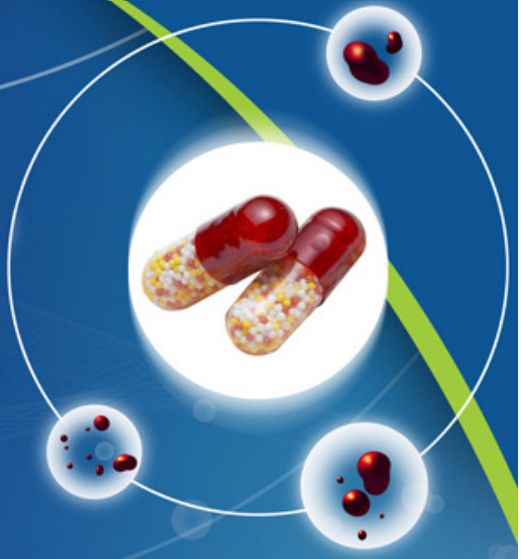

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Review Article

OVERVIEW OF QbD: A CHALLENGE TO THE PHARMACEUTICAL INDUSTRY

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ABSTRACT

QbD (Quality by design) is a holistic approach where product specifications, manufacturing process and critical parameters are included in order to ease the final approval and ongoing quality control of new drug. QbD is based upon the ICH Q9 [Quality Risk Management] and Q8 [Pharmaceutical Development]. Also the ultimate objective of this approach is to promote faster and more consistent product and process development activities, and to increase manufacturing flexibility and process robustness in order to reduce production costs. Thus product quality is monitored throughout its development and hence it is an important factor. Similarly, QbD is important in pharmaceutical industry as quality matters in each and every step for the production of the drug. In this review, overall QbD along with its principles and the steps responsible for the implementation of QbD are discussed. Also major steps in the process for the implementation of QbD in Pharmaceutical Industry the pros and cons of QbD with industrial examples are discussed here. Various tools of QbD are been discussed here with a 7 step plan process for QbD. Similarly PAT (Process Analytical Technology) is an important aspect of QbD which is discussed here. QbD is a promising idea which offers pharmaceutical manufacturer with increased self-regulated flexibility while maintaining firm quality standards and real time release of the drug product.

Keywords: *Quality by Design (QbD), Target Product Profile (TPP), Target Product Quality Profile (TPQP), Critical Quality Attributes (CQA), Critical Process Parameter (CPP).*

INTRODUCTION

Quality by Design (QbD) is one of the most influential strategies in the executive toolkit. In mid-2002, the U.S. FDA published a concept paper on current GMPs for the 21st century. This document articulated a desire that companies build quality, safety and efficacy into their new biopharmaceutical products as early as possible. This concept is known as Quality by Design. Then, FDA officials realized that biologics and drugs could also stand to benefit from QBD. By 2004, FDA formed a guidance document entitled Pharmaceutical cGMPs for the 21st Century. The cGMP initiative described a "Desired State" For pharmaceutical manufacturing through QbD in which:

- Product quality and performance are achieved and assured by design of effective and well-organized manufacturing processes.
- Product specifications are based on a mechanistic understanding of how formulation and development factors impact product performance.
- Manufacturers have the capability to affect continuous improvement and continuous "real time." assurance of quality.
- Regulatory policies and procedures are modified to recognize the level of scientific knowledge supporting product applications, process validation and process capability.

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- Risk-based regulations are commensurate with the level of scientific understanding of how formulation and manufacturing development affect product quality, performance and the capability of process control strategies to prevent the risk of producing a poor quality product [1].

The Food and Drug Administration (FDA) Office of Generic Drugs (OGD) has developed a question-based review (QbR) for its chemistry, manufacturing, and controls (CMC) assessment of abbreviated new drug applications (ANDAs) [2].

This new QbR system incorporates some elements of QbD [3]. It recommends that ANDAs be submitted using the common technical document (CTD) and contain the quality overall summary (QOS) that addresses all the QbR questions.

The main benefits of this QbR system are to:

- Assure product quality through design and performance-based specifications,
- Facilitate constant improvement and reduce CMC supplements,
- Improve the quality of CMC reviews through standardized review questions, and
- Reduce CMC review time when applicants submit a QOS that addresses the QbR questions.

This commentary focuses on the QbD for generic drugs. The concept of QbD was mentioned in the ICH Q8 guidance [4], which states that "quality cannot be tested into products, i.e., quality should be built in by design".

