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QUALITY BY DESIGN: THE MODERN APPROCH TO ENSURE PHARMACEUTICAL QUALITY

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Abstract

The modern approach to ensuring pharmaceutical quality is Quality by Design (QbD). This method employs QbD principles to maintain the quality of pharmaceuticals. The review outlines the concept of QbD, identifying its key components. It establishes process parameters and quality attributes for each production stage. The benefits, opportunities , and steps in applying QbD to pharmaceuticals are explained. The approach is based on ICH Guidelines such as Q8 for pharmaceutical development, Q9 for quality risk management, and Q10 for pharmaceutical quality systems. The review illustrates the implementation of QbD in pharmaceutical development and manufacturing, encompassing the Quality Target Product Profile, critical quality attributes, and fundamental QbD aspects. The foundation of QbD is firmly rooted in ICH Guidelines.

Introduction

Quality by design (QbD) was first described by Joseph M. Juran1 , and applied heavily, particularly in the automotive industry. The fundamental premise behind QbD is that quality can be “designed in” to processes through systematic implementation of an optimization strategy to establish a thorough understanding of the response of the system quality to given variables, and the use of control strategies to continuously ensure quality. The FDA has recently begun to advocate the QbD methodology for the pharmaceutical sector.2

In order to describe quality by design, we must first define what we mean by quality. In a 2004 paper, Janet Woodcock (Director for the Centre for Drug Evaluation and Research) defined pharmaceutical quality as a ‘product that is free of contamination and reproducibly delivers the therapeutic benefit promised in the label to the consumer’.3

Pharmaceutical industry is constantly searching the ways to ensure and enhance product safety, quality and efficacy. However, drug recalls, manufacturing failure cost, scale up issues and regulatory burden in recent past produce huge challenge for industry. In traditional, the product quality and performance are predominantly ensured by end product testing, with limited understanding of the process and critical process parameters. Regulatory bodies are therefore focusing on implementing quality by design (QbD), a science based approach that improves process understanding by reducing process variation and the enabling process-control strategies:

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 analysed 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 [1-3]

All the major objectives with regard to quality issues are being addressed by the ICH guidelines. The three ICH guidelines which throw light upon quality-by design and related aspects include Q8 Pharmaceutical development, Q9 Pharmaceutical risk management and Q10 Pharmaceutical Quality systems. In fact, the ICH guideline Q8 is sub-divided into two parts: part one deals with pharmaceutical development and Part II is the annex to the guideline which states the principles for Quality-

by-Design. According to ICH Q8(R2) guideline, Quality by Design (QbD) is "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"[4-6].

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 [7]. In Order to initiate a successful QbD program, the first step is to identify those process parameters that are essential to product quality and develop well –validated analytical methodologies to monitor those parameters. The objective of this review article is therefore to provide a comprehensive understanding on various aspects of QbD, along with addressing the concerns related to its implementation.

Key characteristics of QbD [8-9].

1. A tool for focused & efficient drug development Dynamic and systematic process
2. Relies on the concept that Quality can be built in as a continuum
3. It is applicable to Drug Product and Drug Substance development (chemicals / biologics)
4. It is applicable to analytical methods Can implemented partially or totally.
5. Can be used at any time in the life cycle of the Drug.
6. Always encouraged by Regulators.

Basic considerations of QbD

As far as pharmaceutical industry is considered safety of patient and providing a quality product have been given prime importance; and to achieve this target QbD assist it by thorough understanding of process which is the ultimate goal of QbD.

Advantages of QbD can be summarize as

Patient safety and product efficacy are focused.

Scientific understanding of pharmaceutical process and methods is done.

It involves product design and process development.

Science based risk assessment is carried.

Critical quality attributes are identified and their effect on final quality of product is analysed.

It offers robust method or process Business benefits are also driving force to adopt QbD .Method design concept helps to avoid cost involved with post approval changes (Vince et al. (2011a)).

