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# An Examination of the Pharmaceutical Quality by Design (QBD) Approach

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**Abstract - To guarantee the security of pharmaceuticals, the contemporary approach is Quality by Design. It explains how to guarantee pharmaceutical quality using Quality by Design. This study provides an overview of Quality by Design and identifies its key components. Each unit activity has its own set of quality features and process elements. There is discussion of the process, possibilities, and advantages of medical product quality by design. This is made feasible by the ICH Guidelines Q8, Q9, and Q10, which pertain to pharmaceutical quality systems, quality risk management, and pharmaceutical research, respectively. It goes on to explain how pharmaceutical companies apply Quality by Design in their research and development processes. Ensuring the consistent performance of high-quality items and manufacturing systems is the primary objective of pharmaceutical development. While quality cannot be forced into products, it must be considered throughout the design process. Quality by Design, the product description for the quality objective, and critical quality variables all play a role. Additionally, it compares the product's quality as measured by testing the final product to that which is based on Quality by Design. Quality by Design is based on the ICH Guidelines**.

**Keywords – ICH, Quality, Design, pharmaceutical, contemporary.**

## 1. INTRODUCTION

Instead than trying to force quality into a product, it should be incorporated into it. This is the core concept of QBD. "Design space" refers to the physical location of the product's production, which includes all of the necessary equipment, materials, personnel, and working conditions. Obtaining official approval requires a well-defined design space. Working inside the design area is seen as a positive development, whereas working outside of it is not. When manufacturing moves outside of the planning area, several elements are monitored to determine their impact on the final product's quality. Using QBD as a tool, all of these things are examined and conclusions are made. The government file contains all of these details.
Potentially novel approaches to pharmaceutical formulation might be derived from product development research. The product's QTPPs, with the end product's quality in mind, must be determined throughout development studies. To achieve the target product quality, more evaluations are required. There is space for design, specifications, and manufacturing regulations in the product's QTPP.first to third (4,5) Get it done. Efficiency requirements and consumer demands are both taken into account throughout production. The output quality criteria are always met since the procedure is designed to do so.

The raw ingredients and process variables are known to impact the final product's quality.
The primary factors that lead to process inconsistency are identified and managed.

In order to maintain consistent quality, the method is always being reviewed and adjusted.

Definition [ICH Q 8(R1)]
A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science andquality risk management. [6]

Definition [FDA PAT Guidelines, Sept. 2004]
Measurements of essential quality and performance characteristics of new and in-process materials and processes are taken throughout processing to plan, analyse, and manage production. The purpose is to ensure the safety of the final product. the five and six
Quality by Design, or QBD, is a methodology that aims to improve processes and products by gaining a better scientific understanding of critical qualities, building controls and tests around those limits during development, and then using what we learn throughout the product's lifetime to create an environment where we can continuously improve. QBD is a method for developing pharmaceuticals that involves designing and developing formulations and manufacturing processes in a way that maintains the specified product quality. For the purpose of establishing and using topic knowledge in an autonomous and integrated manner, mathematical models and guidelines are used.

Benefits of QBD [1,3,5,6]

- QBD is good Business
- Eliminate batch failures
- Minimize deviations and costly investigations
- Avoid regulatory compliance problems

- Organizational learning is an investment in thefuture
- QBD is good Science
- Better development decisions
- Empowerment of technical staff

Opportunities [7, 8]

- Efficient, agile, flexible system
- Increase manufacturing efficiency, reducecosts and project rejections and waste
- Build scientific knowledgebase for allproducts
- Better interact with industry on science issues
- Ensure consistent information
- Incorporate risk management

## 2. STEPS INVOLVED IN QUALITY BY DESIGN PRODUCTS [7-9]

- 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

**Seven steps of quality by design start up plan**

- Hire an independent Quality by design expert.
- Audit your organization and process with theexpert conducting a gape analysis.
- Hold a basic quality by design workshop withall your personal.
- Review the expert's report and recommendation.
- Draft an implementation plan, timelines and estimated costs.
- Assign the resources (or contract out).
- Retain the independent expert as your"Project Assurance" advisor.