PHARMACEUTICAL QUALITY BY TESTING

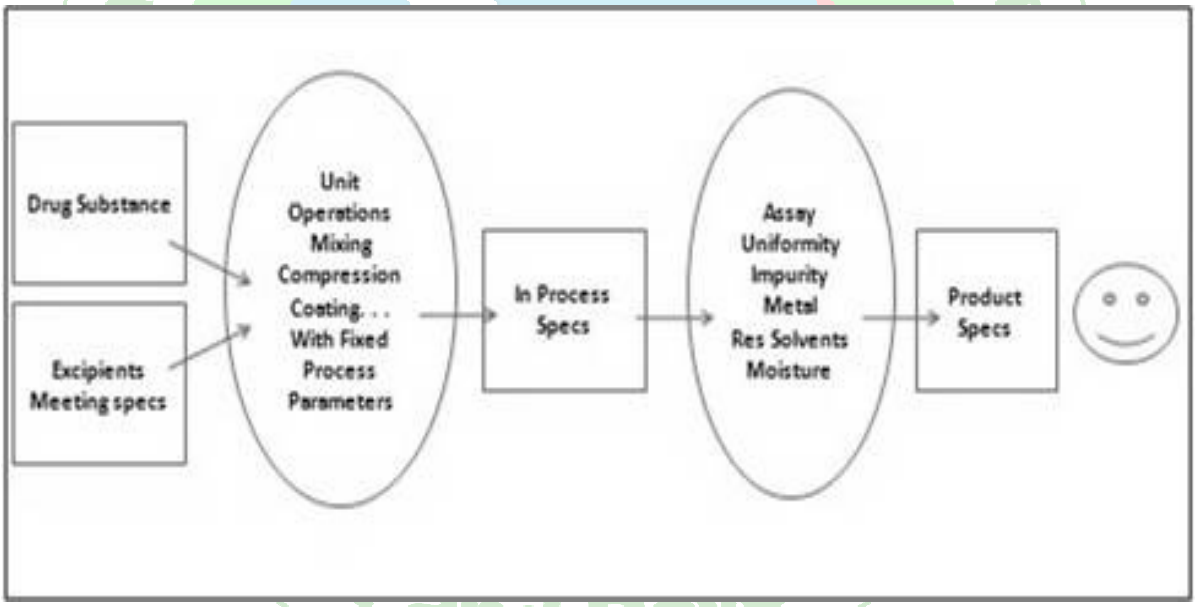

Figure1: Simplified quality control diagram using QbT

It shows a simplified quality control diagram under the current quality by testing (QbT) regulatory framework for generic drugs. In this system, product quality is ensured by raw material testing, drug substance manufacturing, a fixed drug product manufacturing process, in-process material testing, and end product testing.

Finished drug products are tested for quality by assessing that whether they meet the specifications or not. If not, they are discarded. Under the current paradigm, the specification is tight since it is used to assure consistency of manufacturing processes. The stringent specification has resulted in recalls in addition to drug shortages [5]. As a result, the FDA has been overwhelmed by the number of Chemistry, Manufacturing, and Controls (CMC) supplements filed in recent years [6]. Under the traditional regulatory evaluation system, all products are treated uniformly without regard to the risk to the consumer [7].

QbD REDfEFINED

In addition to this new concept being considered by FDA in its cGMP initiative, two important regulation documents were published as part of International Conference on Harmonization (ICH) guidelines: Q8 *[Pharmaceutical Development]* and Q9 [*Quality Risk Management]*. The previous describes the expectations for the pharmaceutical development section of the Common Technical Document (CTD); the later presents approaches to producing quality pharmaceutical products using present scientific and risk based approaches. Q10 Pharmaceutical Quality System also describes model for an effective quality management system for pharmaceutical industry [1].

The following equation indicates where quality comes from:

PharmaceuticalQuality=

f(Drug substance, excipient, manufacturing, packaging)

Quality by design (QbD) encompasses designing and developing formulation and manufacturing process which ensure predefined product specification. In 2002 the FDA announced a new initiative (cGMP for the 21st century: A risk based Approach). This initiative intended to modernized the FDAs regulation pharmaceutical quality, and establish new regulatory framework focused on QbD, risk management, quality system [2,6].

PHARMACEUTICAL QUALITY BY DESIGN

QbD requires identification of all critical formulation attributes and process parameters as well as determining the extent to which any variation can impact the quality of the finished product. QbD has four key components:

- Defining the product design goal
- Discovering the Process Design space
- Understanding the control space
- Targeting the operating space

Proper implementation of QbD can potentially provide three main benefits for development:

- More efficient use of development time and costs
- Ability to meet FDA submission guidelines and expectations
- Reduced approval times and fewer queries from FDA.

