

A Review on quality by design approach (QBD) for Pharmaceuticals

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Abstract:

Quality by Design is the modern approach for quality of pharmaceuticals. It describes use of Quality by Design to ensure quality of Pharmaceuticals. In this review, the Quality by Design is described and some of its elements identified. Process parameters and quality attributes are identified for each unit operation. Benefits, opportunities and steps involved in Quality by Design of Pharmaceutical products are described. It is based on the ICH Guidelines Q8 for pharmaceutical development, Q9 for quality risk management, Q10 for pharmaceutical quality systems. It also gives application of Quality by Design in pharmaceutical development and manufacturing of pharmaceuticals. The aim of the pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product. Quality cannot be tested into products but quality should be built in by design. It includes the Quality target product profile, critical quality attributes and key aspects of Quality by Design. It also gives comparison between product quality by end product testing and product quality by Quality by Design. The foundation of Quality by Design is ICH Guidelines.

Keywords: Quality by Design (QbD), Process Analytical Technology (PAT), Quality target product profile, Critical quality attributes

INTRODUCTION

The basic concept of QbD is "The Quality cannot be tested into the product, but it should be built into it." The design space is defined as a manufacturing area of the product including Equipment, Material, and Operators and Manufacturing Conditions. The design space should be well defined prior to regulatory approval. Working with design space is not considered as a change, but working out of design space is considered as a change. Different variables are monitored for their effect of product quality when the manufacturing is done out of design space. All these variables are assessed and conclusions will be drawn which serves as a tool to QbD. All these data are included in the regulatory submission dossier

The pharmaceutical product formulation can be developed based on the data obtained from product development studies. The process

variables that are emerged during development stages will serve as a source for QRM. Before conducting the development studies the QTPPs of the product must be determined and having the final product quality in mind and evaluation is performed to obtain the desired quality of product. The QTPP of product includes design space, specifications and manufacturing controls.^[1-3]

Design [4, 5]

- Product is designed to meet patient needs and performance requirements.
- Process is designed to consistently meet product quality attributes.
- Impact of starting raw materials and process parameters on product quality is understood.
- Critical sources of process variability are identified and controlled.
- The process is continually monitored and updated to allow for consistent quality over time.

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 and quality risk management. [6]

Definition [FDA PAT Guidelines, Sept. 2004]

A system for designing, analyzing and controlling manufacturing through timely measurements (i.e. during processing) of critical quality and performance attributes of new and in-process materials and processes, with the goal of ensuring final product safety. [5, 6]

The concept of "Quality by Design" (QbD) was defined as an approach which covers a better scientific understanding of critical process and product qualities, designing controls and tests based on the scientific limits of understanding during the development phase and using the knowledge obtained during the life-cycle of the product to work on a constant improvement environment. QbD describes a pharmaceutical development approach referring to formulation design and development and manufacturing processes to maintain the prescribed product quality. Guidelines and mathematical models are used to ensure the establishment and use of the knowledge on the subject in an independent and integrated way. **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 the future
- QbD is good Science
- Better development decisions
- Empowerment of technical staff

Opportunities [7, 8]

- Efficient, agile, flexible system
- Increase manufacturing efficiency, reduce costs and project rejections and waste
- Build scientific knowledge base for all products
- Better interact with industry on science issues
- Ensure consistent information
- Incorporate risk management

STEPS INVOLVED IN QUALITY BY DESIGN PRODUCTS

[7-9]

1. Development of new molecular entity

- Preclinical study
- Nonclinical study
- Clinical Study
- Scale up
- Submission for market Approval

2. Manufacturing

- Design Space
- Process Analytical Technology
- Real time Quality Control

3. Control Strategy

- Risk based decision
- Continuous Improvement
- Product performance

Seven steps of quality by design start up plan

1. Hire an independent Quality by design expert.
2. Audit your organization and process with the expert conducting a gap analysis.
3. Hold a basic quality by design workshop with all your personal.
4. Review the expert's report and recommendation.
5. Draft an implementation plan, timelines and estimated costs.
6. Assign the resources (or contract out).
7. Retain the independent expert as your "Project Assurance" advisor.

Quality by design (QbD) and well understood product 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 other industries in terms of manufacturing efficiency and productivity.

Current scenario in the Pharmaceutical Industry:

- Cost of revalidation
- Off-line analysis for in-process - need based
- Product specifications as primary means of control
- Unpredictable Scale-up issues
- Inability to understand failures

Systematic approach to development:

- That begins with predefined objectives
- Emphasizes products and process understanding
- 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 in order to reproducibly deliver the therapeutic benefit 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 Product Profile (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 pharmaceuticals)
- Generates and enables knowledge sharing.
- An iterative, learning, life-cycle process for optimizing decision-making and the therapeutic 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) consistent with the desired in vivo performance of the product.

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 Bioavailability Criticality etc. It is based on the impact of quality attribute/ parameter on the safety, efficacy & quality (manufacturability) of the product.
 - 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 to quality.
 - 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 patient continuum of Criticality. Several levels of criticality 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.

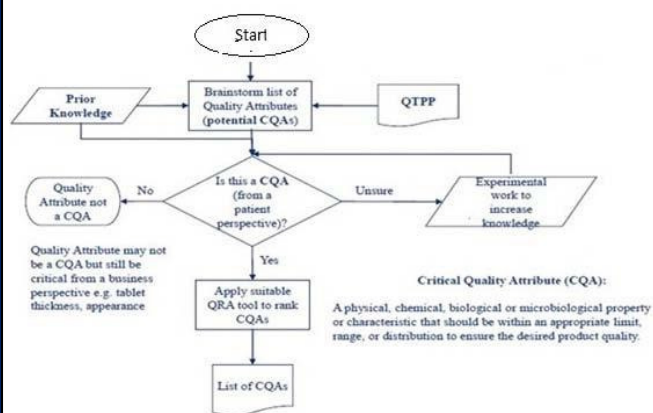


Figure 2: Decision Tree to Decide CQAs

Certain Key Aspects of QBD [15-17]

- **The Target Product Quality Profile (TPQP)**

Target Product Quality Profile (TPQP) is a tool for setting 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 qualities by end product testing vs. quality by design (Figure 3, 4).



