QUALITY BY DESIGN (QBD) IN PHARMACEUTICAL FIELD: A REVIEW

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ABSTRACT

Quality by design (QbD) is the modern, systematic and holistic approach for pharmaceutical quality. It has become a best ever solution to both industry and FDA to apply a more scientific, risk based, proactive approach to pharmaceutical development. The Rational behind this paper is to discuss the new approach of QbD and its certain key elements. The origin of QbD is from three ICH guidelines ICH Q8, ICH Q9 and ICH Q10 guidelines. QbD is based on principle that “Quality cannot be tested into the product but should be built in by design.” The main aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product. While applying QbD approach one needs to understand and define QTPP, CQA (CMA and CPP). This paper also gives a brief account of risk based assessment, development and implementation of control strategy, concept of design space. QbD tries to find the root cause of failure and monitor it throughout manufacturing so that quality product is achieved. It is a beneficial approach for industry from both time and economic point of view over the current QbT approach.

KEYWORDS: QbD, QTPP, CQA, Design Space, Control strategy.

INTRODUCTION

Nowadays the industries are mainly focusing on adopting the holistic, risk based and scientific approach of QbD. Also FDA and other regulatory authorities are promoting the use of QbD for pharmaceutical development. QbD has changed the current scenario in the pharmaceutical industry. It looks beyond QbT (Quality by end product testing) which is
traditional approach of pharmaceutical development used by industries. QbD is combination of three ICH guidelines.

\[
\text{ICH Q8} + \text{ICH Q9} + \text{ICH Q10} = \text{QbD}
\]

QbD is mainly based on ICH Q8 guideline, which state that “\text{Quality cannot be tested into the product i.e. quality should be built within by design}”. Pharma industries are working hard in order to develop, manufacture and bring a new chemical entity i.e. drugs into market and to comply with regulatory requirement to demonstrate that the drugs are having safety as well as efficacy. This modern approach QbD of drug development will increase efficiency, provide regulatory relief and flexibility and also offer important business benefits throughout the products life cycle. This paper mainly describes a comprehensive, concise, universal approach for determining QTPP quality target product profile which is the summary of drug development program, also helps for determining criticality for quality attribute which include process parameter and material attributes. Paper also covers risk based assessment, concept of control strategy and design space.

**Traditional approach-Quality by end product testing (QbT)**

Traditionally pharmaceutical quality was defined as - The product meeting prespecifies quality attribute and regulatory specification. There is a no link between product quality attribute and clinical performance. The quality is ensured by raw material testing, drug substance manufacturing as fixed drug product manufacturing process, in process materials testing and end product testing. Fig. 1 shows simplified quality control diagram under QbT regulatory framework for generic drugs.
Finished product are tested for quality by assessing whether they meet the manufacturer proposed and FDA approved specification .if yes; they are ok and can be released into the market and; if not they are discarded without investigating the root cause behind the failure.

Table 1 Current V/s QbD approach to pharmaceutical development.

<table>
<thead>
<tr>
<th>Sr.no.</th>
<th>Current (QbT)</th>
<th>QbD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pharmaceutical development is empirical.</td>
<td>Pharmaceutical development is systemic based on multivariate experiment</td>
</tr>
<tr>
<td>2</td>
<td>Use frozen and fixed manufacturing process; discourages any kind of changes.</td>
<td>Uses flexible processes which are adjustable within design space hence, providing opportunity for continuous improvement as well as new innovation.</td>
</tr>
<tr>
<td>3</td>
<td>Product specifications are entirely based on</td>
<td>Product specification are based on product</td>
</tr>
</tbody>
</table>
**QbD: Quality by Design**

In mid-2002, the US food and drug administration (FDA) published a concept paper on current good manufacturing practices for the 21st century. The document express a desire that company build quality, safety and efficacy into their new biopharmaceutical products as early as possible. This concept become known as quality by design (QbD) the FDA produce a guidance document entities pharmaceutical cGMP for the 21st century. This publication defined QbD as

- Developing your product to meet predefined product quality, safety and efficacy, and
- Designing your manufacturing process to meet predefined product quality, safety and efficacy.

International conference on harmonization (ICH) develop the Q8R2 guideline for pharmaceutical development using risk based approach i.e. QbD. Quality by design is “a systemic approach to development that beings with predefined objective and emphasis product and process understanding and process control, based on sound science and quality by risk management, it means designing and developing formations and manufacturing process to ensure a predefined quality.” It can also be defined as “An approach which covers a better scientific understanding of critical process and product qualities designing controls and tests based on scientific limit of understanding during the development phase and using the knowledge obtained during the life cycle of the product to work on a constant improvement environment”. QbD requires an understanding how formulation and process variables influence product quality.

**Benefits of QbD**

- Eliminates batch failure.
- Minimize deviation and costly problems.
Better development decisions.
Empowerment of technical staff.
Better interact with industry on science issue.
Build scientific knowledge based for all products.

