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Regulatory Requirement for the Quality Improvement Plan for a Stabilized Product Development

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A B S T R A C T
The application of quality by design (QbD) in pharmaceutical product development is now a thrust area for the regulatory authorities and the pharmaceutical industry. International Conference on Harmonization and United States Food and Drug Administration (USFDA) emphasized the principles and applications of QbD in pharmaceutical development in their guidance for the industry. QbD attributes are addressed in question-based review, developed by USFDA for chemistry, manufacturing, and controls section of abbreviated new drug applications. QbD principles, when implemented, lead to a successful product development, subsequent prompt regulatory approval, reduce exhaustive validation burden, and significantly reduce post-approval changes. The key elements of QbD viz., target product quality profile, critical quality attributes, risk assessments, design space, control strategy, product lifecycle management, and continual improvement are discussed to understand the performance of dosage forms within design space. Design of experiments, risk assessment tools, and process analytical technology are also discussed for their role in QbD. This review underlines the importance of QbD in inculcating science-based approach in pharmaceutical product development.
Keywords: USFDA,risk assessments, QbD

A R T I C L E I N F O

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C O N T E N T S

1. Introduction

All the goods and services that are around us are the result of a development process. Product development is a conversion process where market requirements are converted into some concrete product ideas that we experience (Figure 1). The design and development of new product is expensive and risky. There are few reasons to it:

- Most of the product ideas which go to product development stage never reach the market due to non-availability of money, technology, manpower or due to change in demand.
- Many products that do reach the market are not successful mainly due to inferior quality, high product cost, poor functionality, poor marketing skills or change in demand.
- Successful products tend to have a shorter life due to change in demand, stiff competition or rapid technological changes.

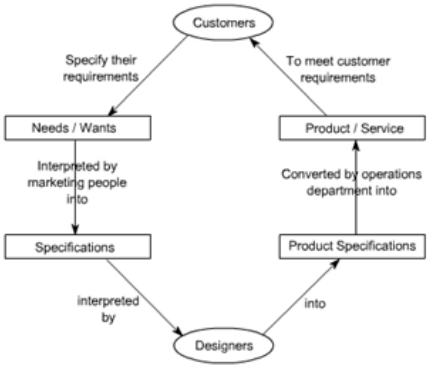

Figure 1

Table.1

Form	Parameter	Critical quality attributes
Drug substance	Physicochemical	Description
		Identification
		Impurities
		pH
		Melting point/range
		Refractive index
		Particle size
		Bulk density
		Polymorphic forms
		Enantiomeric purity
		Water content
	Biological	Activity
		Permeability
	Microbiological	Total count of aerobic organisms
		Total count of yeast and molds
		Absence of specific objectionable bacteria
Excipients	Physicochemical	Concentration
		Stability
		Manufacturability
		Performance of functionality
		Particle size
		Bulk density
		Tap density
		Hygroscopicity
	Biological	Effect on bioavailability of active/s
	Microbiological	Total count of aerobic organisms
		Total count of yeast and molds
		Absence of specific objectionable bacteria
In-process materials		Assay
		Water content
		Hardness and friability of tablet cores (which will be coated)
		pH of a solution
		Disintegration time
		Friability
Drug product	Physicochemical	Description
		Identification
		Assay
		Impurities
		Particle size
		Polymorphic forms
		Tablets (coated and uncoated) and hard capsules
		Dissolution
		Disintegration
		Hardness/friability
		Uniformity of dosage units
		Water content
		Oral liquids
		Uniformity of dosage units
		pH
		Antimicrobial preservative content
		Antioxidant preservative content
		Extractables
		Alcohol content
		Dissolution
		Particle size distribution (oral suspensions)
		Redispersibility (oral suspensions)
		Rheological properties (viscous solutions and suspensions)
		Reconstitution time (dry powder for reconstitution)
		Water content (dry powder for reconstitution)
		Parenteral drug products
		Uniformity of dosage units
		pH
		Particulate matter
		Water content
		Antimicrobial preservative content
		Antioxidant preservative content
		Extractables
		Functionality testing of delivery systems (packaged in prefilled syringes, autoinjector cartridges etc.)
		Osmolarity
		Particle size distribution
		Redispersibility (injectable suspensions)
		Reconstitution time (products for reconstitution)
	Biological	IVIVC (for extended release products)
	Microbiological	Total count of aerobic organisms
		Total count of yeast and molds
		Absence of specific objectionable bacteria
		Parenteral drug products
		Sterility
		Endotoxins/pyrogens

IVIVC: In vitro - in vivo correlation

2. Methodology

Pharmaceutical Product Development: A Quality by Design Approach

The annex of International Conference on Harmonization (ICH), ICH Q8 (R2) guidance, describes the principles of quality by design (QbD). It defines quality as the suitability of either a drug substance or drug product for its intended use. ICH Q8 (R2) defines QbD as 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. Figure depicts an overall QbD system where RA and risk control for the product and process is involved.