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

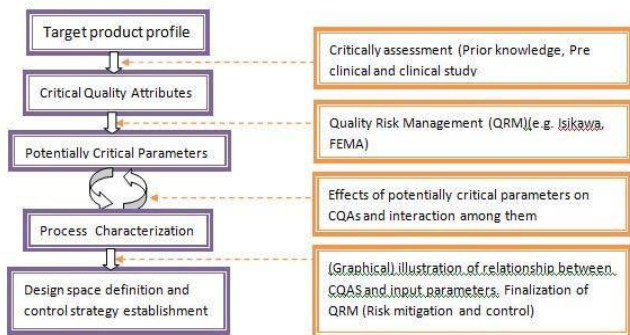


Figure 4: Simplified flow-chart of QBD process

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 with regulatory flexibility
- ✓ Laws and processes in place to protect intellectual property (IP)

Designed to consistently meet desired product quality^[17-19]

- ✓ Design space concept
- ✓ Experimentally defined process operating space based on scientific principles.
- ✓ Critical process parameters identified.
- ✓ Critical - impact product quality.
- ✓ Space - operating range yielding acceptable product 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 by regulator
- Defined regulator
- Once design space is approved, regulatory post approval change requirements will be simplified
- approval Inside vs. outside design space
Inside space
- Regulatory flexibility to operate within the design space Regulatory space.

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 reorganized staff –
- 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 and regulatory 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 June 2007
- Successful in ensuring that questions address issues
- regarding QbD

BENEFITS OF IMPLEMENTING QbD FOR FDA

- Enhances scientific foundation for review
- Provides for better coordination across review,
- compliance and inspection
- Improves information in regulatory submissions
- Provides for better consistency
- Improves quality of review (establishing a QMS for CMC)
- Provides for more flexibility in decision making
- Ensures decisions made on science and not on 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

- o Improves interaction with FDA –deal on a science level instead of on a process level
- o Allows for continuous improvements in products and manufacturing process.

Pharmaceutical Development

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

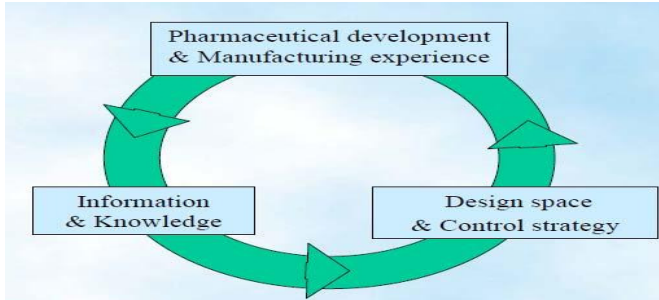


Figure 6: Pharmaceutical developments

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 goal of ensuring final product quality (Figure : 7).

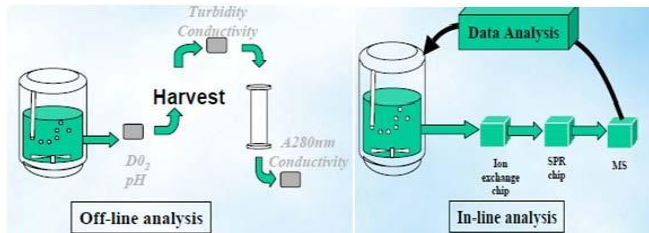


Figure 7: Off-line & On-line Analysis Design Space

- o Multidimensional combination of and interaction of input variables and process parameters that have been demonstrated to provide Quality Assurance
- o Linkage between process inputs (inputs variables and process parameters) and critical quality attributes
- o Proposed by Applicant
- o Subject to regulatory assessment and approval
- o Implementation before or after MA

- o Established for one or more unit operation(s) or up to complete process
- o Working within the design space: not considered as a change.

Quality by design approach in coating process

- o Quality cannot be tested into product but it should be built in product. Parameters that affect the coating process are given below (Figure: 8).

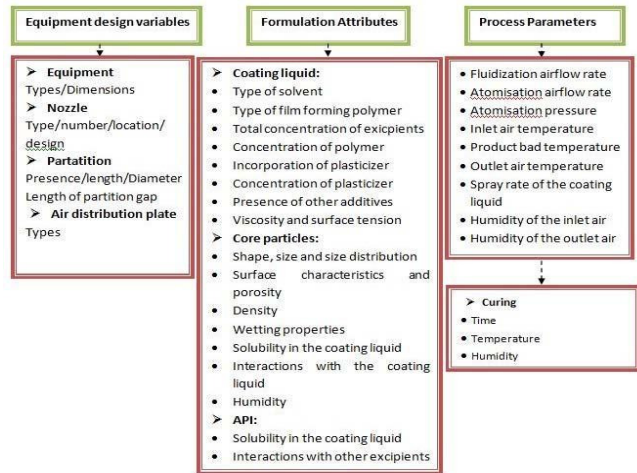


Figure 8: Parameters of the coating process

Quality target product profile for the ANDA product

The Quality Target Product Profile (QTPP) is “a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the 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 quality target 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.

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 analytical factors 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 and added 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 be adopted. 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, a method evaluation and, if appropriate, an equivalency exercise should be performed to ensure method performance criteria are still met.

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