Quality target product profile (QTPP)
QTPP can be defined as a summary of the drug development program, which plays a central role in the entire drug discovery and development process. It relate to quality safety and efficacy “considering and planning with the end in mind” e.g. Route of administration, dosage form, bioavailability, strength, stability. It also helps for effective optimization of drug candidate, decision making within an organization with regulatory authority. Recently QTPP is used in development, planning, clinical and commercial decision making, regulatory agency interaction and risk management. QTPP is currently expressed in clinical terms such as

Clinical pharmacology Precaution
Indication and uses Adverse drug reactions
Contraindications Drug abuse
Warning Dependence and overuses

QTPP is simply natural extension of target product profile which links drug development activities to specific statement intended for inclusion in the drug label. QTPP aids formulation scientist to establish formulation strategies and keep the formulation effort focused and efficient. QTPP is related to physical characteristics like identity, assay, and dosage form, purity, stability in the label. E.g. typical QTPP of an immediate release solid oral Ramipril tablet would include,

Table 2 QTPP for Ramipril immediate release tablet

<table>
<thead>
<tr>
<th>QUALITY ATTRIBUTE</th>
<th>TARGET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage form</td>
<td>Tablet</td>
</tr>
<tr>
<td>Dose design</td>
<td>Immediate release</td>
</tr>
<tr>
<td>Route of administration</td>
<td>oral</td>
</tr>
<tr>
<td>Dose strength</td>
<td>10mg</td>
</tr>
<tr>
<td>Physical attribute</td>
<td>Tablet conforming to description shape and size</td>
</tr>
<tr>
<td>Assay</td>
<td>90-110%</td>
</tr>
<tr>
<td>Content uniformity</td>
<td>As per USP standard</td>
</tr>
<tr>
<td>Hardness</td>
<td>50-60 N</td>
</tr>
<tr>
<td>Friability</td>
<td>Not more than 1.0%</td>
</tr>
<tr>
<td>Disintegration time</td>
<td>Not more than 120 sec.</td>
</tr>
<tr>
<td>Dissolution</td>
<td>Not less than 70% at 45 min.</td>
</tr>
</tbody>
</table>
The QTPP is a quantitative surrogate for aspects of clinical safety and efficacy which can be used to design and optimize a formulation and manufacturing processes. The QTPP is not a specification since it includes test such as bioequivalence or stability that are not carried out batch to batch release. The QTPP should only include pattern relevant product performance e.g. Spreadability of semisolid, suspendability for oral suspension etc.

**Critical quality attributes (CQA)**

CQA is a physical, chemical, biological and microbiological property or characteristics that should be within an appropriate limit range or distribution to ensure the desire product quality. CQA related with materials are termed as critical materials attribute (CMA) and those related with process termed as critical process parameter (CPP). Critical material attribute (CMA) are associated with materials i.e drug and excipients used during manufacturing of pharmaceutical product. In order to achieve desired quality product, a through characterization of drug substance with respect to physical, biological, chemical, and mechanical properties such as solubility, polymorphism, particle size, stability and flow property, compatibility with excipients should be considered along with its characterization. Critical process parameters (CPPS) are process inputs that have a direct and significant influence on CQA when they are varied within regular operation range. A pharmaceutical manufacturing process is usually comprised of series of unit operation to produce the desisted quality product. A unit operation is a discrete quality that involves physical or chemical changes such as mixing, milling, granulation, drying, compaction and coating.