**Quality by design (QBD) and well understoodproduct and processes [4,7,8]**

All critical sources of variability are identified and explained.
Variability is controlled by the process.
Product quality attributes can be accurately and reliably predicted over the design space established for materials used, process parameters, environmental and other conditions.
To gain enhanced knowledge of product performance over a range of material attributes, manufacturing process options and process parameters considering
Appropriate use of quality risk management principles.

**QBD BY PHARMACEUTICALS [8-10]**

Even though the pharmaceutical industry has focus on quality, it has failed to keep up with otherindustries in terms of manufacturing efficiency andproductivity.
Current scenario in the Pharmaceutical Industry:
Cost of revalidation
Off-line analysis for in-process - need based
Product specifications as primary means ofcontrol
Unpredictable Scale□up issues
Inability to understand failures
Systematic approach to development:
That begins with predefined objectives
Emphasizes products and processunderstanding
Process control (Figure 1)


Figure 1: Process control

**QUALITY TARGET PRODUCT PROFILE [10, 11]**

A summary of the drug development program described in terms of labeling concepts and it mainly focus on the safety and efficacy.

- Description
- Clinical Pharmacology
- Indications and Usage
- Contraindications
- Warnings
- Precautions
- Adverse Reactions
- Drug Abuse and Dependence
- Over dosage
- Dosage and Administration
- How Supplied
- Animal Pharmacology and/or Animal Toxicology
- Clinical Studies

A natural extension of Target Product Profile for product quality – Quality characteristics (attributes) that the drug product should possess inorder to reproducibly deliver the therapeuticbenefit promised in the label guide to establish formulation strategy and keep the formulation effort focused and efficient. It facilitates identification of what's needed/critical for the patient/consumer in the Quality Target ProductProfile (such as Critical Quality Attributes, CQAs)
Identifies risks and best approaches to manage.
Uses tools/enablers in an optimized fashion (such as integration of QBD and bio pharmaceutics)
Generates and enables knowledge sharing.
An iterative, learning, life-cycle process for optimizing decision-making and thetherapeutic outcomes for the patient benefit.
A drug product designed, developed and manufactured according to Quality Target Product Profile with specification (such as dissolution/release acceptance criteria) consistentwith the desired in vivo performance of the product.

## 3. CRITICAL QUALITY ATTRIBUTES [12-14]

It is necessary to identify the quality attributes that are critical, i.e. those defining purity, potency and surrogate for BioavailabilityCriticality etc. It is based on the impact of quality attribute/ parameter on the safety, efficacy & quality (manufacturability) of theproduct.

Establish a link between CPP & CQAs: Identification of attribute or parameters that can be used as a surrogate for clinical safety & efficacy (important to patient) (Figure 2).
Manufacturability is also an attribute (important to business) that is critical toquality.
The level of criticality may differ for an API manufacturing process relative to a drug product manufacturing process
API is one component of a drug product and one step further away from the patientcontinuum of Criticality. Several levels ofcriticality may be used to describe multiple levels of risk.
As attribute or parameter boundaries approach edges of failure, the level of critically increased with the risk.

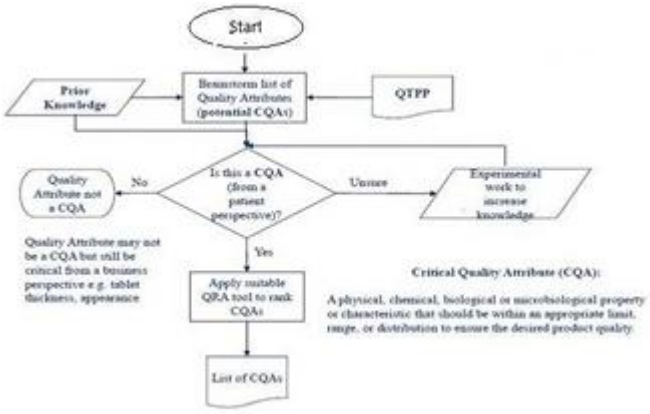


Figure 2: Decision Tree to Decide CQAs

**Certain Key Aspects of QBD [15-17]**

The Target Product Quality Profile (TPQP) Target Product Quality Profile (TPQP) is a tool forsetting the strategic foundation for drug development — "planning with the end in mind."More recently an expanded use of the TPP in development planning, clinical and commercial decision making, regulatory agency interactions,and risk management has started to evolve.

