

QUALITY BY DESIGN- A NEW APPROACH TO DRUG DEVELOPMENT

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REVIEW ARTICLE

¹Dey Rumel*, ²Chowdhury DR.

¹Regulatory Affairs Department, SQUARE Pharmaceuticals Ltd., Dhaka Unit, Bangladesh.

²Product Management Department, Eskayef Bangladesh Limited, Dhaka, Bangladesh.

*Corresponding Author's E-mail: rumel206@gmail.com, donaroy07@yahoo.com

ABSTRACT

Quality by design is an essential part of the modern approach to pharmaceutical quality. A new approach to drug development could increase efficiencies, provide regulatory relief and flexibility, and offer important business benefits throughout the product's life cycle. QbD has become the answer to assist both industry and FDA to move towards a more scientific, risk based, holistic and proactive approach to pharmaceutical development.

Keywords: Food and Drug Administration (FDA), Quality by Design (QbD).

INTRODUCTION

Quality by Design (QbD) is a modern, scientific approach that formalizes product design, automates manual testing, and streamlines troubleshooting. It uses a systematic approach to ensure quality by developing a thorough understanding of the compatibility of a finished product to all of the components and processes involved in manufacturing that product. Instead of relying on finished product testing alone, QbD provides insights upstream throughout the development process. As a result, a quality issue can be efficiently analyzed and its root cause quickly identified.

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. The more information generated on the impact – or lack of impact – of a component or process on a product's quality, safety or efficacy, the more business flexibility Quality by Design provides. (1)

According to ICH Q8 (R2) -"Quality by Design" A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management. Quality by Design is everything you do to improve safety, efficacy

and quality of your product from proof of concept to the point at which customers are buying it on a regular basis. (2)

COMPONENTS OF QbD (3)

QbD has four key components:

Defining the Product Design Goal

In this step, you define the Quality Target Product Profile (QTPP) and identify all the critical quality attributes (CQA) for the product. The QTPP includes the factors that define the desired product and the CQAs include the product characteristics that have the most impact on the product quality. These provide the framework for the product design and understanding. The components are characterized and the compatibility of the components is evaluated.

Discovering the Process Design Space

Understanding your processes is the key to defining the design space. ICH Q8 defines design space as an "established multidimensional combination and interaction of material attributes and/or process parameters demonstrated to provide assurance of quality." Critical process parameters (CPPs) are identified by determining the extent to which any process variation can affect the quality of the product.

When you define your design space, you are able to anticipate issues and plan how to control the process. Actual experimental data, product experience, or literature guidance can be used to define the extremes of the parameter sets to be refined.

Understanding the Control Space

Based on the process design space, a well-executed control space can be defined. This enables you to understand your processes in a way that ensures product quality from known variability of the production process. This disciplined approach will keep your complex production processes under control.

To illustrate the concept of a control space study, think of a reference product data set with tightly clustered data points that represent the output of a tightly controlled process. Plotting the output of your process and comparing it to such a reference will give a clear indication of whether your process is in control. One technique to help avoid such a disparity is to conduct a Design of Experiments (DOE) study on your product in the development stage. Considerable wasted effort can be eliminated with such an approach as can any unexpected adverse outcome from the lack of control space understanding.

Targeting the Operating Space

The operating space is the best set of parameters, determined statistically, which enable you to accommodate any natural variability in CPPs and CQAs. For generic products, the operating space should be within the control space and should allow a reference product to be tested with the same set of parameters.

For new products, the operating space should be within the design space and compliant with regulatory guidelines. Innovators can gain a competitive advantage by thoroughly exploring the design space, including testing multiple batches of formulations to truly refine their product.

THE BENEFITS OF QbD

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 the FDA

Likewise, QbD can potentially provide significant benefit in manufacturing. Even after your drug has gained FDA approval, routine QC testing may detect an out of specification (OOS) result. For a company that did not use a QbD approach, an OOS result can mean a seemingly endless quest to find the root cause. Absent the data that QbD provides, test results may be suspect, questions difficult to answer, and long delays inevitable. Without knowing where to look, your team may resort to a trial-and-error approach to resolve any OOS occurrences.

One recent article presented several scenarios that could cause a 4- to 9-fold increase in testing to clear up an OOS investigation – a costly and time-consuming prospect. (3) The impact of poor quality that spirals out of control into an OOS event can be horrendous.