### Table 3 Typical unit operation process parameter and quality attribute for tableting.

<table>
<thead>
<tr>
<th>Sr.no.</th>
<th>Pharmaceutical unit operation</th>
<th>Critical process parameters</th>
<th>Potential quality attributes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Roll Compaction</td>
<td>Roll Speed</td>
<td>Appearance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gap Setting</td>
<td>Ribbon/ Particle Size and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Roll Pressure</td>
<td>shape</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oscillation Degree / Speed</td>
<td>Ribbon density, strength,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Screen Size</td>
<td>thickness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Screen Type</td>
<td>Granule Porosity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Feed Rate if separate mill</td>
<td></td>
</tr>
</tbody>
</table>
| 2 | Wet Granulation | **High Shear Granulation**  
Dry mix time  
Impeller speed, configuration and location  
Chopper speed and configuration, and location  
Spray nozzle type and location  
Method of binder addition  
Binder Fluid temperature  
Binder addition rate and time  
Post granulation mix time  
Bowel temperature  
**Fluid Bed Granulation**  
Mixing Time  
Spray Nozzle (Type/configuration/pattern)  
Binder fluid temperature  
Binder fluid addition rate and time  
Inlet air flow, vol., temperature, dew point  
Product temperature  
Exhaust air temperature and flow  
Filter properties and size  
Shaking interval  
| Power consumption  
Blend uniformity  
Flow Characteristics  
Moisture content  
Particle size distribution  
Granule Strength and uniformity  
Granule size and distribution |
| 3 | Drying | **Fluid Bed Drying**  
Inlet air flow, vol., temperature, dew point  
Product temperature  
Exhaust air temperature and flow  
Filter properties and size  
Shaking interval  
Total drying time  
**Tray Drying**  
Quantity of carts and trays per chamber  
Quantity of product per tray  
Drying time and temperature  
Air flow  
Inlet Dew Point  
**Vacuum /Microwave**  
Jacket Temperature  
Condenser Temperature  
Impeller Speed  
Vacuum Strength  
Microwave potency  
Electric field  
Energy Supplied  
Product Temperature  
| Granule size and distribution  
Granule Strength and uniformity  
Flow Characteristics  
Bulk/Tapped Density  
Moisture Content  
Residual Solvents |
| 4 | Milling | **Impact/ Cutting/ Screening Mills**  
Mill Type  
Speed  
Blade Configuration and type  
Screen size and type  
Feeding rate  
**Fluid energy Mill**  
Number of grinding nozzles  
| Particle Size  
Particle Size Distribution  
Particle shape  
Bulk/Tapped Density  
Flow Properties  
Polymorphic Form |
<table>
<thead>
<tr>
<th></th>
<th>Feed rate</th>
<th>Nozzle pressure</th>
<th>Classifier</th>
<th>Type and geometry of mixer</th>
<th>Type and geometry of mixer</th>
<th>Order of addition</th>
<th>Mixer load level</th>
<th>Number of rotation (time/ speed)</th>
<th>Agitating Bar (on/off pattern)</th>
<th>Blend Uniformity</th>
<th>Particle Size Distribution</th>
<th>Bulk/ Tapped Density</th>
<th>Moisture content</th>
<th>Flow properties</th>
<th>Separation Potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Mixing</td>
<td>Pre-Compression Force</td>
<td>Main compression Force</td>
<td>Press Speed – Dwell Time</td>
<td>Force Feeder Speed</td>
<td>Feeder Type</td>
<td>Hopper design, height, vibration</td>
<td>Tablet weight and thickness</td>
<td>Depth of Fill</td>
<td>Punch Penetration Depth</td>
<td>Roller Type</td>
<td>Auger screw rate</td>
<td>Hopper fill</td>
<td>Ejection Force</td>
<td>Target Weight</td>
</tr>
<tr>
<td>6</td>
<td>Compression</td>
<td>Product Temperature</td>
<td>Total Pre heating Time</td>
<td>Spray Nozzle (Type/ Pattern/ Configuration)</td>
<td>Spray Rate (Total/ Individual)</td>
<td>Pan Rotation Speed</td>
<td>Atomization Air pressure</td>
<td>Inlet air flow, temperature, dew point</td>
<td>Total Coating Time</td>
<td>Gun Location</td>
<td>Gin to bed distance</td>
<td>Appearance</td>
<td>Visual attributes</td>
<td>% weight gain</td>
<td>Film thickness</td>
</tr>
<tr>
<td>7</td>
<td>Coating</td>
<td>Risk assessment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tbody>
</table>

ICH Q9 Quality risk management indicates that manufacturing and use of drug product entails some degree of risk. Hence the evaluation of risk to quality should be done by using scientific knowledge. This study will help to determine which variable are critical or which are not, which will help for establishment of control strategy for in process, row material and final testing.

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). 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.

**Design space**

ICH Q8 (R2) 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. 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. Therefore, Design-space verification at the commercial scale becomes essential unless it is demonstrated that the Design space is scale-independent.

The development and refinement of the Design Space begins at product conceptualization and continues to evolve throughout the lifecycle of the product. At the time of filing a submission, the Design Space can be considered to be a snap-shot in time representative of the current process knowledge. It continues to evolve as additional knowledge and information is generated during the commercialization of the product, which may lead to post-approval changes. Movement out of the Design Space is considered to be a change and would normally initiate a regulatory post approval change process.
A design space may be constructed for a single unit operation, multiple unit operations, or for the entire process. Submission of a design space to FDA is a pathway for obtaining the ability to operate within that Design space without further regulatory approval. A Design space is a way to represent the process understanding that has been established. The benefits of having a Design space are clear; one challenge to the effective use of a Design space is the cost of establishing it.

**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, 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.

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 API and Drug Product manufacture, packaging and distribution.

**Product Lifecycle Management**
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. The model maintenance is an example of activity that can be managed within a company’s own internal quality system provided the design space is unchanged.

CONCLUSION
Application of QbD principles facilitate development of quality products and their assessment throughout their lifecycle, and ultimately, result in greater patient benefit. QbD focuses on building quality into the product and manufacturing processes, as well as continuous process improvement – reduction of variability. The backbone for Continuous Improvement is the Pharmaceutical Quality System (PQS). PQS should facilitate continual improvement and help to: “Identify and implement appropriate product quality improvements, process improvements, variability reduction, innovations and pharmaceutical quality system enhancements, thereby increasing the ability to fulfil quality needs consistently”. Quality risk management can be useful for identifying and prioritizing areas for continual improvement. If the rate of QbD adoption is going to increase in the marketplace, the emphasis behind QbD must evolve to a business proposition: one that resonates with the generics industry as a foundation for business competitiveness. To be successful QbD must facilitate a generic product development organization whose primary objective is to be first to file. In the end, the factor that may well drive the industry toward QbD may be the new pivotal guidance itself.

REFERENCE