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
- 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 gape 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" advisory

Qbd development process includes

- QbD development process include :(4,5)
- Begin with a target product profile that describes the use, safety and efficacy of the product .
- Define a target product quality profile that will be use by formulators and process engineers as a quantitative surrogate for aspects of clinical safety and efficacy during product investigations.
- Gather relevant prior knowledge about the drug substance, potential excipients and process operations into a knowledge space. Use risk assessment to prioritize knowledge gaps for further investigation .
- Design a formulation and identify the critical material (quality) attributes of the final product that must be controlled to meet the target profile.
- Design a manufacturing process to produce a final product having these critical material attributes
- Identify the critical process parameters and input (raw) material attributes that must be controlled to achieve these critical material attributes of the final product. Use risk assessment to prioritize process parameters and material attributes for experimental verification. Combine prior knowledge with experiments to establish a design space or other representation of process understanding.
- Establish a for the entire process that may include input material controls, process controls and monitors, design spaces around individual or multiple unit operations, and/or final product tests.
- The control strategy should encompass expected changes in scale and can be guided by a risk assessment. Continually monitor and update the process to assure consistent quality.
- Design of experiments (DOE), risk assessment, and

process analytical technology (PAT) are tools that may be used in the QbD process when appropriate. They are not check-box requirements.

- ICH Guidelines Q8 for Pharmaceutical Development, Q9 for Quality Risk Management, Q10 for Quality systems are foundation of QbD .

Elements of pharmaceutical industry

QbD comprises all elements of pharmaceutical development mentioned in the ICH guideline Q8. Pharmaceutical Development section is projected to provide a complete understanding of the product and manufacturing process for reviewers and inspectors. To design a quality product and its manufacturing process to consistently deliver the intended performance of product is the aim of pharmaceutical development.

The information and knowledge gained from pharmaceutical development studies and manufacturing experience provide scientific understanding to support the establishment of the specifications, and manufacturing controls (Patricia, 2007).

1. Different elements of pharmaceutical development include
2. Defining an objective
3. Quality target product profile (QTPP)
4. Determination of critical quality attributes (CQA)
5. Risk assessment
6. Development of experimental design
7. Designing and implementing control Strategy
8. Continues improvement