Drug Substance and Excipient Properties

To consistently achieve the drug-product quality specified in the label, the drug substance needs to be thoroughly characterized with respect to its physical, chemical, biological, and mechanical properties such as solubility, polymorphism, stability, particle size, and flow properties.

Formulation Design and Development

Not all prototype formulations can be evaluated in human subjects, which mean that developing sensitive in vitro dissolution methods is crucial to an effective development program.

**Manufacturing Process Design and Development**

Process development and formulation design cannot be separated because a formulation cannot become a product without a prescribed process. Process design is the initial stage of process development, in which an outline of the commercial manufacturing processes is documented, including the intended scales of manufacturing. The outline should include all the factors that need to be considered for the design of the process, including facility, equipment, material transfer, and manufacturing variables. Other factors to consider during process development are the QTPP and CQAs

Product quality by end product testing vs QBD [17,18]

Comparison is shown between product qualitiesby end product testing vs. quality by design (Figure 3, 4).

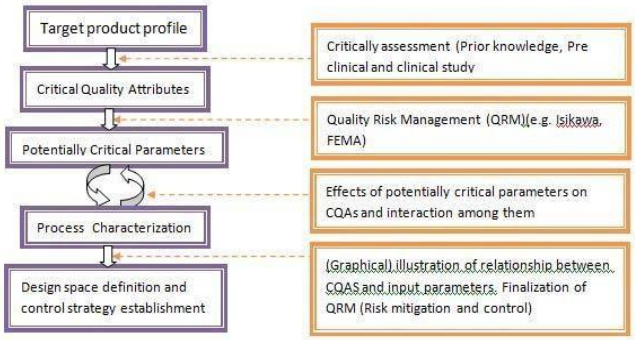


Figure 3: Flow-chart for Product Quality by End Product Testing

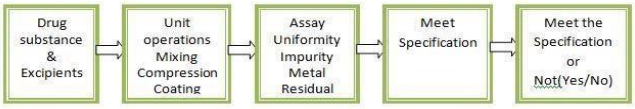


Figure4: Simplified flow-chart of QBD process

Successful adoption[17,18]

- Regulatory flexibility to accommodate quality by design submissions
- Common dossier accepted worldwide by regulatory agencies
- Post-approval changes within pre-defined design space can be implemented withregulatory flexibility
- Laws and processes in place to protect intellectual property (IP)

Designed to consistently meet desired productquality [17-19]

- Design space concept
- Experimentally defined process operating space basedon scientific principles.
- Critical process parameters identified.
- Critical - impact product quality.
- Space - operating range yielding acceptableproduct Space.
- Critical process parameters are consistently controlled.
- Product of process is always desired quality
- Product.
- End product testing might be reduced.

**Designed to facilitate continuous improvement [17,18]**

Process control strategy: control of the process.
Performance and continuous process improvement.
Real-time process feedback Process improvements within design space Knowledge builds with experience Leverage information/new technologies to improve process efficiency Key opportunity to continuously improve the process. E.g. increased supply, more efficiency

**ICH Q8, Q9, Q10 GUIDELINES: THE FOUNDATION OF QBD [2,3,6,18]**

ICH Guidelines Q8 for Pharmaceutical Development, Q9 for Quality Risk Management, Q10 for Quality systems are foundation of QBD(Figure: 5)