“For manufacturers, there are potentially huge external costs for delayed product launches or approvals, or severe actions such as consent decrees,” notes one editor of an industry journal, plus “the internal costs of wasted raw materials, scrap batches, and the cost of investigation and remediation.”(4)

Imagine the damage to your brand such an event would have. To add further insult, you may have to spend an enormous amount of money just to get your product back to market.

QbD minimizes these risks by mapping all the possible variables of the product attributes and processes into a known control space. This means that if any quality issues occur, your team can use specific methods to quickly pinpoint the scientific variables that are most likely causing the issues.

The business benefits can be significant, including:

- Fewer lost batches, typically costing \$250 - \$500K per batch

- Fewer manufacturing deviations, saving hundreds of costly hours and \$10 - \$15K per deviation
- Faster time to market and more reliable supply, when each day on the market could mean \$100K (or more)
- Fewer inspections of manufacturing sites
- A many-fold ROI via cost savings and increased revenue. (5)

THE CHALLENGES OF ADOPTING QbD

Despite the many financial and operational benefits of QbD, and even with the new FDA recommendations, not all companies have adopted this approach. As the saying goes “you either pay now, or pay later.” Implementing QbD beginning at the development phase requires a dedicated, disciplined, and sustained commitment by an organization. Understanding the effort necessary to implement QbD is a key component to successful adoption. Some of the most common barriers to adoption include:

- Insufficient understanding of the process and its benefits
- Organizational resistance to change
- Denial of the need (“Our process is under control”)
- Competing priorities
- Lack of resources and expertise in QbD. (5)

When you consider the tremendous potential financial gain, faster time to market, process improvements, and quality assurance generated by a successful implementation of QbD, these obstacles seem to pale in comparison.

Elements in QBD

- Quality Target Product Profile (QTPP)
- Critical Quality Attributes (CQA)
- Risk Assessment
- Design Space
- Control Strategy
- Lifecycle Management

