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Quality by Design: An Analysis of the Contemporary Method for Improving the Safety and Efficacy of Pharmaceuticals

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Abstract

Quality by design (QbD) is the modern method to ensuring pharmaceutical safety and efficacy. This review describes quality by design and identifies some of its features to assure pharmaceutical quality. Each unit operation's process parameters and quality characteristics are identified. This article discusses the advantages, opportunities, and procedures involved in pharmaceutical product quality through design. The ICH quality recommendations Q8, Q9, and Q10 for pharmaceutical development, quality risk management, and pharmaceutical quality systems, respectively, provide examples of how to use quality by design in pharmaceutical development and manufacture.

The goal of pharmaceutical development is to create a high-quality product and manufacturing method that consistently delivers the product's expected performance. Throughout the product's development, steps should be done to add to or improve its quality. It contains the Quality goal product profile, vital quality attributes, and other important Quality by Design features. QbD also compares the quality of a product based on end-product testing to the quality of a product based on quality by design. Quality by Design is a concept that was described and presented in an international conference for harmonisation.

Keywords: *Critical quality attributes, critical material attributes, critical process parameters, international conference for harmonization, quality by design, quality target product profile*

INTRODUCTION

The product should be created to fulfil the demands of the patient as well as the intended use. Product performance that can be obtained through a more systematic approach to development (also known as quality by design) can include the incorporation of prior knowledge, the results of studies using design of experiments, the use of quality risk management, and the use of proper risk assessing management throughout the product's lifecycle [13]. A methodical strategy like this might help achieve the target product quality. Product and process knowledge that may be updated as the product lifecycle/product development progresses. Pharmaceutical development entails the following steps:

Defining the quality target product profile (QTPP), which relates to quality, safety, and efficacy, taking into account factors such as route of administration, dosage form, bioavailability, strength, and stability; identifying potential critical quality attributes (CQAs) of the drug product, so that the characteristics of excipients or API used have an impact on product quality can be studied and controlled [4]. Determining the important quality features of the drug substance, excipients, and so on, as well as selecting the kind and amount of excipients to provide the drug product with the necessary quality efficacy, may be done without fail. It is also critical to choose an acceptable production process and define a control plan. The current review article goes through every feature of QBD in great depth [2].

ELEMENTS OF QBD

Before understanding the concept of Quality by Design let’s have a look at QbD’s definition:

Definition

A systematic approach to pharmaceutical product development that begins with established objectives and focuses on product and process understanding, as well as process control, and is based on solid scientific knowledge and quality risk management [1].

Quality by design allows the systematic approach in doing so, and are explained as follows:

Predefined Objectives

- Define the Quality Target Product Profile
- Identify CriticalQualityAttributes (CQA)

Product and Process Understanding

- Identify Critical Material Attributes (CMA)
- Identify Critical Process Parameters (CPP)
- Establishing the functional relationships between CMA/CPP and CQA.

Process Control

To develop appropriate Control Strategy, including justifications.

Sound Science

Science driven development (Scientific literature, prior knowledge, design of experiment)

Quality Risk Management

Risk-based development

Pharmaceutical product development by following approaches of quality by design

Quality Target Product Profile

The quality target product profile provides an understanding of the aspects that ensure quality, safety, and efficacy of a specific product. As per ICH Q8 (R2), QTPP is defined as a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality taking into consideration safety and efficacy. In short, provides a label to the pharmaceutical product that promises the safety and efficacy [2].

The quality target product profile forms the basis of design for the development of the product. Considerations for the quality target product profile could include:

- Deciding the Intended use of a drug for the clinical setting, route of administration, dosage form, delivery systems;
- To formulate a drug in different dosage strength(s).
- Type of container closure system can be used to ensure the compatibility of the product and the material of the packaging material.
- Active Therapeutic moiety release or delivery of it from being developed

dosage form and different attributes affecting pharmacokinetic characteristics such as disintegration, dissolution, aerodynamic performance appropriate to the drug product.

Final Drug product quality criteria (e.g., sterility, purity, stability, and drug release) appropriate for the intended marketed product [6, 7].

