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Review Article

Review on Quality by Designing for Metered Dose Inhaler Product Development

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Abstract: Pharmaceutical industry is constantly looking for ways to ensure and enhance product safety, quality and efficacy by implementing quality by design (QbD), a science based approach that improves process understanding by reducing process variation and the enabling process control strategies. This review presents a detailed summary illustrating how inhalation products development can be established by implementing quality by design (QBD). A QbD development involves risk assessment, designing of experiments and multivariate statistical tools to assemble a product and process design space and linking of critical parameters to the product safety and efficacy. It is important to begin by understanding the factors like active, excipients, formulation, container closure systems, and process variables, and how these factors affect the critical quality attributes and therefore the finished product's performance within the design space. QBD intends to identify quality target product profile (QTPP), critical quality attributes (CQA), critical process parameters and quality risk assessment.
Keywords: Quality by design (QbD), Metered dose inhaler, Quality target product profile, critical quality attributes, quality risk assessment, Design space.

INTRODUCTION

Quality by design (QbD) includes designing and developing formulations and manufacturing processes which ensures predefined product specifications. The concept of QbD was mentioned in the ICH Q8 guideline, which states that "quality cannot be tested into products, i.e., quality should be built in by design." According to ICH Q8 QbD is defined 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. In 2002, the FDA announced an initiative and establishes a new regulatory framework focused on QbD, risk management, and quality system. This initiative leads the way for industry to look beyond quality by testing (QbT) for ensuring product quality and performance. The peculiar feature of QbD is that it enables to understand how process and formulation parameters affect the product characteristics and subsequent optimization of these parameters should be identified in order to monitor these parameters online in the production process [1].

The application of QbD principles to inhalation product development and manufacturing has gained a lot of interest in the literature recently. The article illustrates the design to implement QbD in the inhalation product industry and also explain key aspects of QbD process in the pharmaceuticals. While there has been a lot of work and discussion of the application of quality by design to many other dosage forms, there has not been as much of a focus on inhalation dosage forms, e.g. pressurised metered dose inhalers (pMDIs) and dry powder inhalers (DPIs). With regard to the inhalation products development, QbD is especially challenging for a number of reasons.

Some of the challenges confronted by QBD in inhalation product development are as follows:

- Inhalation product is a function of both the device and the formulation, in combination.
- Product handling and patient's operating technique may affect received dose.
- Environmental effects may influence product manufacture.
- Low testing efficiency of aerodynamic particle size determination methods.
- Lack of clear in vitro -in vivo correlations.
- Inhalation manufacturing often exhibits low process capability.

QbD development process includes stages as described below:

- Defining of quality target product profile which describes the use, safety and efficacy of the product. (QTPP).
- Designing a formulation and identification of the critical material attributes (CMA) of the product.
- Designing a manufacturing process to produce a final product having critical material attributes.
- Identifying the critical process parameters (CPP) and establishment of a design space.
- Establishing a control strategy for the entire process with input material controls and process controls.
- Continuous monitoring and updating the process to assure consistent quality [2].