Likewise, QbD can potentially provide significant benefit in manufacturing. Even after the drug has gained FDA approval, routine QC testing may detect an out of specification OOS result can be easy to find the root cause. The pharmaceutical industry has been a highly regulated industry in the past for many good reasons. While pharmaceuticals have greatly improved the mortality and morbidity rates, there is still some element of risk of patients. Juran is often credited with introducing the concepts behind Quality by Design (QbD) [8,9].

ICH Q8 [4] defines quality as "The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength, and purity." ICH Q6A [10] emphasizes the role of specifications stating that "Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities."

Thus, some of the QbD elements may include:

- Define target product quality profile
- Design and develop product and manufacturing processes
- Identify critical quality attributes, process parameters, and sources of variability
- Control manufacturing processes to produce consistent quality over time

However current dissolution acceptance limits are selected based on data from a small number of batches in the context of their ability to distinguish batches with limited regard to clinical relevance. Under the QbD, the dissolution tests should be developed to reflect in vivo performance as much as possible. For example, the acceptance criteria for BCS Class I and III IR tablets may be much wider than that from batch data because, for these BCS classes, dissolution is highly unlikely to be the rate limiting step in vivo [11-13]. Similarly, dissolution tests for BCS Class II and IV drugs may need to be carefully examined to better reflect in vivo dissolution [14]. The biological safety level is generally

determined by safety and/or clinical studies although it may be also determined by toxicity studies [15]. Therefore, the acceptance criteria for impurities are usually those found in clinical study materials or reference listed drugs for generic drugs [15,16].

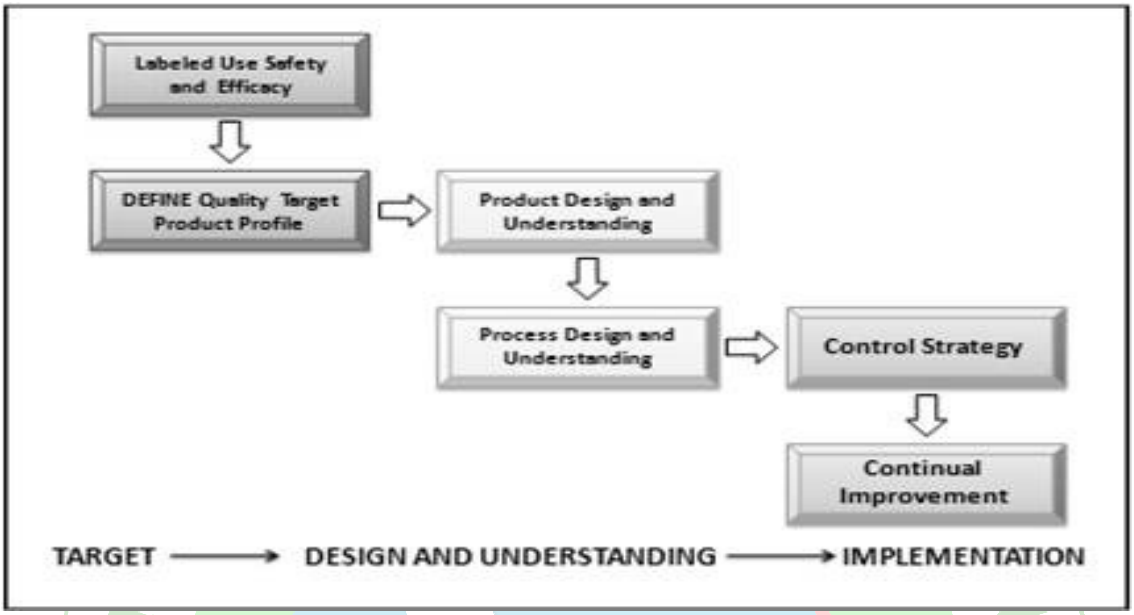

Figure 2: Overview of QbD

Why QbD? [17]

Pharmaceutical QbD is a systemic approach to development that begins with pre- defined objectives and emphasizes product and process understanding based on sound science and quality risk management (ICH Q8R2)
Quality by design helps for

- Higher level of assurance of product quality.
- Cost saving and efficiency for industry and regulators.
- Facilitate innovation
- Increase manufacturing efficiency.
- Reduce product rejects.
- Minimize and eliminate potential compliance action.
- Enhance opportunities for first cycle approval.
- Streamline post approval changes and regulatory processes.

