Piramal
Pharma Solutions

QUALITY BY DESIGN IN PHARMACEUTICAL DEVELOPMENT

INTRODUCTION

Quality by design (QbD) is a systematic approach to product development that begins with predefined objectives and emphasizes product and process understanding and controls based on sound science and quality risk management (ICH Q8). The emphasis of QbD began with the recognition that increased testing does not essentially improve product quality; however, quality must be built into the product. The regulatory agencies encourage risk-based approaches and the adoption of QbD principles in drug product development and manufacturing. At Piramal we are applying QbD approach in product development, which is characterized by following principles:

- **Designing product and its manufacturing process to meet patient needs with respect to safety and efficacy**
- **Designing manufacturing process to consistently produce product meeting pre-defined quality criteria**
- **Understanding impact of input parameters on product quality to adequately build the controls at the critical points in the process**

QbD principally is a scientific, logical, and preemptive scheme that will incorporate quality control into each and every step of drug development and the manufacturing process. It is a target-oriented approach which we define Quality Target Product Profile (QTPP) at initial stages of product development. The QTPP describes the desired performance based on intended clinical aspects, dosage strength, delivery mode, pharmacokinetics, drug product quality criteria and the container closure system. The next step is identification of key elements of QbD as follows:

Critical Quality Attributes (CQA):

A CQA is a physical, chemical, biological, or microbiological characteristic of an output drug product that should be within an appropriate limit to ensure the desired product quality. The quality attributes of a drug product may include identity, assay, content uniformity, degradation products, residual solvents, drug release, moisture content, microbial limits, and physical attributes such as color, shape, size, odor, score configuration, and friability. These attributes can be critical or not critical. Criticality of an attribute is mainly based upon its influence on the safety and efficacy in the patient.

Risk Assessment:

There are many attributes of the drug substance and excipients that could potentially impact the CQAs of the intermediates and finished drug product. It is impractical for the formulation scientist to investigate all the identified material attributes and process parameters during the formulation optimization studies. Therefore, a risk assessment would be valuable in identifying material attributes and process parameters that are critical. The assessment should be based on scientific knowledge and expertise of the formulation scientist. A material and process attributes

are considered to be critical when a change in that attribute can have a significant impact on the quality (CQA) of the output material. The risk assessment is performed through linking raw material attributes and process parameters to CQAs to arrive at the severity of risk using tools like Basic risk management methods (flowcharts, check sheets, etc.), Failure Mode Effects Analysis (FMEA), Risk ranking and filtering etc. Risk can be categorized depending upon likelihood and its impact on process or formula (Figure 1). Considering 3 different levels (high, medium, and low), decision on action/investigation required to mitigate that risk will be considered.