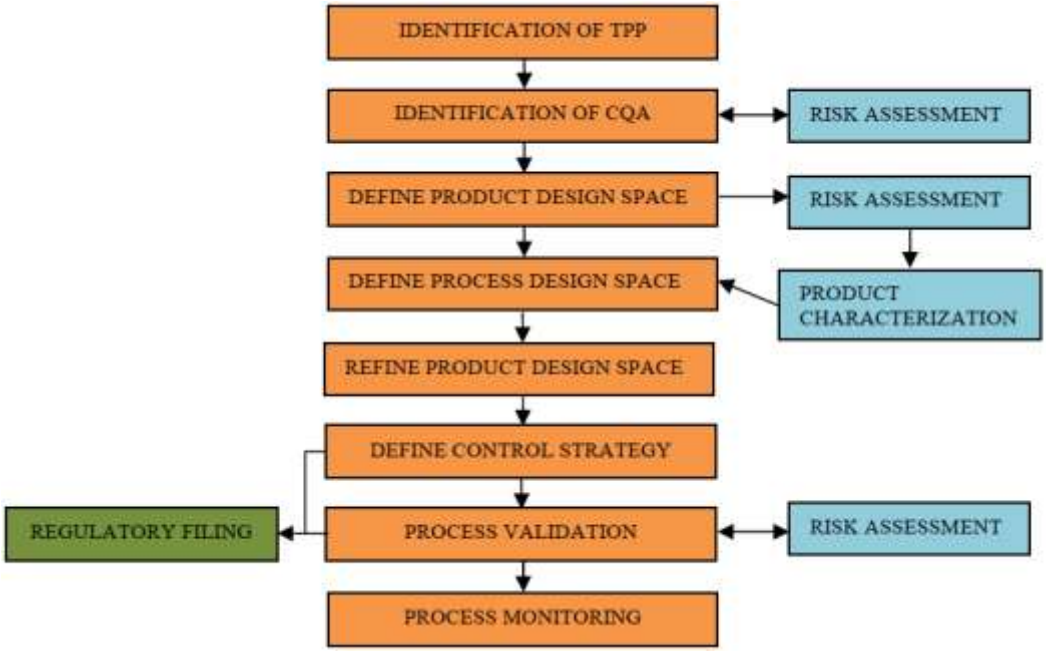

Fig. 1 QBD approach for product development [3]

QBD IN INHALATION PRODUCT DEVELOPMENT

During the development of an inhalation product (or for any form of drug product) by QBD, it is essential to begin by understanding the factors such as input materials, formulation, container closure systems, and process variables, and how these factors affect the critical quality attributes and therefore the finished product's performance within the design space. The operating space is used to define the range for the process variables in quality by design, so that companies can be assured about provided the performance the variables remain within the range. Any processes that link to the drug product manufacturing process, such as those controls the physicochemical properties of the input drugs/ materials, or functional packaging components and secondary packaging, will also need to have their own design space. Typically, inhaled products such as pMDIs and DPIs will have multiple design spaces requiring definitions and knowledge spanning API manufacture, formulation processes, filling and finally packaging. There are a number of variables and factors that companies wishing to apply quality by design to inhalation product development which need to take into account and to be assessed to consider their impact on the overall performance [4].

There are likely to be other factors involved and these need to be considered on a case-by-case basis. Using the input drug in a suspension MDI or DPI product as an example, the particle size distribution is critical and the finished product performance can only be assured when the drug particle size distribution is well controlled within a certain range (design space). An understanding of the size reduction/control processes and their effect on other physicochemical properties of the drug substance is equally essential as these properties could have a significant impact to the finished product performance or stability. All these variables need to be evaluated in the quality-by-design studies during the product development phase in order to create and populate a robust database. This will help to understand the design space and justify the selected operating range.

Likewise, variables in the process, such as the mixing speed and time required for the dry-powder blend formulation manufacturing need to be evaluated, and their impact on the key product performance needs

to be well understood. This includes requirements such as consistently-delivered doses, as well as the desired aerosolisation performance parameters, which are typically determined by fine particle dose, fine particle fraction and mass medium aerodynamic diameter (MMAD). Building quality-by-design elements into the scale-up process also allows better definition of a robust process design space.

TOOLS OF QBD

Identifying a Quality Target Product Profile (QTPP):

The quality target product profile (QTPP) as defined as a summary of the quality characteristics or attributes of a drug product that ideally will be achieved and thereby ensure the safety and efficacy of a drug product. The QTPP forms the basis of design for the development of the inhalation product and is developed with the end product in mind. The QTPP may be updated or revised at various stages of development as new information is obtained during the development process. The FDA has published a guidance defining the target product profile (TPP) that focuses on the consumer (patient) and the desired product label. During the development of inhalation product QTPP is depends upon reference listed drug product (RLD) as given in table 1. Which involves oral inhalation route of administration, formulation type suspension or solution dosage form, drug product quality attributes dosage strength, Container closure system, and administration.

Table-1: Quality Target Product Profile (QTPP) for MDI

QTP Element		Target	Justification
Dosage form		Metered Dose Inhaler	Pharmaceutical equivalence requirement: same dosage form
Dosage design		Suspension or solution dosage form	Same dosage form designing as RLD to meet Q1 and Q2
Route of administration		Oral Inhalation route of administration	Pharmaceutical equivalence requirement: same route of administration
Dosage strength		In mcg per spray	Pharmaceutical equivalence requirement: same strength
Pharmacokinetics		T_{max} and C_{max} same to RLD; Bioequivalent to RLD	Bioequivalence requirement
Stability		At least 24-month shelf-life at room temperature	Equivalent to or better than RLD shelf-life
Drug product quality attributes	Assay	Pharmaceutical equivalence requirement: Must meet the same compendial or other applicable (quality) standards (i.e., identity, assay, purity, and quality).	
	APSD		
	UDD		
	Impurities		
	Spray Pattern and Plume geometry		
	Water content		
Container closure system		Container, Valve and Actuator same as RLD drug product	Needed to achieve the target shelf-life and to ensure same product profile
Administration/Concurrence with labeling		Similar as RLD	-
Alternative methods of administration		None	None are listed in the RLD label.