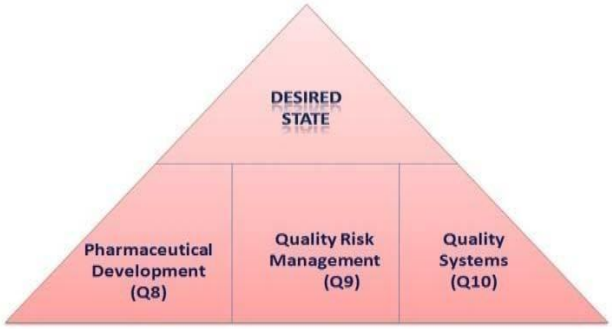


Figure 5: The Foundation of QBD

Quality by Design relative to ICH [20,21]

- Concepts aligned
- Design Space - Key to understanding
- Process robustness
- Design of Experiments (DOE)
- Quality management Quality management

**Critical Concept: Design Space [19-21]**

Multidimensional combination with interactions Multidimensional interactions put variables (e.g.raw material attributes) and process parameters

Demonstrated to provide assurance of quality

Defined by applicant and reviewed byregulator

Defined regulator

Once design space is approved, regulatory post approval change requirements will besimplified

approval Inside vs. outside design space Inside space

Regulatory flexibility to operate within the design space Regulatory space.

## 4. APPLICATIONS OF QUALITY BY DESIGN (QBD)[7,8,10,22-29]

Quality by design (QBD) – a comprehensive systematic approach to pharmaceutical development and manufacturing Advancement in the pharmaceutical development and manufacturing by QBD can be explained against traditional approach

In Pharmaceutical Development

To design a quality product and a manufacturing process to consistently deliver the intended performance of the product

In life cycle management

Continual improvement enabled within design space

**QBD IN CMC REVIEW OFFICES**

Office of New Drug Quality Assessment (ONDQA)

- Science-based assessment
- Restructured organization and reorganizedstaff –
- premarket staff and post market
- CMC Pilot
- A number of applications submitted
- Lessons learned
- Evaluation of information
- Implementation of PMP

**Office of Generic Drugs (OGD)**

QbR contains the important scientific andregulatory review questions

- Evaluate whether a product is of high quality
- Determine the level of risk associated with the manufacture and design of this product.
- 416 applications received using QbR by June2007
- Successful in ensuring that questions address issues regarding QBD

**BENEFITS OF IMPLEMENTING QBD FOR FDA**

Enhances scientific foundation for review

Provides for better coordination acrossreview, compliance and inspection

Improves information in regulatory submissions

Provides for better consistency

Improves quality of review (establishing aQMS for CMC)

Provides for more flexibility in decision making

Ensures decisions made on science and noton empirical information

Involves various disciplines in decision making

Uses resources to address higher risks

Benefits to Industry

- Ensures better design of products with less problems in manufacturing
- Reduces number of manufacturing supplements required for post market changes –rely on process and risk understanding and risk mitigation
- Allows for implementation of new technology to improve manufacturing without regulatory scrutiny
- Allows for possible reduction in overall costs of manufacturing –less waste
- Ensures less hassle during review –reduced deficiencies –quicker approvals
- Improves interaction with FDA –deal on a science level instead of on a process level
- Allows for continuous improvements in products and manufacturing process.

Pharmaceutical Development

Widely used in pharmaceutical development and manufacturing (Figure: 6).

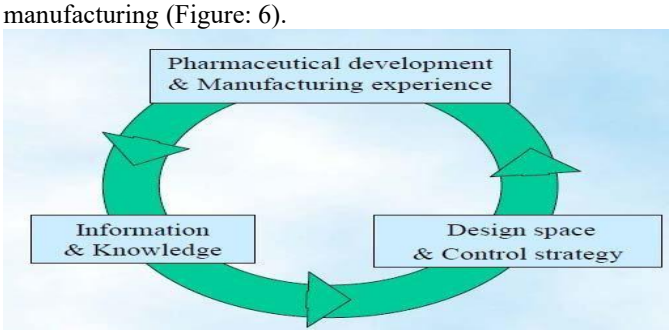


Figure 6: Pharmaceutical developments

Used in PAT

A system for designing, analyzing and controlling manufacturing through timely measurement of critical quality performance attributes of raw and in process materials and processes with the goalof ensuring final product quality (Figure : 7).