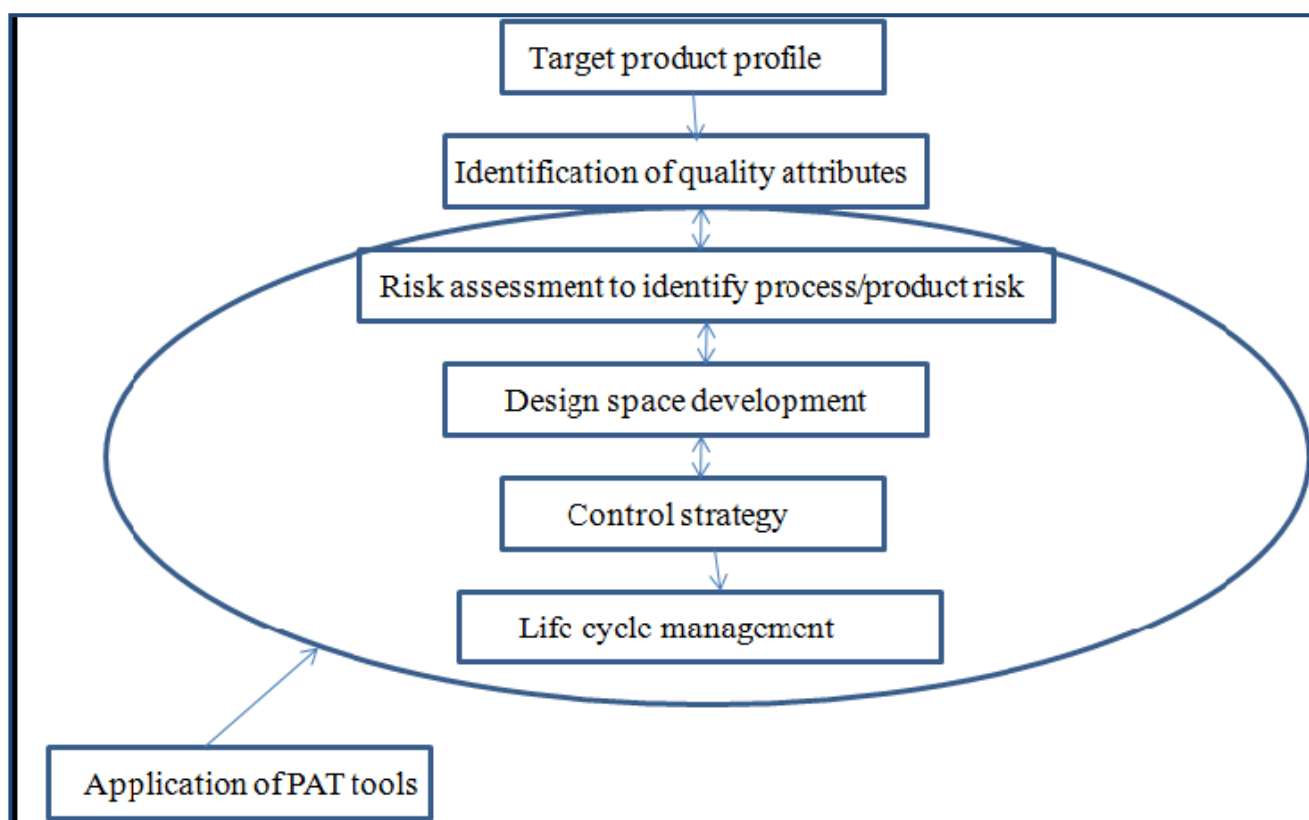


Figure1: Elements of QbD

a) Quality Target Product Profile (QTPP):

The quality target product profile (QTPP) as defined in ICH Q8(R1) (6,7) is a summary of the quality characteristics or attributes of a drug

product that ideally will be achieved and thereby ensure the safety and efficacy of a drug product. The QTPP forms the basis of design for the development of the product and is developed with the end in mind. It is both prospective, that

is, it describes the goals for the development team, and dynamic, that is, the QTPP may be updated or revised at various stages of development as new information is obtained during the development process. The FDA has published a guidance defining the Target Product Profile (TPP) (8), that focuses on the consumer (patient) and the desired product label. The QTPP is a subset of the TPP and is more oriented towards the chemistry, manufacturing and controls (CMC) aspects of development.

b) Critical Quality Attributes (CQA):

A critical quality attribute as defined by ICH Q8(R2) is 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. CQAs are generally associated with raw materials (drug substance, Excipients), intermediates (in-process materials), and drug product. Drug product CQAs derived from the QTPP are used to guide the product and process

development. Drug product CQAs are the properties that are important for product performance, that is, the desired quality, safety, and efficacy. Depending on the CR dosage form, these may include the aspects affecting the purity, potency, stability, drug release, microbiological quality, and so on. CQAs can also include those properties of a raw material that may affect drug product performance or manufacturability. An example of this would be drug substance particle size distribution (PSD) or bulk density that may influence the flow of a granulation and therefore the manufacturability of the drug product. Similarly, the dissolution from a controlled release dosage form is dependent on the particle size of the polymer and the hardness of tablet. In this example, PSD and hardness can be designated as CQA's. They are also commonly referred to as critical material attributes (CMA).

A Summary Quality Target Product Profile and Identification of Critical Quality Attributes for a Typical Oral Controlled Release Product are shown in below table.

Table 1: Summary Quality Target Product Profile and Identification of Critical Quality Attributes for a Typical Oral Controlled Release Product

Quality Attribute	Target	Criticality
Dosage form	Dosage form could be matrix tablet, maximum weight XX mg	
Potency	Dosage form label claim	
Dosing	One tablet per dose, once daily	
Pharmacokinetics	For example, controlled release over a period of 12 or 24 hr	Related to dissolution
Appearance	Dosage form description	Critical
Identity	Positive for drug name	Critical
Assay	95.0-105.0%	Critical
Impurities	List specified impurities with appropriate limit; unspecified impurities with limit; total impurities with limit	Critical
Water	Current limit (eg., NMT 1.0%)	Critical/Not critical depending on API sensitivity to moisture
Content Uniformity	Meets USP/EP/other pharmacopoeia	Critical
Hardness	NLT X SCU (preferred for film coating) for a tablet	For example, can be critical if related to dissolution
Friability	Current limit (eg., NMT 1.0%)	

Dissolution	Conforms to USP (eg., use a 5 point profile or NLT 10% in 0.1 N HCl for enteric coated tablets)	Typically critical
Microbiology	If testing required, meets harmonized ICH criteria	Critical only if drug product supports microbial growth

Quality Attributes Important to the Performance of the Drug Product

From a clinical perspective, safety and efficacy (product performance) is of prime importance. Thus, for an oral CR product, it is important to consider attributes that are potential surrogate(s) for performance. This may be drug dissolution /release, potency, polymer concentration, polymer viscosity, glass transition temperature (T_g) of composite, etc., or any other attribute that can either be substituted for drug release or clinical design space.