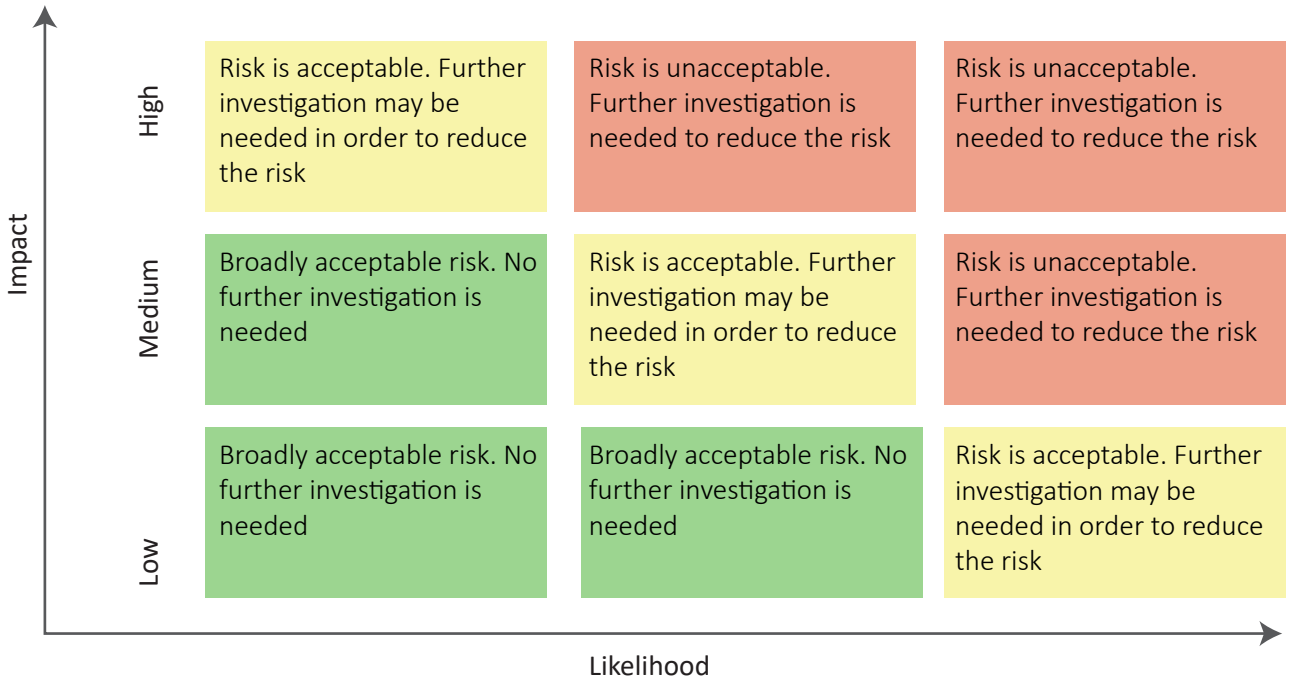


Figure 1 Categorizing Risk levels depending upon Likelihood and impact.

Critical Material Attributes (CMA):

A CMA of a drug substance, excipient, and in-process materials is a physical, chemical, biological, or microbiological characteristic of an input material that should be consistently within an appropriate limit to ensure the desired quality of that drug substance, excipient, or in-process material. The CMA is likely to have an impact on CQA of the drug product.

Critical Process Parameters (CPP):

A CPP of manufacturing process are the parameters which, when changed, can potentially impact product CQA and may result in failure to meet the limit of the CQA.

Design Space:

As per ICH Q8, this is the multidimensional combination and interaction of input variables (e.g.,

material attributes) and process parameters that have been demonstrated to provide assurance of quality. A design space may be built for a single unit operation or for the entire process. The design space could be the direct outcome of analysis of the DoE data or other validated models. 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.

Control Strategy:

Based on process and product understanding, during product development sources of variability are identified. Understanding the sources of variability and their impact on processes, in-process materials, and drug product quality can enable appropriate controls to ensure consistent quality of the drug product during the product life cycle.