Critical Quality Attributes (CQA):

A critical quality attribute as defined by ICH Q8 (R2) is 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 is associated with raw materials (drug substance and excipients), in-process and drug product. Drug product CQAs are the properties that are important for product performance, means the desired quality, safety, and efficacy. Drug product CQAs derived from the QTPP is used to guide the product and process development. CQAs can also include those properties of a raw material that may affect drug product performance or manufacturability.

An example of this would be drug substance particle size distribution (PSD) that may influence the homogeneity of suspension and therefore the stability of the drug product. Similarly, the deposition of drug in lungs is dependent on the particle size of the API. In this example, PSD can be designated as CQA or critical material attributes (CMA) [5].

Table-2: Critical Quality Attributes (CQA) for MDI

Quality Attributes	Target	Is this a CQA?	Justification
Appearance	Color, appearance of formulation and primary packaging material as per specification	No	Color and appearance are not directly linked to safety and efficacy .
Identification	RT of API should matches with the RT of standerd	Yes	Though identification is critical for safety and efficacy, this CQA can be effectively controlled and will be monitored at drug product release.
Assay	95 % to 105 %	Yes	Assay variability will affect safety and efficacy. Thus, assay will be evaluated throughout product and process development.
APSD	Mass Balance should be in between 85 to 115 % of label claim	Yes	Failure to meet the APSD specification can impact lung deposition bioavailability. Both formulation and process variables affect the APSD. This CQA will be investigated throughout formulation and process development.
UDD	Delivery of the dose should be between 75 to 125 % of label claim	Yes	Variability in uniformity of delivered dose will affect safety and efficacy. Both formulation and process variables impact UDD, so this CQA will be evaluated throughout product development.
Spray Pattern and Plume Geometry	Equivalent to RLD	Yes	Variability in Spray Pattern will affect safety and efficacy. Both formulation and device variables impact Spray Pattern, so this CQA will be evaluated throughout product development.
Degradation Product	Meet ICHQ3A AND Q6A for impurities	Yes	Degradation products can impact safety and must be controlled based on compendial/ICH
Shot Weight	±15% target shot weight	No	Both formulation and process variables impact on Shot Weight but it is not directly linked to safety and efficacy .
Microbial Limits	Meet Pharmacopoeial criteria	Yes	In case of inhalation product Non-compliance with microbial limits will impact patient safety.

Quality Risk Assessment

The quality risk assessment in product development is intended to identify the material attributes and process parameters affecting the drug product CQAs. This helps to understand and predict sources of variability in the manufacturing process so that an appropriate control strategy can be implemented. The identification of critical process parameters (CPP) and critical material attributes (CMA) is a continuous process; prior knowledge serves as the primary basis. The risk assessment tools used in earlier phases of development therefore tend to be more qualitative and serve as a means to prioritize the experimentation. Typical tools used include risk ranking and filtering, input–process–output diagrams, Ishikawa diagram, and so on. Risk filtering and ranking is a tool for comparing and ranking risks [6].