PROBLEMS IN IMPLEMENTING QbD [1]

Logically, 10 key challenges are the most problematic for QbD adoption. These challenges are evaluated by their relevancy against different drug types as well as different levels of adoption.
The 1st to 4th challenges occur within companies and the 5th to 10th challenges are directly related to the FDA:

- ***Internal misalignment*** (i.e., Disconnect between cross functional areas, e.g., R&D and manufacturing or quality and regulatory).

- ***Lack of belief in business case*** (e.g., "There is a lot of uncertainty over timing of and investment requirements for QbD implementation.")
- ***Lack of technology to execute*** (e.g., Difficulty managing data, limited understanding of Critical Quality Attribute (CQA) implications).

- ***Alignment with third parties*** (i.e., How to implement QbD with reliance on suppliers and contract manufacturers?).
- ***Inconsistency of treatment of QbD across FDA*** (e.g., "Although a number of people in the FDA are supportive of QbD – this is not consistent").
- ***Lack of tangible guidance for industry*** (e.g., "We understand what you are asking for broadly, but there are hundreds of

variables-there's got to be an end in mind – a tangible one we can deliver on").

- ***Regulators not prepared to handle QbD applications*** (i.e., reviewers at different levels of understanding and acceptance).
- ***The way promised regulatory benefits are currently being shared does not inspire confidence*** (e.g., "At the end of the day it is still unclear whether the FDA will actually back these filings.").
- ***Misalignment of international regulatory bodies*** (i.e., Difficulty gaining acceptance of QbD applications in other countries).
- ***Current interaction with companies is not conducive to QbD*** (e.g. "we are treated with suspicion, it does not feel like collaboration").

COMPARISION OF CURRENT STATE TO THE FUTURE DESIRED STATE IN PHARMACEUTICAL INDUSTRY [8,9]

Table I: Comparison of the current state to the future desired QbD state

Aspect	*Current state*	*Desired QbD State*
Pharmaceutical development	Empirical; typically uni-variant experiments	Systematic; multivariate experiments
Manufacturing Process	Locked down; validation on three batches; focus on reproducibility	Adjustable within design space; continuous verification within design space; focus on control strategy
Process control	In- process testing for go/no-go; offline analysis	PAT utilized for feedback and feed forward in real time
Product Specification	Primary means of quality control; based on batch data	Part of overall quality control strategy; based on product performance
Control strategy	Mainly by intermediate and end product testing	Risk- based; controls shifted upstream; real- time release
Lifecycle management	Reactive to problems and OOS; post approval changes Needed.	Continual improvement enabled within design space

Process understanding is the major goal of QbD program. Thus there are some characteristics of a successful QbD program:

- Involves product design and process development
- Risk based, science based
- Primary focus is patient safety and product efficacy
- Business benefits are also drivers
- Results in improved process understanding
- Results in improved process capability / robustness
- Systematic development
- Holistic-applies to all aspects of development
- Multivariate-Interactions are modeled
- Provides PAR, design space, or suitable equivalent
- Requires a significant reduction in regulatory oversight post approval.

IMPORTANCE OF QbD [9]

- High level of assurance of product quality
- Cost saving and efficiency for industries and regulators
- Increase manufacturing efficiency, reduce cost and product rejects

- Minimize potential compliance actions, costly penalties and recalls
- Enhance opportunities for first cycle approval
- Streamline post approval manufacturing changes and regulatory processes
- Opportunities for continual improvement

QbD has four key components:

- Defining the product design goal
- Discovering the Process Design space
- Understanding the control space
- Targeting the operating space

Proper implementation of QbD can potentially provide three main benefits for development:

- More efficient use of development time and costs
- Ability to meet FDA submission guidelines and expectations
- Reduced approval times and fewer queries from FDA

The holistic as well as systematic approach of QbD was relatively new to the pharmaceutical industry at the beginning of twenty first century. A process is well understood when

- All the critical sources of variability are identified and explained
- Variability is managed by the process

QbD ACROSS THE PRODUCT LIFE SPAN [1]

Quality by design (QbD) encompasses designing and developing formulations and manufacturing processes which ensures predefined product specifications. QbD is a strategic, systemic approach to get the new product pipeline to market faster, easier, and for less.As per the Product Lifespan, following stages makes a crucial role call:

- Development
  Preclinical
  Nonclinical
  Clinical

- Scale-up Submissions for Market approval
  Manufacturing
  Design space
  Process Analytical Technology (PAT)
  "Real Time" Quality Control