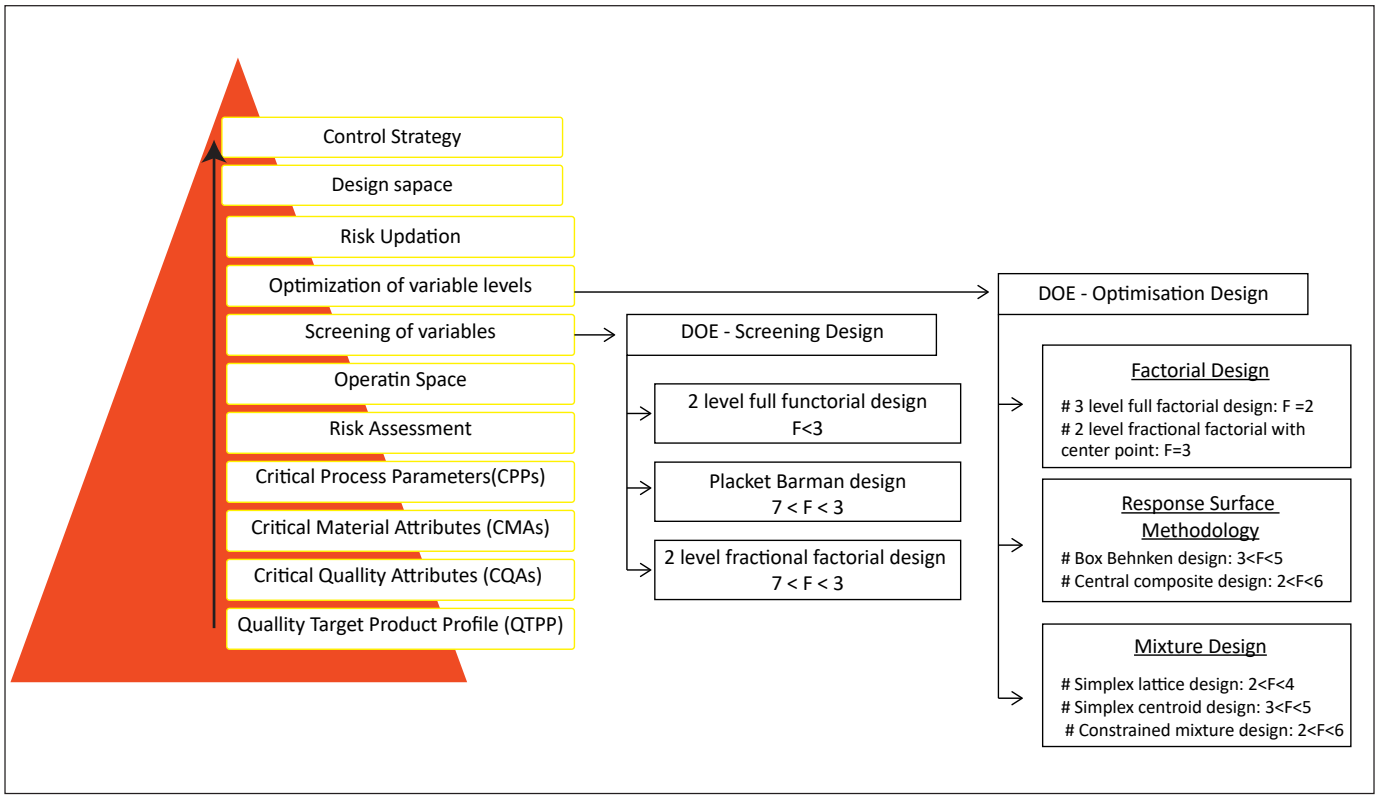


Figure 2 Schematic representation of elements involved in QbD based product development

Schematic representation of QbD approach in product development is given in Figure 2. based on scientific knowledge and expertise of the formulation scientist. A material and process attributes are considered to be critical when a change in that attribute can have a significant impact on the quality (CQA) of the output material. The risk assessment is performed through linking raw material attributes and process parameters to CQAs to arrive at the severity of risk using tools like Basic risk management methods (flowcharts, check sheets, etc.), Failure Mode Effects Analysis (FMEA), Risk ranking and filtering etc. Risk can be categorized depending upon likelihood and its impact on process or formula (Figure 1). Considering 3 different levels (high, medium, and low), decision on action/investigation required to mitigate that risk will be considered.

TOOLS APPLIED IN QBD APPROACH

Design of Experiment (DoE):

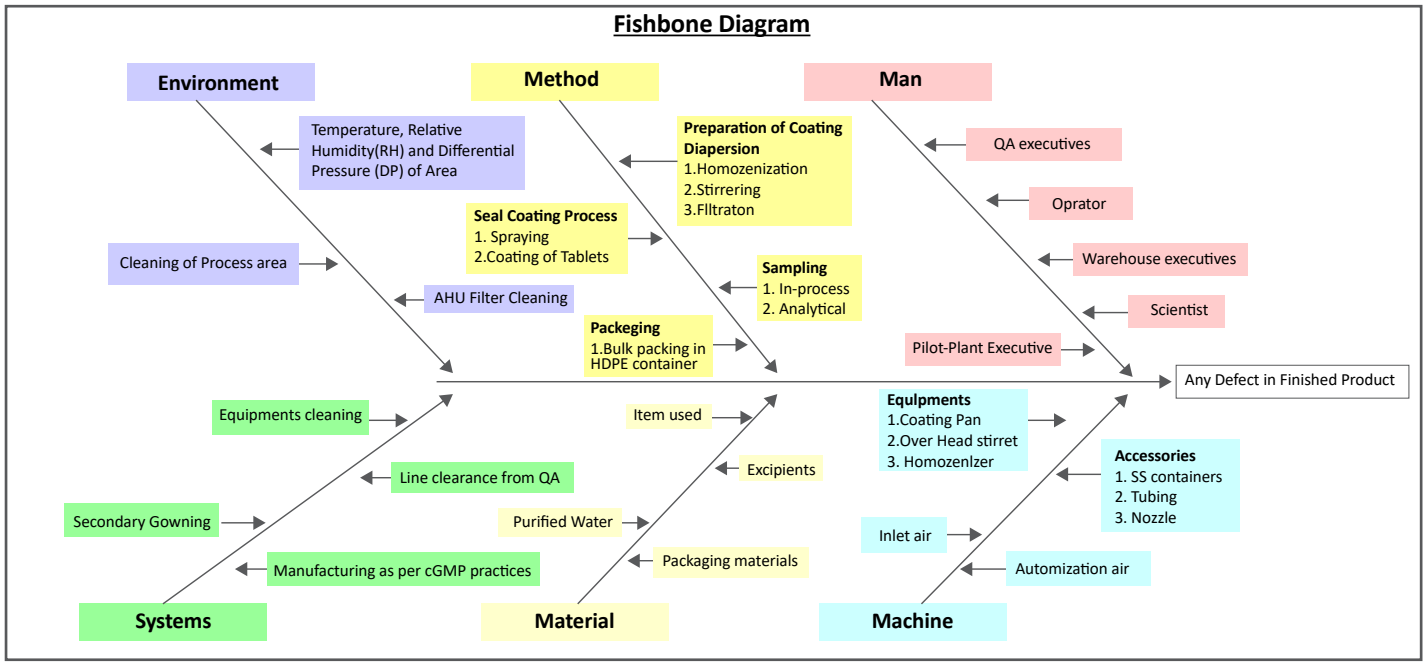
This is a systematic approach applied to conduct experiments to obtain maximum output. We have capability and expertize to perform DoE in product development using software like Minitab and Statistica.