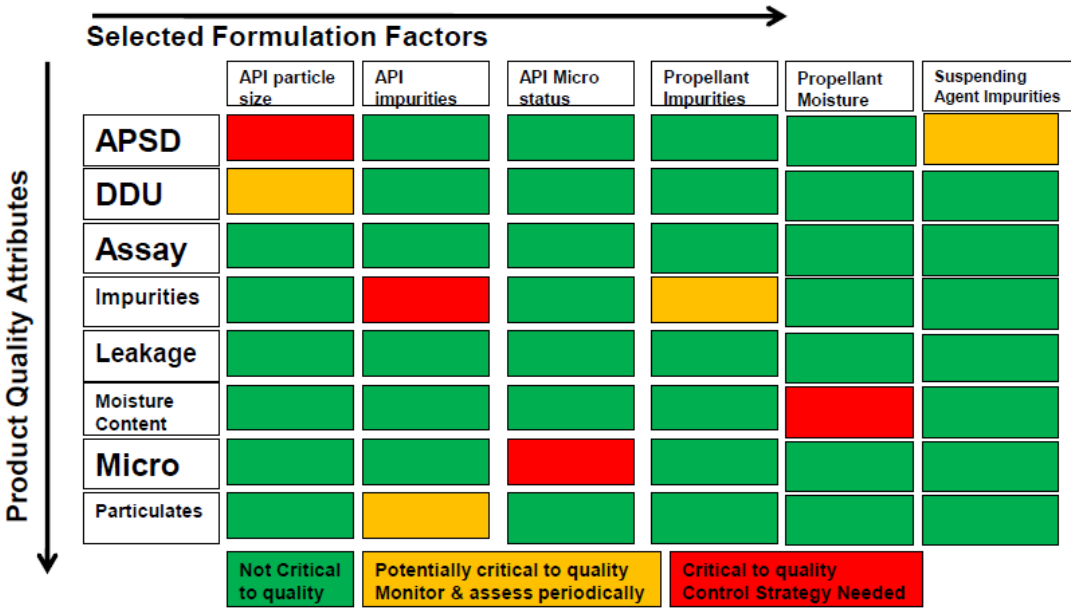

Fig-2: Quality Risk Assessment

Critical process parameters (CPP):

Critical process parameter (CPP) defined as any measurable input (input material attribute or operating parameter) or output (process state variable or output material attribute) of a process step that must be controlled to achieve the desired product quality and process consistency. A parameter is critical when a realistic change in that parameter can cause the product to fail to meet the TPQP. Thus, whether a parameter is critical or not depends on how large of a change one is willing to consider. Example is that an homogenizer speed affect the homogeneity and consistency in manufacturing therefore homogenization time and speed is CPP in manufacturing of MDI.

Thus process parameters should define in the range of interest which we call the potential operating space (POS). The POS is the region between the maximum and minimum value of interest to the sponsor for each process parameter. Our criteria for identifying critical and non-critical parameters are that a parameter is non-critical when there is no trend to failure within the POS [3].