- Control Strategies
  Risk-based decisions
  Continuous improvement
  Product performance

PROCESS UNDERSTANDING AND ELEMENT OF QbD [1,18]

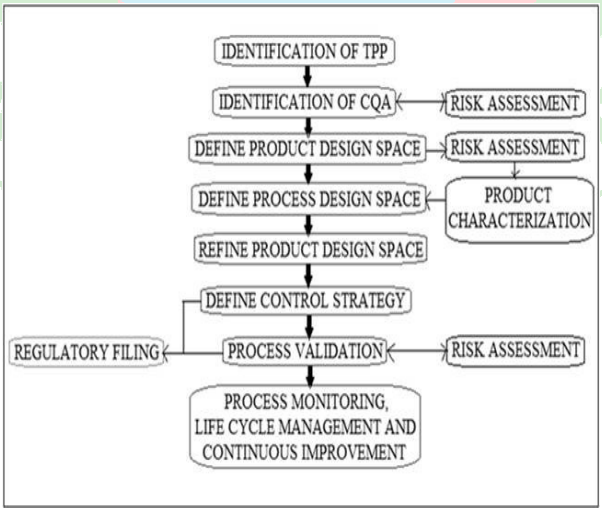

Figure 3: Key Steps In Implementation of QbD for a Pharmaceutical Product
TPP-Target Product Profile, CQA-Critical Quality Attributes

QbD TOOLS

TPP

TPP (Target Product Profile) provides a statement of the overall intent of the drug development program, and gives information about the drug at a particular time in development. Usually, the TPP is organized according to the key sections in the drug labelling and links drug development activities to specific concepts intended for inclusion in the drug labelling. The TPP is a patient and labelling centered concept, it can be thought of as the "user interface" of the drug product. Thus a generic version and its reference product would be expected to have the same TPP. A generic product may use a different formulation or design to implement the TPP. For further use in a quality by design process, it is a role of pharmaceutical scientist to translate the quantitative TPP into the Target Product Quality Profile (TPQP)

TPQP (ICH Q8R2)

TPQP (Target Product Quality Profile) TPQP is a quantitative substitute for aspects of clinical safety and efficacy that can be used to design and optimize a formulation and manufacturing process. The TPQP is not a specification because it includes tests such as bioequivalence or stability that are not carried out in batch to batch release. The TPQP should only include patient relevant product performance.

Identifying Target Product Quality Profile (TPQP)

The target product profile (TPP) has been defined as a "prospective and dynamic summary of the quality characteristics of a drug product that ideally will be achieved to ensure that the desired quality, and thus the safety and efficacy, of a drug product is realized" [19]. This includes dosage form and route of administration, dosage form strength(s), therapeutic moiety release or delivery and pharmacokinetic characteristics (e.g., dissolution and aerodynamic performance) appropriate to the drug product dosage form being developed and drug product-quality criteria (e.g., sterility and purity) appropriate for the intended marketed product [20]. The TPQP guides formulation scientists to establish formulation strategies and keep formulation efforts focused and efficient. TPQP is related to identity, assay, dosage form, purity, stability in the label [21].

Identifying CQAs

Once TPP has been identified, the next step is to identify the relevant CQAs.

CQAs (Critical Quality Attributes-As per ISPE PQLI) have been defined as "a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality" [22]. Identification of CQAs is done through risk assessment as per the ICH guidance Q9 (Figure 3).

The outcome of the risk assessment would be a list of CQAs ranked in order of importance. Use of robust risk assessment methods for identification of CQAs is novel to the QbD paradigm.

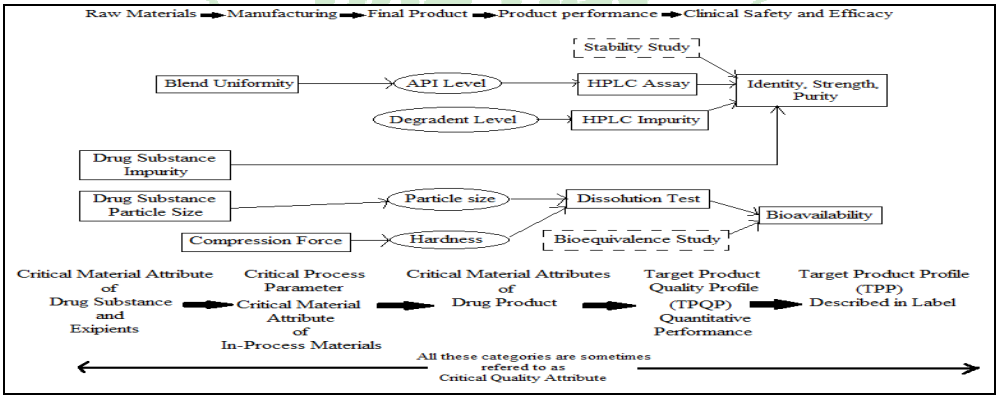

Figure 4: An illustration of how under QbD the identification of critical process parameters and critical material attributes is linked to the QTPP and finally to TPP that represents the clinical safety and efficacy [18]