Table 1 gives examples of QTPP for solid dosage form is given in the following table [5]

Table 1: Examples of QTPP.

QTTP Elements	**Target**	**Justification**
Dosage form	Tablet	For Pharmaceutical equivalence, same dosage form has to be
Dosage Design	Sustained-release	To meet label claims
Route of Administration	Oral	For Pharmaceutical equivalence,
Dosage Strength	20mg	For Pharmaceutical equivalence,
Pharmacokinetics	Sustained-release enabling Tmax in 5.5 hrs or less and should be bioequivalent to Reference listed drug	Bioequivalence required and required to ensure sustained release of drug from the dosage form
QTTP Elements	**Target**	**Justification**
Drug product : Physical appearance Identification AssayContent uniformity Dissolution Degradation products Residual solvents Water content Microbial Limits	Pharmaceutical equivalence requirement: Must meet the applicable standards	

Critical Quality Attributes

The quality target product profile serves as the foundation for the creation of CQAs, which are described as physical, chemical, or biological characteristics that must be within an acceptable limit, range, or distribution to assure the intended quality of final product. CQAs of solid oral dosage forms often alter product purity, strength, drug release, and stability [3].

CQAs for various delivery modalities can also incorporate product-specific elements including aerodynamic qualities for inhaled medicines, sterility for parenteral, and adhesive properties for transversal patches. CQAs for drug ingredients, raw materials, and intermediates might also contain attributes that impact drug product CQAs (e.g., particle size distribution, bulk density) [6].

To guide product and process development, potential drug product CQAs generated from the quality target product profile and past information are employed. The list of potential CQAs can be amended when the formulation and manufacturing technique are selected, as product expertise and process understanding improve.

Quality risk management may be used to prioritise the list of possible CQAs for further evaluation. CQAs may be detected using the quality risk management and experimentation method, which offers information about the amount to which their fluctuation might affect the quality of the medicinal product [10, 11].

Approach to Identify CQAS

To take into account all physical, chemical, and microbiological drug product qualities such as identification, moisture content, water content, pH, and test, content homogeneity, dissolution, drug release from dosage form, residual solvents, and microbial limits. It assures or makes the scientist certain of the qualities that must be preserved and how to produce a medicinal product while keeping the needed quality traits in mind.

Identifying a CQA based on the severity of undesirable effects on a patient, i.e., safety and effectiveness, resulting in the drug product failing to fulfil all quality criteria. Pre-determining the quality attributes that indicate the influence on the drug product and the extent to which those qualities are crucial aids in the development of a safe and efficient drug product in an appropriate dose form [4, 5].

Table 2 gives examples of CQAs

Quality Attributes of the Drug Product		Target	Is this CQA?	Justification
Physical	Appearance	Color, shape, and no visual defects of tablet it makes it acceptable to the patient	No	Color, shape, and appearance are not directly linked to safety & efficacy. Therefore, they are not critical. The target is to ensure patient acceptability
	Odor	No unpleasant odor	No	Generally, a noticeable odor is not directly linked to safety & efficacy, but odor can affect the patient acceptability. For this product, neither the drug substance nor the excipients should be of an unpleasant odor.
	Friability	NMT 1.0%	No	Friability is a routine test as per compendia requirements for tablets. A target of NMT 1.0% w/w of mean weight loss assures a low impact and minimizes customer and patient complaints.
Identification		To be done before its use in formulation	Yes	The identification of API and excipients being used is critical for safety & efficacy, this CQA can be effectively controlled by the quality management system. Therefore this parameter is not considered as CQA during formulation & process development, it's a preliminary test parameter than an In-process test.
Assay		100% w/w of label claim	Yes	Assay variability will affect safety & efficacy. Process variables may affect the assay of the drug product. Hence, it is mandatory to perform the assay of formulation throughout the process and product development.
Content uniformity		Conforms to USP<905> monograph	Yes	Both formulation and process variables affect the uniformity of drug through the batch; hence, uniformity is maintained throughout the drug product development process.