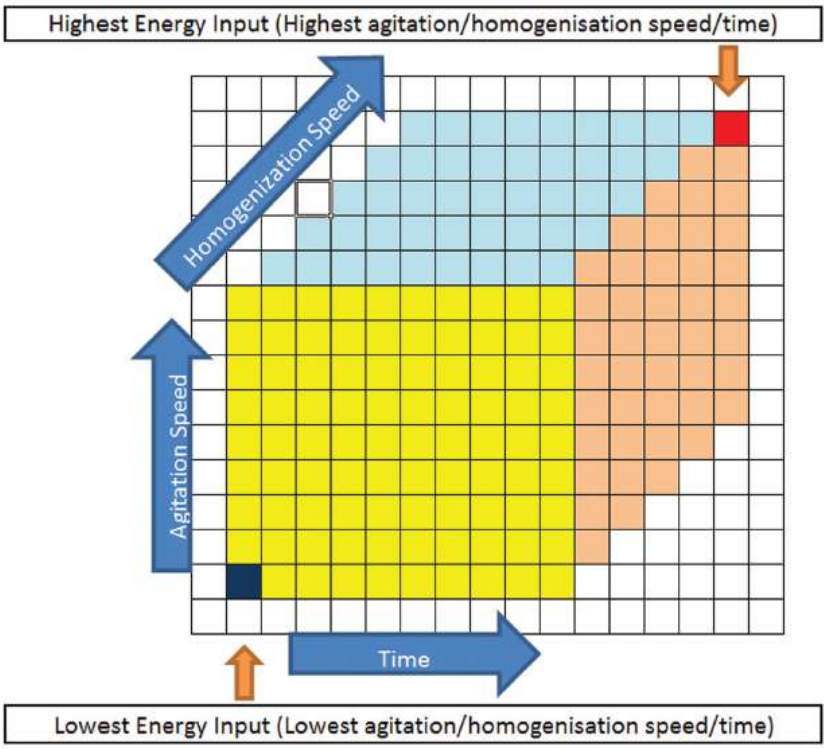

Fig-3: Critical Process Parameters in MDI manufacturing

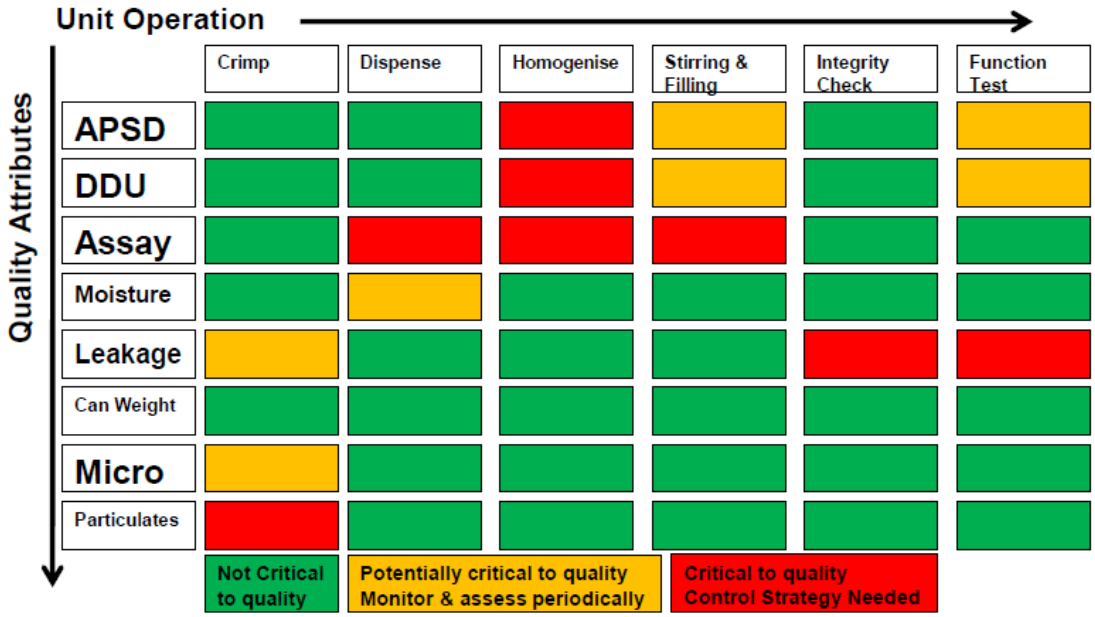

Fig-4: Critical process parameters

Design of Experiments (DOE)

Design of experiments (DOE) is a structured and organized method to determine the relationship among factors that influence outputs of a process. It has been suggested that DOE can offer returns that are four to eight times greater than the cost of running the experiments in a fraction of the time. When DOE is applied to a pharmaceutical process, factors are the raw material attributes (e.g., particle size) and process parameters (e.g., speed and time), while outputs are the critical quality attributes such as APSD, assay, UDD and spray pattern. DOE results can help identify optimal conditions, the critical factors that most influence CQAs and those who do not, as well as details such as the existence of interactions and synergies between factors [7].

Process Analytical Technology (PAT)

PAT has been defined as "a system for designing, analyzing, and controlling manufacturing through measurements, during processing of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality". These parameters are the primary focus of on-, in- or at-line PAT applications. In principle, real-time PAT assessments could provide the basis for continuous feedback and result in improved process robustness [8].

Risk Management Methodology

Quality risk management is defined as "a systematic process for the assessment, control, communication and review of risks to the quality of the drug product across the product lifecycle". Risk assessment is a helpful science-based method, used in the quality risk management that can help in identifying the material attributes and process parameters that potentially have an effect on product CQAs. Risk assessment is generally performed in the pharmaceutical development process and is repeated as more information becomes available and greater knowledge is obtained. Risk assessment tools can be used to identify and level parameters (e.g., process, equipment, and input materials) with potential to have an impact on product quality, based on prior knowledge and primary experimental data [9].

CONCLUSION

Quality by design builds quality in from the product development phase, making commercialisation a focus. This ensures that the inhaled products maintain quality, safety, and efficacy, and keeps the production process as cost-effectively as possible. Successful quality by design relies on a full understanding of the effects from input materials, formulations, container closure systems, and process variables on the CQAs of the products. Proper study design and execution allows us to define the design space of all variables that can be controlled during product manufacturing. Quality by design ensures product quality through data driven risk assessment and product lifecycle management. QbD approach is recognized as the desired state for drug development, more so for inhalation products due to their complex nature. Furthermore, since the quality it integrated in each process operation, regulatory authorities are more comfortable in approving the drug application.

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