Defining Product Design Requirements and Critical Quality Attributes [18]

In order to design quality into a product, the requirements for the product design and performance must be well understood in the early design phase. In pharmaceuticals, these product requirements can be found in a Target Product Quality Profile (TPQP). In addition to defining the requirements to design the product, the TPQP will help identify critical quality attributes such as potency, purity, bioavailability or pharmacokinetic profile, shelf-life, and sensory properties. In some cases, these attributes are directly measurable, for example, potency.

CPP

There is confusion about what is a process parameter. Previously, some have defined a critical process parameter (CPP) as any measurable input (input material attribute or operating parameter) or output (process state variable or output material attribute) of a process step that must be controlled to achieve the desired product quality and process consistency. For a given unit operation, there are four categories of parameters and attributes

- Input material attributes
- Output material attributes
- Input operating parameters
- Output process state conditions

A parameter is critical when a realistic change in that parameter can cause the product to fail to meet the TQPP. Thus, whether a parameter is critical or not depends on how large of a change one is willing to consider. Thus the first step in classifying parameters is to define the range of interest which we call the potential operating space (POS). The POS is the region between the maximum and minimum value of interest to the sponsor for each process parameter. The POS can also be considered as the extent of the sponsor's quality system with respect to these parameters. The POS defines the scope of the application and the sponsor's quality system so that going outside of the POS must need an amendment or supplement to the application. Thus sponsors benefit from defining a large feasible POS [22, 23].

Unclassified Process Parameter

We recognize that there are many material attributes and process parameters that are important and even essential to product quality, but it is of little value to define all parameters as critical. Thus we propose three categories for attributes or parameters: unclassified, critical, or non-critical. The criticality of an unclassified parameter is undetermined or unknown. These UPP may later be classified as critical or non-critical.

Uniqueness of CPP (Critical Process Parameters)

The set of CPP is not unique, but the chosen set must be sufficient to ensure product quality. Different sets of CPP can have several origins. One is that the definition of operating parameters depends on the engineering systems installed on a piece of process equipment.

Table II: Classification of process parameters [18]

Parameter type	*Definition*	*Sensitivity*
Non critical process parameters	Not critical	**1.** No failure in target product quality profile observed or predicted in the potential operating space (POS) and **2.** No interactions with other parameters in the proven acceptable range (PAR)
Unclassified Process parameters(UPP)	Critically unknown	**3.** Not established **4.** The default in the absence of pharmaceutical development
Critical process parameters(CPP)	Critical (control needed to ensure quality)	**5.** Failure in target product quality profile (TPQP) observed or predicted in the potential operating space (POS), or **6.** Interactions with other parameters in the proven acceptable range

7-Step QbD Startup Plan [1]

The best way to assess how to implement QbD in the organization without making the same mistakes that other companies have made is to utilize a simple 7-step process:

- Hire an independent QbD expert
- Audit the organization and processes with the expert conducting a gap analysis
- Hold a basic QbD workshop with all the personnel
- Review the expert's report and recommendations
- Draft an implementation plan, timelines, and estimated costs
- Assign the resources (or contract out)
- Retain the independent expert as the "Project Assurance" advisor.

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" [24]. The control strategy in the QbD paradigm is established via risk assessment that takes into account the criticality of the CQA and process capability. The control strategy can include the following elements: procedural controls, in process controls, lot release testing, process monitoring, characterization testing, comparability testing and stability testing.