Critical Process Parameter and Critical Material Attribute

To guarantee that all critical quality characteristics are satisfied or to achieve CQA, further factors such as critical process parameters and critical material attributes must be evaluated. Before delving into these factors in depth, let's first define them:

Critical Process Parameter

A process parameter whose variability affects a crucial quality characteristic and should thus be monitored or regulated to ensure that the technique provides the desired quality.

Critical Material Attribute

To assure the intended quality of output material, i.e. completed product, a physical, chemical, biological, or microbiological property or feature of an input material, such as Excipients and API, should be chosen within a suitable limit, range, or distribution. Figure 1 depicts the link between CMAs, CPPs, and CQAs.

Risk Assessment: Linking Material Attributes and Process Parameters to Drug Product CQAS

Risk assessment might be a beneficial science-based tool used in quality risk management to identify which material qualities and process factors are likely to have an influence on product CQAs. Risk assessment is frequently undertaken early in the pharmaceutical development process and is ongoing as more data becomes available and more information is gathered [9, 10].

Risk assessment tools will be used to identify and rank parameters (e.g., process, equipment, input materials) with the potential to have an impact on product quality, supporting past knowledge, and preliminary experimental data. Any investigations will update and prioritise the initial list of probable factors, which will be rather extensive (e.g., through a mixture of style of experiments, mechanistic models).

Experimentation will be used to improve the list and determine the impact of individual factors and potential relationships. Once the various factors are known, they may be investigated in any way (e.g., through a combination of style of experiments, mathematical models, or studies that create mechanistic knowledge) to get a higher degree of method understanding control plan [7].

A control strategy is intended to guarantee that a product of the required quality is consistently produced. The components of the control approach mentioned in the dossier should explain and justify how in-process checks and controls of input products (API and excipients used in product development), intermediates (in-process materials), container closure system, and drug products contribute to final product quality [11]. These checks should be based on product knowledge, formulation, and procedure, and should involve, at a minimum, control of important process parameters and material attributes.

A thorough pharmaceutical development strategy will improve process and product understanding while identifying sources of unpredictability [7]. Variability in product quality is caused by a variety of factors, which must be discovered and managed in order to avoid additional quality changes. And this may be accomplished by comprehending all material, process, and equipment factors such that none of them modify the necessary critical quality features in the end-product [9].

Understanding the material, process, and product, in conjunction with quality risk management, aids in avoiding undesirable changes in product quality. Thus, knowing the process enables a researcher to offer an alternate production paradigm in which any undesirable modifications in the product may be limited. Instead, a solid procedure must be designed to ensure that even minor modifications in the manufacturing process do not affect the final product quality [8].

A better understanding of the product can justify the usage of auxiliary ways in fulfilling its quality attributes, which can help to execute accurate real-time research. Any formulation or product being developed in accordance with GMP guidelines must undergo a content uniformity test. Content uniformity is concerned with the uniform distribution of the dose in the formulation and is carried out both in-process and final product, and if it meets the need, real-time studies must be carried out [13, 7].

A control strategy shall consider the following:

- Control over material attributes such as API's, excipients, packing materials) which have impact on the process ability and product safety and efficacy.

- Establishing the In-process and final product specification(s).

- Developing or using a robust unit operations such that simple alterations in the process should not have impact on the product quality. This helps as researcher to overcome the repetitive formulation of the product to meet the specifications.

- In-process or real-time release testing instead of end-product testing (e.g., measurement and control of CQAs during processing).

- A monitoring program (e.g., full product testing at regular intervals) for verifying multivariate prediction models.

A control strategy can include different elements. For example, one element of the control strategy could rely on end-product testing [5], whereas another could depend on real-time release testing. The rationale for using these alternative approaches should be described in the submission.