Design of experiments- screening: Designs applied to screen large number of factors in minimal number of experiments to identify the significant ones. Main purpose of these designs is to identify main effects and not the interaction effects. For such studies common designs used are Plackett-Burman and fractional factorial design.

Design of experiments-optimization: Experimental designs considered to carry out optimization are mainly full factorial design, surface response methodology (e.g. Central composite, Box-Behnken), and mixture designs. These designs include main effects and interactions and may also have quadratic and cubic terms require to obtain curvature. These designs are only applied once selected factors are identified, which seem to be contributing in process or formulation.

Risk assessment methodology:

Cause and Effect Diagrams (fish bone/Ishikawa): This is very basic methodology to identify multiple possible factors for a single effect (Figure 3). Various cause associated with single effect like man, machine, material, method, system, and environment need to be considered to identify root cause.



Primary branch represents effect, whereas major braches in diagram are associated with major causes and minor branches supports the possible detailed cause.

Failure Mode Effect Analysis (FMEA): This is an important tool to evaluate potential failure modes in any process. Quantification of risk by interaction of probability functions of severity, occurrence, and detectability of any event can be done. FMEA can be effectively performed with good understanding of process.

PAT:

Control Strategy: Assurance of product quality during intermittent steps using Process Analytical Technology (PAT) is recommended by regulatory authorities, which is yet to be extensively accepted by the pharmaceutical industry over conservative methodologies. It involves advanced online monitoring systems like NIR (Near IR), Handheld Raman Spectrometer, Online Particle Size Analyzer etc. We are experienced in application of NIR and Raman Spectrometer to monitor processes viz. blending and wet granulation. These technologies further make assurance of continuous improvement in process and product quality through its life cycle.

To summarize, the aim of implementing pharmaceutical QbD is to reduce variability and defects in product, thereby enhancing efficiency in product development and manufacturing. It can be achieved by designing a robust formulation and manufacturing process and establishing clinically relevant specifications. The key elements of pharmaceutical QbD can include the QTPP, understanding of product and process design, scale up, control strategy, and continual improvement. Prior knowledge of various tools, risk assessment, DoE and PAT is valuable to facilitate QbD implementation.

Piramal Pharma Solutions is a contract development and manufacturing organization (CDMO), offering end-to-end development and manufacturing solutions across the drug life cycle. We serve our clients through a globally integrated network of facilities in North America, Europe and Asia. This enables us to offer a comprehensive range of services including Drug Discovery Solutions, Process & Pharmaceutical Development services, Clinical Trial Supplies and Commercial supply of APIs and Finished dosage forms. We also offer specialized services like development and manufacture of Highly Potent APIs, Antibody Drug Conjugation and are well versed in technologies such as Bio-catalysis, Route Scouting etc. Our capability as an integrated service provider & experience with various technologies enables us to serve Innovator and Generic companies worldwide.

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