A review on quality by design: A new approach in formulation development

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ABSTRACT

Quality by Design (QbD) refers to a new approach to product development that could increase efficiencies, provide regulatory relief and flexibility, and offer important business benefits throughout the product life cycle. During designing and development of a product in QbD, a company needs to define desire product performance profile (Target Product Profile (TPP), Target Product Quality Profile (TPQP)) and identify critical quality attributes (CQA). It also gives comparison between product quality by end product testing and product quality by Quality by Design. It is based on the ICH Guidelines Q8 for pharmaceutical development, Q9 for quality risk management, Q10 for pharmaceutical quality systems. It also gives application of Quality by Design in pharmaceutical development and manufacturing of pharmaceuticals.

Keywords: Quality by design, Design of experiment, Pharmaceutical manufacturing, Critical quality attributes, Quality risk management, Design space, Quality target product profile.

INTRODUCTION

Quality by Design (QbD) is increasingly becoming an important and widely used technique in the pharmaceutical industry [1]. QbD is a systematic approach to pharmaceutical development that begins with predefined objectives and emphasises product and process understanding and process control.

International Conference on Harmonization (ICH) Q8 guideline was published in May 2006 for pharmaceutical product development, and has been complemented by the ICH Q9 on Quality Risk Management and ICH Q10 for a Pharmaceutical Quality System.

The quality of raw materials including drug substance and excipients is monitored by traditional testing methods. If they meet the manufacturer’s proposed and/or FDA approved specifications for drug substance or excipients, they can be utilized for the manufacturing of the products. Since only limited numbers of drug product (e.g. tablets) out of several million are tested, drug manufacturers are usually required to conduct comprehensive in-process testing, such as blend uniformity, tablet hardness, tablet disintegration in order to ensure that the outcome of in-process testing meets the FDA approved testing specifications.[2]

Benefits of QBD [4,5,6]
(1) QbD is good Business
(2) Eliminate batch failures
(3) Minimize deviations and costly investigations
Avoid regulatory compliance problems
(5) Organizational learning is an investment in the future
(6) QbD is good science
(7) Better development decisions.

Opportunities [6,19]
(1) Efficient, flexible system
(2) Increase manufacturing efficiency, reduce costs and project rejections and waste
(3) Build scientific knowledge base for all products
(4) Better interact with industry on science issues
(5) Ensure consistent information
(6) Incorporate risk management

Seven steps of quality by design start up plan [6]
(1) Hire an independent Quality by design expert.
(2) Audit your organization and process with the expert conducting a gap 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” advisor

Roadmap for QbD implementation:
It should include, at a minimum, the following elements,

Application of Quality by Design(QbD) [19, 21-23]
Quality by design (QbD) – a comprehensive systematic approach to pharmaceutical development and manufacturing

Advancement in the pharmaceutical development and manufacturing by Qbd can be explained against traditional approach (Table:1).

<table>
<thead>
<tr>
<th>Aspects</th>
<th>Traditional</th>
<th>QbD</th>
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<tbody>
<tr>
<td>Pharmaceutical Development</td>
<td>Empirical</td>
<td>Systematic; Multivariate experiments</td>
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<tr>
<td>Manufacturing Process</td>
<td>Fixed</td>
<td>Adjustable within design space; opportunities for innovation</td>
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<tr>
<td>Process Control</td>
<td>In process testing for go/no-go; offline analysis wide or slow response</td>
<td>PAT utilized for feedback and feed forward at real time</td>
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<tr>
<td>Product Specification</td>
<td>Primary means of quality control; based on batch data</td>
<td>Part of the overall control strategy, based on the desired product performance</td>
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<tr>
<td>Control Strategy</td>
<td>Mainly by intermediate product and end product testing</td>
<td>Risk based; controlled shifted up stream, real time release</td>
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<tr>
<td>Lifecycle Management</td>
<td>Reactive time problem and OOS; Post approval changes needed</td>
<td>Continual improvement enabled within design space</td>
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Elements of QbD
1. Quality target product profile:

QTPP is a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product. 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:
- Intended use in clinical setting, route of administration, dosage form, delivery systems;
- Dosage strength(s);
- Container closure system;
- Therapeutic moiety release or delivery and attributes affecting pharmacokinetic characteristics (e.g., dissolution, aerodynamic performance) appropriate to the drug product dosage form being developed;
- Drug product quality criteria (e.g., sterility, purity, stability and drug release) appropriate for the intended marketed product.