Quality Risk Assessment

A key objective of risk assessment in pharmaceutical development is to identify which material attributes and process parameters affect the drug product CQAs, that is, to understand and predict sources of variability in the manufacturing process so that an appropriate control strategy can be implemented to ensure that the CQAs are within the desired requirements.

The identification of critical process parameters (CPP) and critical material attributes is an iterative process and occurs throughout

development. During the initial phases of development, prior knowledge serves as the primary basis for the designation as there is not sufficient process/product understanding on the product under development. Therefore, the risks identified at the initial phases are perceived risks and as further process/product understanding is gained, the actual risks become clearer and a control strategy can be better defined. The risk assessment tools used in earlier phases of development therefore tend to be more qualitative and serve as a means to prioritize the experimentation. Typical tools used include risk ranking and filtering, input–process–output diagrams, Ishikawa diagram, and so on. Risk filtering and ranking is a tool for comparing and ranking risks. Risk ranking of complex systems typically requires evaluation of multiple diverse quantitative and qualitative factors for each risk. The tool involves breaking down a basic risk question into as many components as needed to capture factors involved in the risk. These factors are combined into a single relative risk score that can then be used for ranking risks. Below table is a typical example of risk filter that is used in early development to prioritize parameters/attributes with higher risk. This is typically qualitative in nature.

Table 2: Initial risk assessment DP QRA, showing the impact of critical parameters/attributes/process and its impact on the CQA

Critical parameters factors DP CQA	Polymer	Roll gap/ Roll force (ribbon Porosity)	Compression force	Amount of fine after RC	Lubricant distribution	Process speed	API PSD	Pre compression force
Appearance	Low	Low	High	Low	High	Low	Low	Low
Identity	Low	Low	Low	Low	Low	High	Low	Low
Assay	Low	Low	Low	Low	Low	Low	Low	Low
CU	Low	Low	Low	Low	Low	Low	Low	Low
Impurity	Low	Low	Low	Low	Low	Low	Low	Low
Dissolution	High	Low	Low	Low	Low	Low	Low	Low
Tablet	High	High	High	High	High	High	Low	High

Hardness								
Friability	High	High	High	High	Low	Low	Low	Low
Yield	Low	Low	Low	Low	Low	Low	Low	Low

Several other tools are also available that help to prioritize the attributes/variables. Some of these include Preliminary Hazard Analysis (PHA), Fault Tree Analysis (FTA), Hazard and Operability Analysis (HAZOP), Hazard Analysis and Critical Control Points (HACCP), Root cause Analysis (RCA), Decision Trees (DT), Probabilistic Risk Analysis (PRA), and so on.

Design Space

The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality ICH(Q8). Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval (ICH Q8(R2)). Product process that impart product

quality, safety/ efficacy are collectively known as Design Space. Changes within Design Space do require regulatory review or approval. After the process design space has been established and validated, the regulatory filing would include the acceptable ranges for all key and critical operating parameters that define the process design space in addition to a more restricted operating space typically described for drug products.

a) Process Parameter

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. In this view, every item in below Figure would be a process parameter.