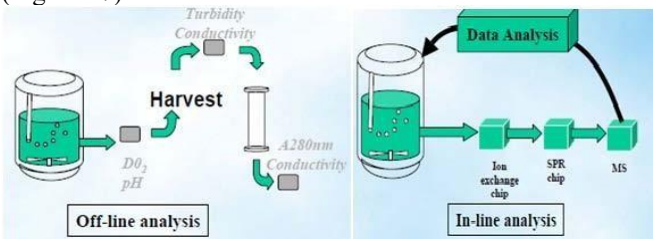


Figure 7: Off-line & On-line Analysis Design Space

Multidimensional combination of and interaction of input variables and process parameters that have been

demonstrated to provide Quality Assurance
Linkage between process inputs (inputs variables and process parameters) and critical quality attributes
Proposed by Applicant
Subject to regulatory assessment and approval
Implementation before or after MA
Established for one or more unit operation(s) or up to complete process
Working within the design space: not considered as a change.
Quality by design approach in coating process
Quality cannot be tested into product but it should be built in product. Parameters that affect the coating process are given below (Figure: 8).

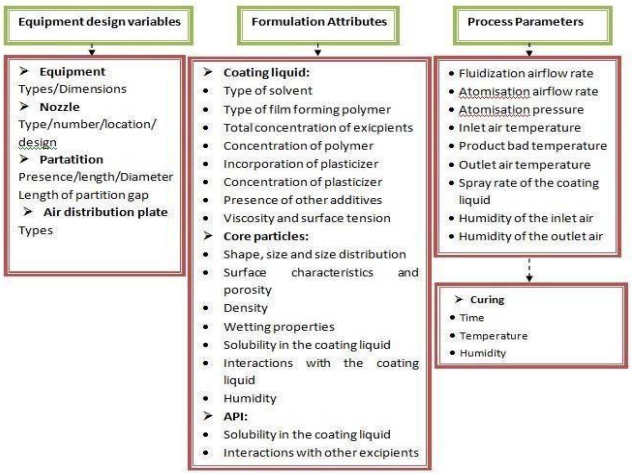

Figure 8: Parameters of the coating process

Quality target product profile for the ANDA product
The Quality Target Product Profile (QTPP) is "a prospective summary of the quality characteristicsof a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy ofthe drug product."
Before developing the product, the quality characteristics of the product are identified. Based on the desired characteristics the design space is utilized to evaluate variable of qualitytarget product profile from which the critical quality attributes as derived. The data obtained from evaluation will serve as a source for risk assessment. The finding of risk assessment is examined and optimized process is developed to produce the products of desired quality.

## 5. CONCLUSION

The goal of a well-characterized method development effort is to develop a reliable method that can be demonstrated with a high degree of assurance to consistently produce data meeting predefined criteria when operated within defined boundaries. QBD can be applied to the development and evaluation of analytical methods. During method development, all potential factors (the inputs) and all critical analytical responses (the outputs) are studied to determine the relationships. Critical analyticalfactors are identified in an approach that parallels what is described for process development in ICH Q8 and Q9. A corporate knowledge repository is required throughout the process to ensure critical information is captured that can be reviewed andadded to in the future such that lessons learned can be applied to the specific method under consideration and also to other similar methods being applied to other products. Such a repository(in line with concepts described in the draft ICH Q10) will enable continuous improvement and change control of the method to take place throughout its lifecycle. Rather than continuing to perform analytical technology transfer exercises and ICH validation, a QBD approach based on a risk-assessed change control procedure should beadopted. Each time a method is changed, a risk assessment should be performed. Where the change is identified as having a potential to take the method outside its known design space, amethod evaluation and, if appropriate, an equivalency exercise should be performed to ensure method performance criteria are still met.

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