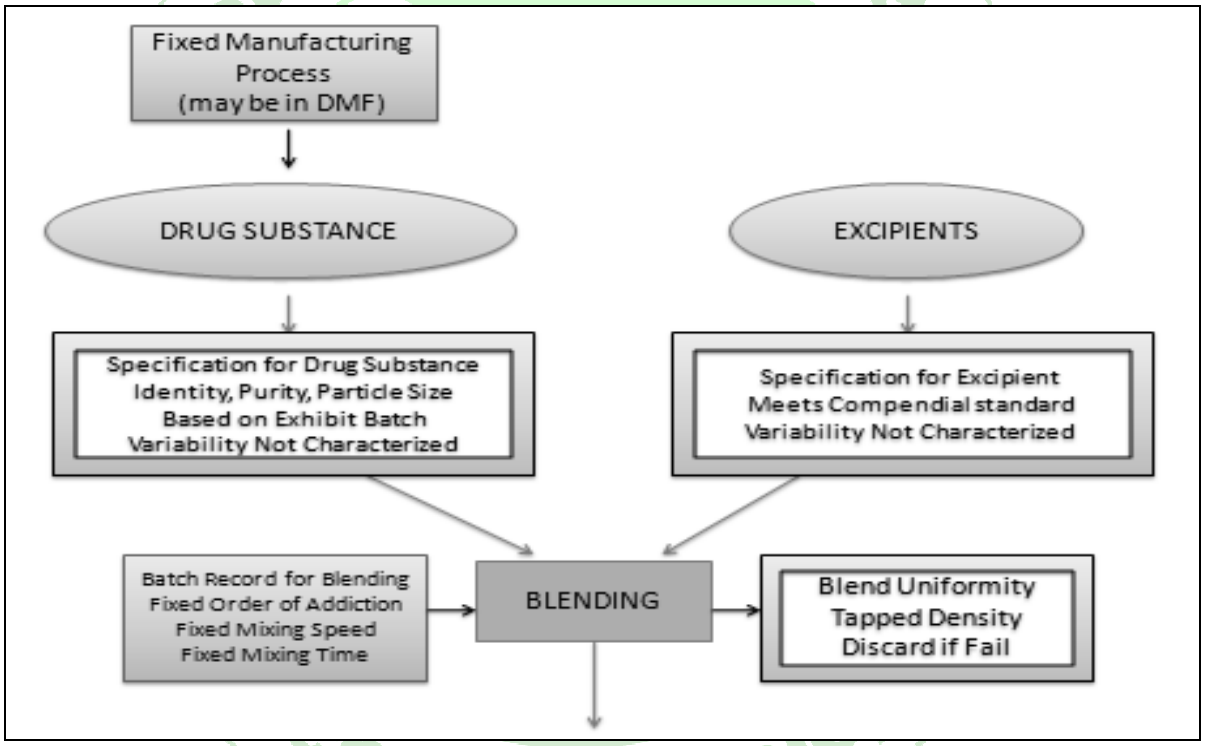

Figure 4: Example of Control Strategy For Pre-QbD Process

Implications of Process Parameter Classification

The classification of process parameters as critical or non-critical is essential to evolve the control strategy toward the QbD based goal. Full classification of all parameters as either non-critical or critical can lead to reduced end-product testing. It is the uncertainty about the UPP that leads to extensive testing. For non-critical parameters it may be possible to designate a normal operation range (NOR) up to (or beyond) the proven acceptable range (PAR) depending on trends and prior knowledge. The superposition of NOR for non-critical parameters would be considered as part of the design space [18].

Classification

Table III: Impact of Classification of Process Paramaters on Control Strategy

Parameter Type	*Potential Control Strategies*
Non-critical process parameter (non-CPP)	Uni-variant range in batch record Under control of sponsors quality system.
Unclassified process parameter (UPP)	Extensive release testing because of uncertainty. Fix at exhibit batch value or narrow range to ensure no interactions.
Critical process parameter (CPP)	Reduced release testing when all critical process parameters are identified monitored and controlled. Proven acceptable range if no evidence of multi-variant interactions Design space to allow multi-variant changes. Feed back control based on measurement of material attributes.

Design Space

In the presence of interacting critical process parameters a design space is one approach to ensure product quality although it is not a check-box requirement.

The current definition of design space is "The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality" [25,26]. This definition evolved from early ICH Q8 drafts where design space was defined as "the established range of process parameters that has been demonstrated to provide assurance of quality" [27].

Feedback Control & PAT

Application of PAT I [28] may be part of a control strategy. ICH Q8(R) [20] identifies one use of PAT as ensuring that the process remains within an established design space. A design space is usually a specified space of process parameters that has been demonstrated to provide acceptable quality. There may be sets of process parameters that lead to acceptable quality but were not explored in the establishment of the design space.