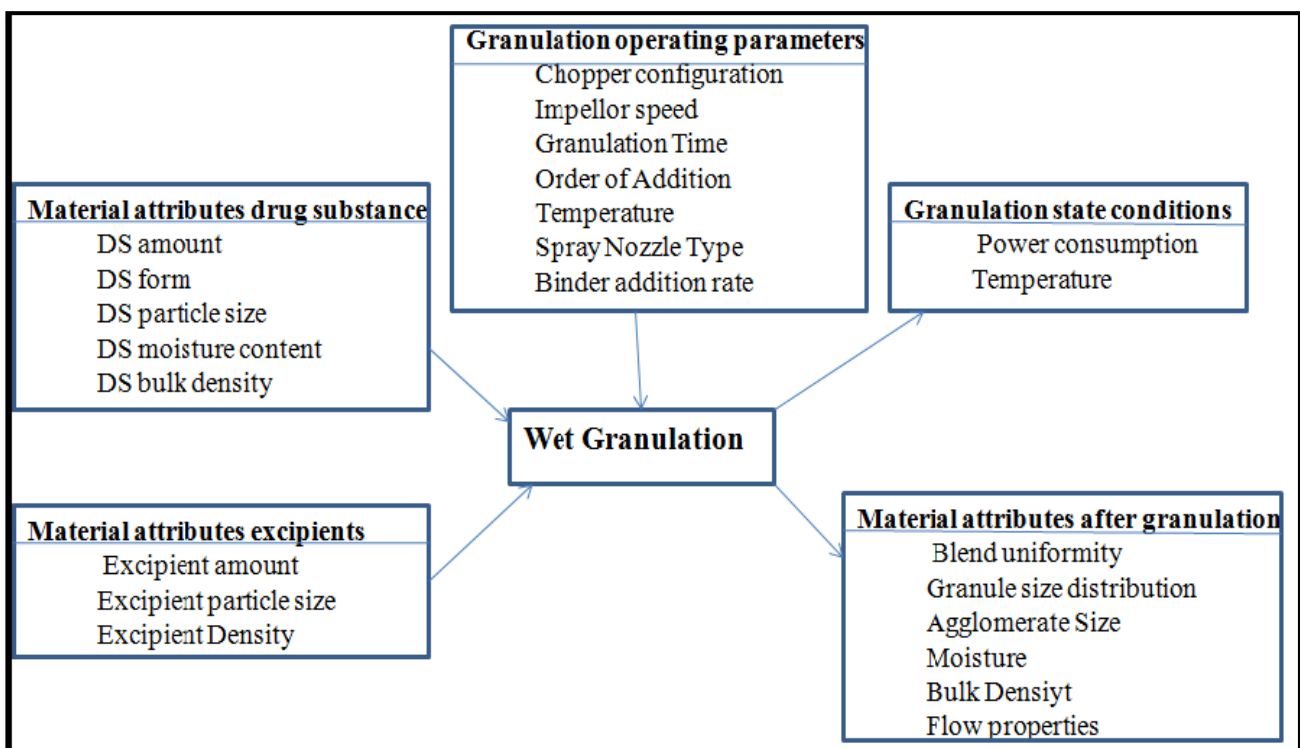


Figure 2: An example of identification of process parameters and material attributes prior to pharmaceutical development

We propose that process parameter be understood as referring to the input operating parameters (mixing speed, flow rate) and process state variables (temperature, pressure) of a process or unit operation. Under this definition, the state of a process depends on its CPPs and the CMAs of the input materials. Monitoring and controlling output material attributes can be a better control strategy than monitoring operating parameters especially for scale up. For example, a material attribute, such as moisture content, should have the same target value in the pilot and commercial processes. An operating parameter, such as air flow rate, would be expected to change as the process scale changes. 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

b) Critical Process Parameter

A parameter is critical when a realistic change in that parameter can cause the product to fail to meet the TPQP. Thus, whether a parameter is critical or not depends on how large of a change one is willing to consider. A simple example is that an impeller speed of zero will always fail. 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. This definition is at the discretion of the application that sponsor must balance the trade-offs in its definition.

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. The cost of a large POS is the need for the pharmaceutical development (in the form of prior knowledge, process models or experimental data) to cover the POS and the increased chance that a parameter will be found critical in the large POS. The only constraint on the narrowness of the POS is that the POS must encompass the variability of the process parameters around their target values. Our criteria for identifying critical and non-critical parameters are that a parameter is non-critical when there is no trend to failure within the POS and there is no evidence of interactions within the proven acceptable range (PAR)(see explanatory footnote on first page of article), which is the range of experimental observations that lead to acceptable quality. A sponsor has the option of conducting experimental observations over the entire POS; in this case the POS could be equivalent to the PAR. Below Table summarizes the proposed classification of process parameters.