The target product profile (TPP) is generally accepted as 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. The target profile is a summary of the drug development program described in the context of prescribing information goals. Target Product Quality Profile (TPQP) is a term that is a natural extension of TPP for product quality. It is the quality characteristics that the drug product should possess in order to reproducibly deliver the therapeutic benefit promised in the label. The TPQP guides formulation scientists to establish formulation strategies and keep the formulation effort focused and efficient. TPQP is related to identity, assay, dosage form, purity, stability in the label. [14,15]
2. Critical quality attributes:
A CQA 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.[8] CQAs are generally associated with the drug substance, excipients, intermediates (in-process materials) and drug product. CQAs of solid oral dosage forms are typically those aspects affecting product purity, strength, drug release and stability. For drug substances, raw materials and intermediates, the CQAs can additionally include those properties (e.g. particle size distribution, bulk density) that affect drug product CQAs. Potential drug product CQAs derived from the quality target product profile and/or prior knowledge is used to guide the product and process development.

3. Risk assessment: linking material attributes and process parameters to drug product CQAs:
Risk assessment is a valuable science-based process used in quality risk management (ICH Q9) that can aid in identifying which material attributes and process parameters potentially have an effect on product CQAs. Risk assessment is typically performed early 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 rank parameters (e.g. process, equipment, input materials) with potential to have an impact on product quality, based on prior knowledge and initial experimental data. The initial list of potential parameters can be quite extensive, but can be modified and prioritized by further studies (e.g., through a combination of design of experiments, mechanistic models). [9] The list can be refined further through experimentation to determine the significance of individual variables and potential interactions. Once the significant parameters are identified, they can be further studied (e.g., through a combination of design of experiments, mathematical models, or studies that lead to mechanistic understanding) to achieve a higher level of process understanding.

4. Design space:
ICH Q8 (R1) 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 [5]. Because design space is potentially scale and equipment-dependent, the design space determined at the laboratory scale may not be relevant to the process at the commercial scale.[1] Therefore, design-space verification at the commercial scale becomes essential unless it is demonstrated that the design space is scale-independent. Currently, generic-drug sponsors obtain information about acceptable ranges for individual CPPs and CMAs at laboratory or pilot scales. Sponsors may occasionally conduct these studies with appropriate design of experiments, including multivariate interactions, which will create a design space at the laboratory or pilot scale. Such a design space, however, will have limited regulatory flexibility because the regulatory scientists will be unable to determine whether the design space is still valid at the commercial scale unless sponsors can provide additional information that shows the design space is scale-independent or actual verification data at the commercial scale. There is confusion among industry and regulatory scientists about the connection between design space and QbD. Many believe design space and QbD are interchangeable terms. This is incorrect. For generic-drug applications, design space is optional. QbD can be implemented without a design space because product and process understanding can be established without a formal design space. It should be pointed out that implementation of QbD is strongly encouraged by FDA. For some complex drug substances or drug products, implementation of QbD is considered a required component of the application. The development and refinement of the Design Space begins at product conceptualization and continues to evolve throughout the lifecycle of the product.

5. Control strategy:
A planned set of controls, derived from current product and process understanding that ensures 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. Specifically, the control strategy may include:
• Control of input material attributes (e.g., drug substance, excipients, and primary packaging materials) based on an understanding of their impact on process-ability or product quality.
• Product specifications
• Procedural controls
• Facility controls, such as utilities, environmental systems and operating conditions
• Controls for unit operations that have an impact on downstream processing or end-product quality (e.g. the impact of drying on degradation, particle size distribution of the granulate on dissolution)
• A monitoring program (e.g., full product testing at regular intervals) for verifying multivariate prediction models. [8]

The Control Strategy should establish the necessary controls based on patient requirements to be applied throughout the whole product lifecycle from product and process design through to final product, including.

6. Product lifecycle management and continual improvement:
Throughout the product lifecycle, companies have opportunities to evaluate innovative approaches to improve product quality (ICH Q10). Process performance can be monitored to ensure that it is working as anticipated to deliver product quality attributes as predicted by the design space. This monitoring could include trend analysis of the manufacturing process as additional experience is gained during routine manufacture. For certain design spaces using mathematical models, periodic maintenance could be useful to ensure the model’s performance. Expansion, reduction of the design space could be desired upon gaining additional process knowledge. Change of design space is subject to regional requirements.

REFERENCES

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