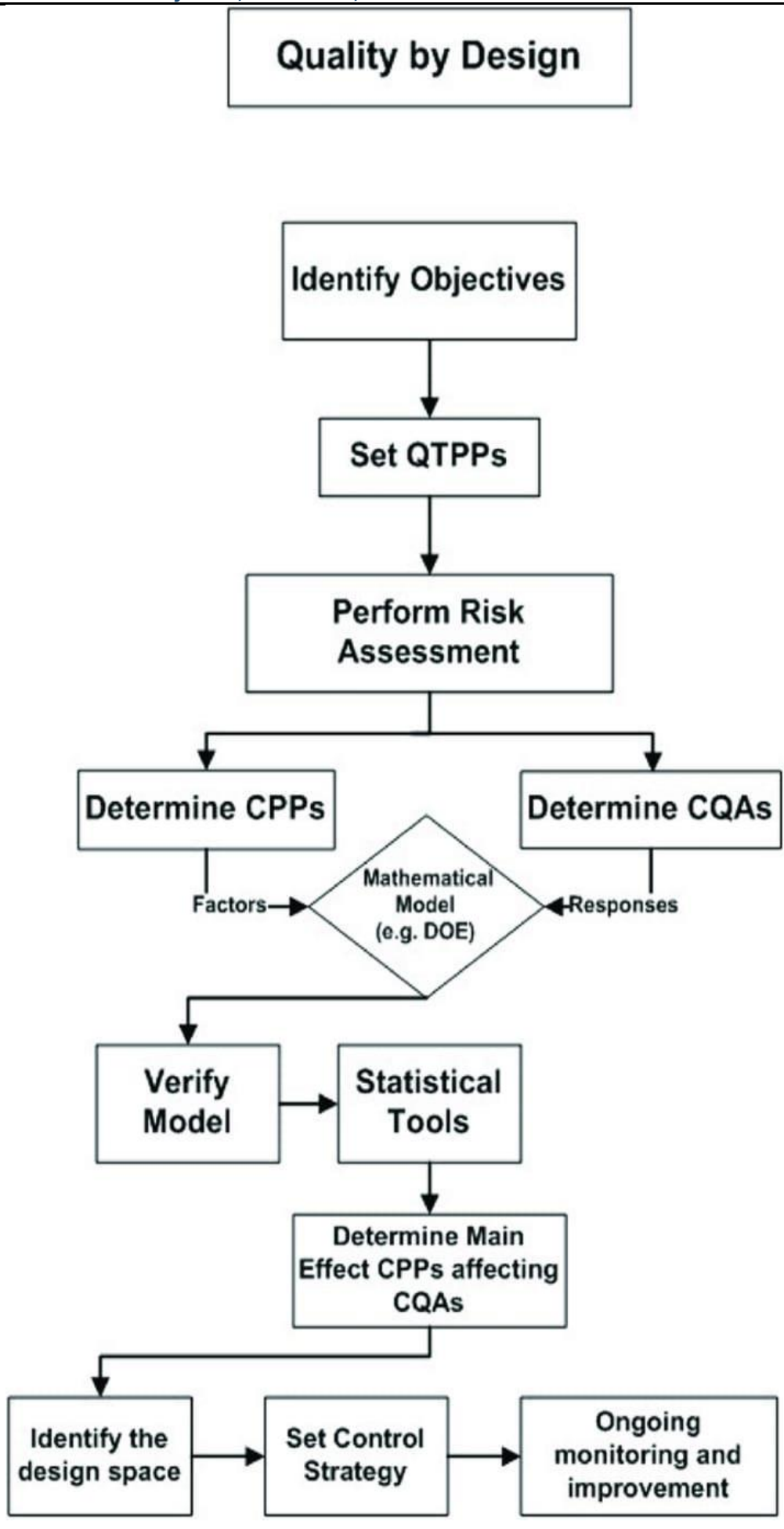


Fig : quality by design

Quality target product profile (QTPP)

A summary of the drug development described in terms of labelling concepts and it Mainly focus on the safety and efficacy.

- ✓ Description
- ✓ Clinical Pharmacology

Indications and Usage

- ✓ Contraindication
- ✓ warning

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 QbD and bio pharmaceutics)
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]

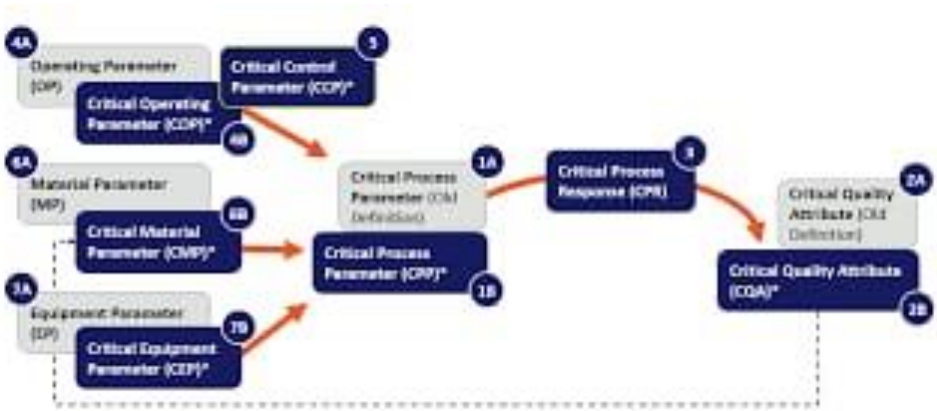
Once QTPP has been identified, the next step is to identify the relevant CQAs. A CQA is defined as "A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product
quality".
CQAs are generally associated with raw materials (drug substance, excipients), intermediates (in-process materials), and drug product.
Drug product CQAs are the properties that are important for product performance, that is, the desired quality, safety, and efficacy
(Fig.2).
This indicates that CQAs are subsets of QTPP that has a potential to be altered by the change in formulation or process variables [14-15].
For example, QTPP may include additional quality attributes of the drug product such as strength and dosage form, which are not the part of CQA as it will not change during drug development process. However, QTTP attributes such as assay, content uniformity,
dissolution, and permeation flux will also be a part of CQA as they may be altered by formulation or process variables.
For example, the CQAs of drug substance are Identification of CQAs is done through risk assessment as per the ICH guidance Q9. Prior product knowledge, such as the accumulated
laboratory, nonclinical and clinical experience with a specific product-quality attribute, is the key in making these risk assessments.
Such knowledge may also include relevant data from similar molecules and data from literature references.

Taken together, this information provides a rationale for relating the CQA to product safety and efficacy [16].
The information provide Product a rationale for relating The CQA To product safety and efficacy.
The use of robust risk assessment methods for identification of CQAs is novel to the QbDparadigm CQAs of solid oral dosage forms are typically those
aspects affecting product purity, strength, drug release and stability.