APPLICATIONS OF QUALITY BY DESIGN (QBD) IN PHARMACEUTICAL INDUSTRIES

- Product and Process Development, Understanding and Control
- Integrated multivariate approach to drug product and process development
- Formulation, processing design and risk assessment on liposomes containing hydrophilic API
- Screening of critical variables, and establishment of design space on liposomes containing hydrophilic API
- In formulation and processing of protein liposomes
- For wet granulation in Pharmaceutical Processing
- For formulation development of Dispersible tablets
- For Biotechnological Products [29-36]

SUMMARY:

Quality by design is an essential part of the modern approach to pharmaceutical quality. This paper clarifies the use of QbD for ANDAs including:

- Emphasis on the importance of the Target Product Quality Profile in articulating a quantitative performance target for QbD.
- Identification of critical material attributes that provide a mechanistic link of the product quality to the manufacturing process.
- Clarification that critical process parameters are operating parameters and should be combined with critical material attributes to describe the relation between unit operation inputs and outputs.
- A definition of non-critical, unclassified, and critical that provides a way to classify process parameters and in-process material attributes.

- The role of the control strategy as the mechanism for incremental implementation of QbD elements into practice.
- An efficient path to a design space through the identification of non-interacting process variables and their exclusion from formal experimental designs.

The overall view of all the steps involved in QbD is shown in figure 6.

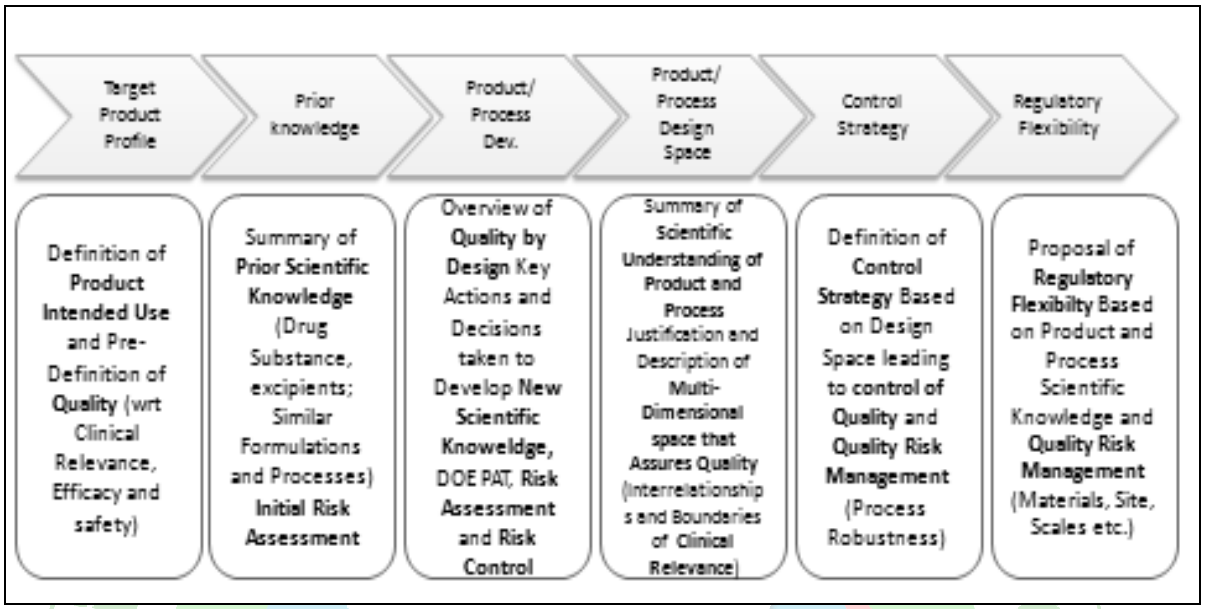

Figure 6: Overall view of the steps involved in QbD

CONCLUSION

Thus we conclude from this review that QbD (Quality by Design) is an important tool used in Pharmaceutical Industry. Thus Qbd is dependent upon two basic guidelines of quality that is ICH Q8 [Pharmaceutical Development] and ICH Q9 [Quality Risk Management]. Also quality by design is a very important aspect as well as a holistic approach where product specifications, manufacturing process and critical parameters are included in order to ease the final approval and ongoing quality control of new drug. It is also considered as critical parameter in each and every step from product development to its registration and marketing. Therefore quality is maintained throughout the development of the dosage form. Similarly another important aspect that is PAT (Process Analytical Technology) is there in pharmaceutical industry which is equally monitored. From all the above review it is proved as well as we can state that quality is very critical part of healthcare industry which is important in each and every aspect.

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