Key Elements of Quality by Design

Target product profile

The TPP summarizes the clinical objectives of a dosage form. For a generic product, TPP is determined by the key portions of innovator product labeling. The components of TPP for a generic capsule/tablet dosage forms can be:

Dosage form: Capsules/tablets

Strength: _____.

Route of administration: Oral

Proposed indication: _____.

Design and development of product

The physio-chemical and pharmacological properties of the active pharmaceutical ingredient (API) determine the critical attributes for pharmaceutical development. The product development must invariably be systematic, scientific, and risk-based to accomplish these predefined objectives

3. Results and Discussion

Risk assessments:

Flow charts, check sheets, process mapping, cause and effect diagrams, etc., are the most commonly used simple methods for RA and management. The influence of the critical process parameters and critical material attributes is then represented as sublines for the diagonal lines figure shows a basic Ishikawa diagram

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.

Process analytical technology

Quality cannot be tested into products; it should be built-in or should be by design is the current approach of FDA to a manufacturing process. FDA defined PAT as a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality.

Critical quality attributes

Critical process parameters may be equipment type, batch size, mixing order, mixing time, other operational conditions, etc. Moreover, critical raw material attributes are its quality and quantity. A product is expected to have the defined quality if the operation is carried out within the

design space. Thus, it describes an established range of process parameters and/or material attributes that produces product of desired quality.

Product Life Cycle Management& Continual Improvement: The guidelines written by the International Conference on Harmonisation (ICH) are of particular significance. The following guidances have recently been developed:

- ICH Q8 Pharmaceutical Development (completed– in implementation phase)
- ICH Q8R (Annex to Pharmaceutical Development Q8(R) –at step 3 of the ICH process)
- ICH Q9 Quality Risk Management (completed –i n implementation phase)
- ICH Q10 Quality Pharmaceutical System (at step 3)

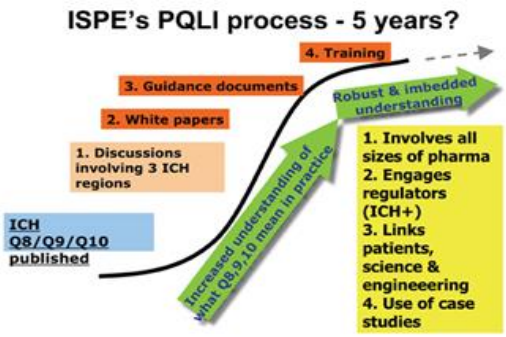

Figure 2

Operational Qualification: This is done to provide a high degree of assurance that the equipment functions as intended. Operational qualification should be conducted in two stages:

- Component Operational Qualification, of which calibration can be considered a large part.

System Operational Qualification:

- To determine if the entire system operates as an integrated whole.

Process Performance Qualification:

- This verifies that the system is repeatable and is consistently producing a quality product.

Approaches to Validation Process

There are two basic approaches to the validation of the process itself (apart from the qualification of equipment used in production, the calibration of control and measurement instruments, the evaluation of environmental factors, etc). These are the experimental approach and the approach based on the analysis of historical data. The experimental approach, which is applicable to both prospective and concurrent validation, may involve

- Extensive product testing,
- Simulation process trials,
- Challenge/worst case trials, and
- Control of process parameters (mostly physical).

The Validation Report

A written report should be available after completion of the validation. If found acceptable, it should be approved and authorized (signed and dated). The report should include at least the following:

- Title and objective of study;
- Reference to protocol;
- Details of material;
- Equipment;
- Programmes and cycles used;
- Details of procedures and test methods;
- Results (compared with acceptance criteria); and
- Recommendations on the limit and criteria to be applied on future basis.

4. Conclusion

Quality by design is a common understanding on the concepts of ICH Q8, Q9 and Q10 and will be essential in the process of formulation. The review explains the use of target product profile, risk assessment, identification the critical material attributes and clears the concept of critical process parameters, implements the control strategy and continues monitoring and updating the process. It also explains application of QbD principles and tools to drug product and process development. It can be concluded Quality by Design (QbD) principles and tools, play an important role in facilitating a higher level of process understanding and create opportunities for investigation and developing control strategies in formulation and process development.

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