CQAs for other delivery systems can additionally include more product specific aspects, such as aerodynamic properties for inhaled products, sterility for parenteral , and adhesion properties for transdermal patches
. For drug substances, raw materials and intermediates, the CQA can Additionally include those properties
(eg: particle size distribution, bulk density) that affect the drug product CQAs.

Critical process parameters

Parameters monitor before or in process that influence the appearance, impurity, and yield of final product significantly. During the QbD process, product design and understanding include the identification of CMAs, which are different from CQAS. CQAS are for output materials while CMAS are for input materials including drug substance, excipients, in-process materials. The CQA of an intermediate may become a CMA of the same intermediate for a downstream manufacturing step. While process design and understanding include the identification of CPPs and a thorough understanding of scale-up principles, linking CMAs and CPPs to CQAS is of special importance. From the viewpoint of QbD, CMAS and CPPs can vary within the established Design Space without significant influence on CQAS, and as a result, the quality of the final product will meet the QTPP



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.

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.

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]

Figure 5 – ICH Q8/Q9/Q10 triangle in QbD paradigm.

ICH Guidelines Q8 for Pharmaceutical Development, Q9 for Quality Risk Management, Q10 for Quality systems are 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

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.

Risk assessments

Risk assessments are carried out through proper use of suitable RA tools.

Risk assessment tools

Basic risk management facilitation methods Flow charts, check sheets, process mapping, cause and effect diagrams, etc., are the most commonly used simple methods for RA and management.[18]

-Process mapping is a technique which relates critical process parameters and/or critical material attributes and critical product quality to a response surface derived from uexperimental data.[19]. For example, development of product specifications to ensure bioequivalence within the limits of acceptable dissolution specifications.

-Cause-effect diagram (also called Ishikawa diagram or fishbone diagram) represents all aspects having influence on a critical product quality.

The diagram will be having a horizontal line, the end of which points toward the affected product quality. The major influencing factors are then represented as diagonal lines.

The influence of the critical process parameters and critical material attributes is then represented as sublines for the diagonal lines.[18,20]

Failure mode effects analysis

This tool can be used to identify any inadequacies in the development of the product.

The method systematically identifies, prioritizes, and estimates the risk and prevents failure. The risk involved in changing a process can also be limited using failure mode effects analysis (FMEA).

Product and process understanding is a must for FMEA. The risk reduction can be used to manage potential failures, once failure modes are established.[18,21]

Failure mode, effects, and criticality analysis

Here, FMEA is evaluated in terms of its degree of severity of the consequences, their respective chances of occurrence, and their detectability.

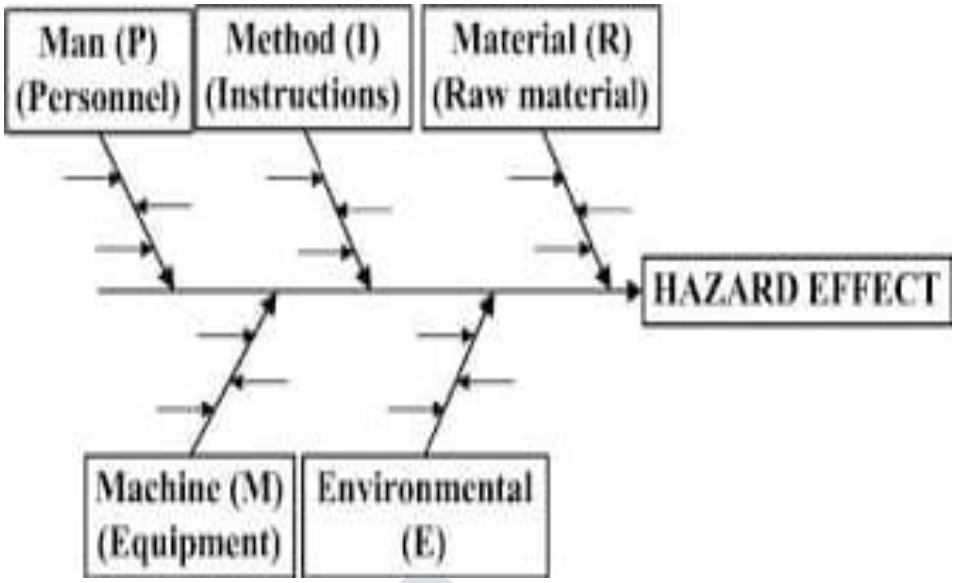
Thus, criticality analysis is used here to chart the probability of failure modes against the severity of their consequences. Failure mode, effects, and criticality analysis is most used for failures and risks associated with manufacturing processes.[18]

Fault tree analysis Fault tree analysis

(FTA) is a structured, graphical, quantitative assessment tool which makes modelling of complex systems easy. FTA is an excellent tool for evaluating multiple factors affecting product quality. It is useful for both RA and monitoring. In this, method is taken as the root of a logic tree.