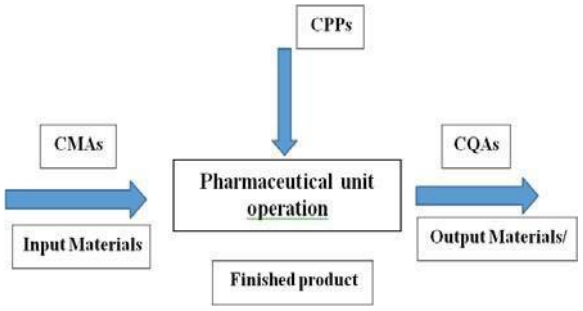

Figure 1: Relationship between CMAs, CPPs, CQAs.

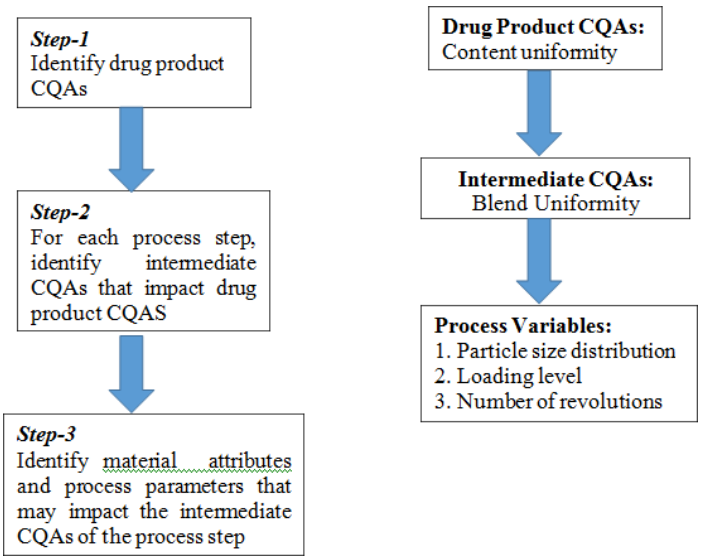

Figure 2: Approach to identify material attributes and process parameters.

Table 3: Identifying potentially high-risk material attributes and process parameters.

Input Material Attributes	Process Parameters	Quality Attributes
Particle size	Mixer load level Order of addition	Blend uniformity
Particle size distribution		Particle size
Particle shape	Number of revolutions(Time and speed) Agitation bar	Particle size distribution
Bulk/Tapped/True density		Cohesive/adhesive properties
Moisture content	Environment temperature & humidity	Microbial free product

Applications of Quality by Design

Quality by design

A thorough systematic approach to pharma ceutical growth and production can be achieved. Advancements in pharmaceutical growth and production by QBD can be clarified against traditional strategy.

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

Continuous improvement of the product can be enabled within design space.

Benefits to Industry

- Ensures better design of products with fewer problems in manufacturing.
- Reduces the number of manufacturing supplements required for post-market changes to rely on process, risk understanding, and risk mitigation.
- Promotes implementation of new technology to improve manufacturing without regulatory audit [8].

CONCLUSION

The purpose of a well-defined methodology is to devote effort into developing a dependable process that will consistently provide outcomes fulfilling stated criteria when operating within set parameters. By employing accurate analytical methodologies, QBD may be used to product creation and assessment. Method development should be carried out by taking into account all possible factors that alter the analytical test performance and establishing the relationship between the factor and its effect on the alteration of response; thus developed method should

be precise and accurate so that method re-development can be avoided; and once completed, the next step is to validate it, which is referred to as Method Validation [9, 10]. The validation process reports whether or not the procedure used is accurate. The ICH-Quality guideline Q8 and Q9 approaches are used to identify critical analytical elements and process development [13, 9]. Throughout product development, a corporate data repository should be maintained to ensure that critical information is retained and may be examined as a backup for resolving problems that have previously occurred in product development or in future development [9]. A repository of this type (in accordance with the notions outlined in the draught ICH Q10) will allow for ongoing improvement and change control of the method throughout its lifespan [10, 11]. Rather of continuing to do analytical technology transfer exercises and ICH validation, a risk-assessed change control technique should be used in a QBD approach [8, 9]. A risk assessment should be completed each time a procedure is altered. When a modification is detected as having the potential to take the method outside of its known design space, a method review and, if necessary, an equivalency exercise should be performed to ensure that the method used will satisfy the need in generating a safe product.

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