Table 3: Summary of the proposed classification of process parameters

Parameter type	Definition	Sensitivity
Non-critical process parameter (non- CPP)	Not critical	<ul style="list-style-type: none"> • No failure in target product quality profile (TPQP) observed or predicted in the potential operating space (POS), and • No interaction with other parameters in the proven acceptable range (PAR)
Unclassified process Parameter (UPP)	Critically unknown	<ul style="list-style-type: none"> • Not established • The default in the absence of pharmaceutical development
Critical process parameter (CPP)	Critical (control needed to ensure quality)	<ul style="list-style-type: none"> • Failure in target product quality profile (TPQP) observed or predicted in the potential operation space (POS), or • Interactions with other parameters in the proven acceptable range (PAR)

CONTROL STRATEGY

A control strategy may include input material controls, process controls and monitoring, design spaces around individual or multiple unit operations, and/or final product specifications used to ensure consistent quality. A control strategy is what a generic sponsor uses to ensure consistent quality as they scale up their process from the exhibit batch presented in the ANDA to commercial production. Every process has a control strategy right now.

The finished drug products are tested for quality by assessing if they meet specifications. In addition, manufacturers are usually expected to conduct extensive in process tests, such as blend uniformity or tablet hardness. Manufacturer are also not permitted to make changes to the operating parameters (a large number of UPPs) specified in the batch record or other process changes without filing supplements with the FDA.

This combination of fixed (and thus inflexible) manufacturing steps and extensive testing is what ensures quality under the current system. A combination of limited characterization of variability (only three pilot lots for innovator products and one pilot lot for generic products), a failure of manufactures to classify process parameters as critical or noncritical, and cautiousness on the part of regulator leads to conservative specifications. Significant industry and FDA resources are being spent debating issues related to acceptable variability, need for additional testing controls, and establishment of specification acceptance criteria. The rigidity of the current system is required because manufacturers may not understand how drug substance, Excipients, and manufacturing process parameters affect the quality of their product or they do not share this information with FDA chemistry, manufacturing and controls (CMC) reviewers.

Lifecycle management

Quality system that aims at improving efficiency by optimizing a process and eliminating wasted efforts in production. These efforts are primarily directed towards reducing variability in process and product quality characteristics.”

QbD focuses on building quality into the product and manufacturing processes, as well as continuous process improvement – reduction of variability. The backbone for Continuous

Improvement is the Pharmaceutical Quality System (PQS). PQS should facilitate continual improvement and help to: “Identify and implement appropriate product quality improvements, process improvements, variability reduction, innovations and pharmaceutical quality system enhancements, thereby increasing the ability to fulfill quality needs consistently. Quality risk management can be useful for identifying and prioritizing areas for continual improvement. “Continuous improvement is not the same as corrective actions preventative actions (CAPA). CAPA occur when product quality characteristics are in question (e.g., out of specification). For continuous improvement efforts, products should already be in compliance with their specifications and process improvement steps should be within the original "design space”.

ADVANTAGES OF QbD

- Better in innovation due to the ability to improve process
- More efficient tech transfer to manufacturing
- Less batch failures
- Greater regulatory confidence of robust product
- Risk based approach and identification
- Innovative process validation approaches
- For the customer greater product consistency
- More product available and decreased failure or rejects
- Improved yields, lower cost, less innovation, reduced testing.
- Cost saving and efficient for industry.

REMARKS OF QbD

- Real time release testing and non-traditional testing
- Techniques provide valuable information for in-process control and improvement
- Regulatory flexibility is achievable by applying QbD approach, but requires High degree of process, product and analytical method understanding

- Robust quality systems
- Applicants are encouraged to discuss 'novel' QbD implementation approaches with the agency prior to submission
- Need to continue to ensure collaboration and coordination between inspectors, compliance and review
- Need training, training, training –both internal and external
- Need to determine how best to handle legacy products in line with those products issued under QbD Need a “Regulatory agreement” or Post market management plan.

CONCLUSION

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

1. Emphasis on the importance of the Target Product Quality Profile in articulating a quantitative performance target for QbD.
2. Identification of critical material attributes that provide a mechanistic link of the product quality to the manufacturing process.
3. 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.
4. A definition of non-critical, unclassified, and critical that provides a way to classify process parameters and in-process material attributes.
5. The role of the control strategy as the mechanism for incremental implementation of QbD elements into practice.
6. An efficient path to a design space through the identification of non-interacting process variables and their exclusion from formal experimental designs.

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CONFLICT OF INTEREST

Author declares that there are no conflicts of interest.

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