Only one top event (root) will be there. Each critical process parameters or critical material attributes is added to the tree as a series of logic expressions. Software can be used to calculate failure probabilities from fault trees. FTA mainly is dependent upon the understanding of the experts about the process to identify the causative factor.[18]

Hazard analysis and critical control points



-Hazard analysis and critical control points (HACCP) is a systematic, preventive approach for assuring product quality, reliability, and safety as a means of prevention rather than finished product inspection.

HACCP can be used to identify and manage risks associated with physical, chemical, and biological hazards (including microbiological contamination)

. It is based on technical and scientific principles and is a structured approach against the risk due to the design, development, and production.

HACCP is based on the following seven principles or steps:

1. Conducting a hazard analysis.

2. Identifying critical control points.

3. Establishing critical limits for each critical control point

4. Establishing critical control point monitoring requirements

5. Establishing corrective actions.

6. Establishing record keeping procedures

7. Establishing procedures for ensuring the HACCP system is working effectively.

Design space

ICH Q8(R2) defines design space as " the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. 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."

Design space may be constructed for a single unit operation, multiple unit operations, or for the entire process. Though according to FDA guideline, defining design space is optional since the product and process understanding can be established without a formal design space, nevertheless, such approach can assist to better understanding and attain overall control of a system.

The Design Space is linked to criticality through the results of risk assessment, which determines the associated CQAs and CPPs.

It describes the multivariate functional relationships between CQAs and the CPPs that impact them, and should include their linkage to or across unit operations.

Such relationships are arrived at by iterative application of risk assessment and experimental design, modelling, as well as the use of literature and prior experience. Methods for determining design space included: one-variable-at-a-time experiments, statistically designed experiments, and Modelling approaches. Methods for presenting design space included graphs (surface-response curves and contour plots), linear combination of parameter ranges, equations, and models. Alternatively, the design space can be explained mathematically through equations describing relationships between parameters for successful operation [19-21].

Control Strategy

ICH Q10 defines a control strategy as "a planned set of controls derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in process controls, finished product specifications and the associated methods and frequency of monitoring and control." A control strategy normally include input material controls, process controls and monitoring, design space around individual or multiple unit operations, and/or final product specifications used to ensure consistent quality [22, 23]. 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.

A QbD based control strategy for blending process is shown in Fig. 4. Pharmaceutical quality is assured by understanding and controlling formulation and manufacturing variables to assure the quality of the finished product. The end product testing only confirms the quality of the product.

Challenges

Though Quality by design is an essential part of the modern approach to pharmaceutical quality, but Lack of understanding regarding the pharmaceutical process is the cause and also the major limitation for QbD implementation. Pharmaceutical companies are traditionally tuned to care more about the end product, with little emphasis on the science-based understanding of the process involved. The majority of pharmaceutical companies feel that there is a need for a more easy guidance on how to actually implement QbD. Companies wanted clarification from FDA on QbD terminologies, acceptable methods, criteria to select and deselect critical quality attributes, standards by which to judge adequacy of controls, and criteria for analytical method substitution [23, 24].

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 first four challenges occur within companies:

- Internal misalignment (Disconnect between cross functional areas, e.g., R&D and manufacturing or quality and regulatory)
- Lack of belief in business case i.e. 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 increasing reliance on suppliers and contract manufacturers?)

The next six challenges are directly related to the regulatory authority:

- Inconsistency of treatment of QbD across regulatory authority

- Lack of tangible guidance for industry
- Regulators not prepared to handle QbD applications
- The way promised regulatory benefits are currently being shared does not inspire confidence
- Misalignment of international regulatory bodies
- Current interaction with companies is not conducive to QbD-It is accepted that the challenges and concerns associated

Conclusion

A goal of a well characterised 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 it's known design space , a method evaluate and if appropriate, an equivalency exercise should be performed to ensure method performance criteria e criteria are still met.

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