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Review on Quality by Design (QbD): A Concept for Development of Quality Pharmaceuticals

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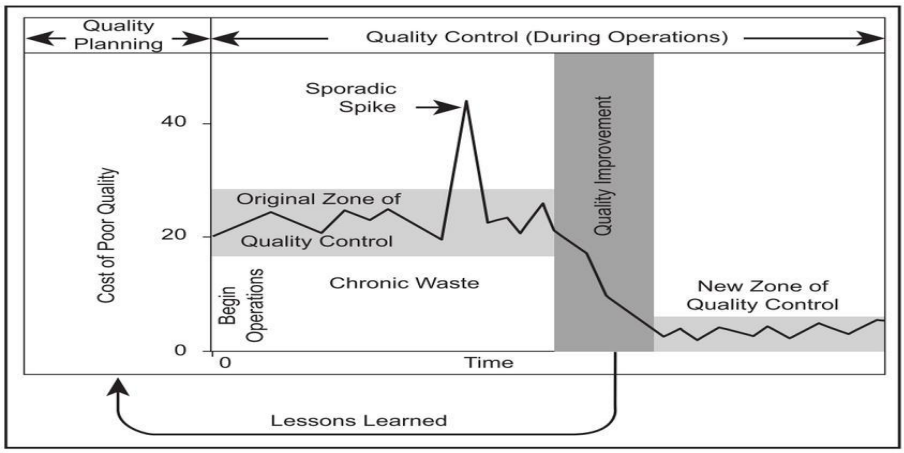
Abstract: *Quality by design (QbD) is the best key to build a quality in all pharmaceutical products. QBD is emerging to increase the promise of providing safe and effective medicines to customers and promises to improve the efficiency of product quality. Under this concepts of be throughout design and growth of product, it is important to identify desire product performance report [Target Product Profile (TPP),Quality Target Product Profile (QTPP)] and identify Critical Quality Attributes (CQA). To recognize the impact of raw material [Critical Material Attributes (CMA)], Critical Process Parameters (CPP) on the CQAs and identification and control sources of changeability. The plan of pharmaceutical development is to design a quality products and its manufacturing process always deliver the future performance of the product. The base of Quality by design is ICH Guidelines Q8 for Pharmaceutical for development, Q9 quality risk management, Q10 for pharmaceutical quality systems.*

Keywords: Quality by Design(QbD), ICH guidelines, Quality Target Product Profile, Process Analytical Technology

I. INTRODUCTION

Pharmaceutical Quality by Design (QBD) is a systematic approach to development that begins with predetermined objectives and emphasizes the understanding of production and processes and process control, based on sound science and quality risk management.[1]In order to describe quality by design, we must first define what we mean by quality. Quality is "standard or suitability for intended use." This term includes such attributes as the identity, potency, and purity.[2]

The term "Quality by Design" was first introduced by Dr. Joseph M. Juran in 1985 in his publication Juran on Quality by Design.He supposed that Quality Cannot be tested into product it has to be build in by design.He proposed Juran's Trilogy in which he described three Quality pillars. These three elements are Quality Planning (the Fig 1. Juran trilogy design stage), Quality Control (ongoing inspections to ensure that processes are in control) and Quality Improvement (including proactive refinement of processes to improve processes). [2]



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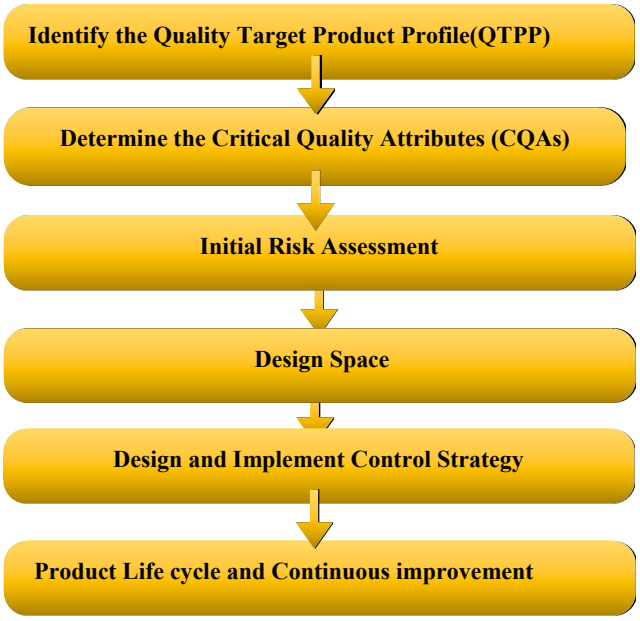
II. KEY ELEMENTS OF QUALITY BY DESIGN



2.1 Target Product Profile (TPP)

Under this title target is important word. Target is nothing but a result that we try to achieve. So, in this we target the drug profile or target product which ensures desired quality, safety & efficacy. TPP is defined as, "A prospective summary of the quality characteristics of drug product that ideally will be achieved to ensure the desired quality, taking in to account safety & efficacy of drug product."(ICH Q8)

Target product profile should includes,

- Dosage form
- Route of administration
- Dosage strength
- Pharmacokinetics
- Stability

The TPP is a patient & labeling centered concepts, because it identifies the desired performance characteristics of the product, related to the patient's need & it is organized according to the key section in the drug labeling. Pharmaceutical companies will use the desired labeling information to construct a target product profile .The TPP is then used to design the clinical trials, safety & ADME studies as well as to design the drug product, i.e. The QTPP.[6]

2.2 Quality Target Product Profile (QTPP)

QTPP is a quantitative substitute for aspects of scientific safety & efficacy that can be used to design and optimize a formulation and mfg. process. It should include quantitative targets for impurities, stability and product specific performance requirements. QTPP is not specification because it includes tests such as bioequivalence or stability that are not carried out in batch to batch release. QTPP should only include patient relevant product performance.

The Quality Target product profile is a term that is an ordinary addition of TPP for product quality. It guides formulation scientists to establish formulation strategies and keep formulation is well-organized. QTPP is related to identity, assay, dosage form, purity, stability in the label. [6]

2.3 Critical Quality Attributes (CQAs)

A CQA has been defined as "a physical, chemical, biological or microbiological property or characteristics that should be within an appropriate limit, range, or distribution to ensure the desired product quality." Identification of CQAs is done through risk assessment as per the ICH Q9. Critical Quality Attributes are generally associated with the drug

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substance, excipients, intermediates and drug product. Critical Quality attributes includes the properties that impart the desired quality, safety, and efficacy. CQAs for biotechnological products are typically those aspects affecting product purity, stability. Drug product CQAs can be identified from the Target product profile. Use of strong risk estimation methods for identification of CQAs is new to the QbD standard.

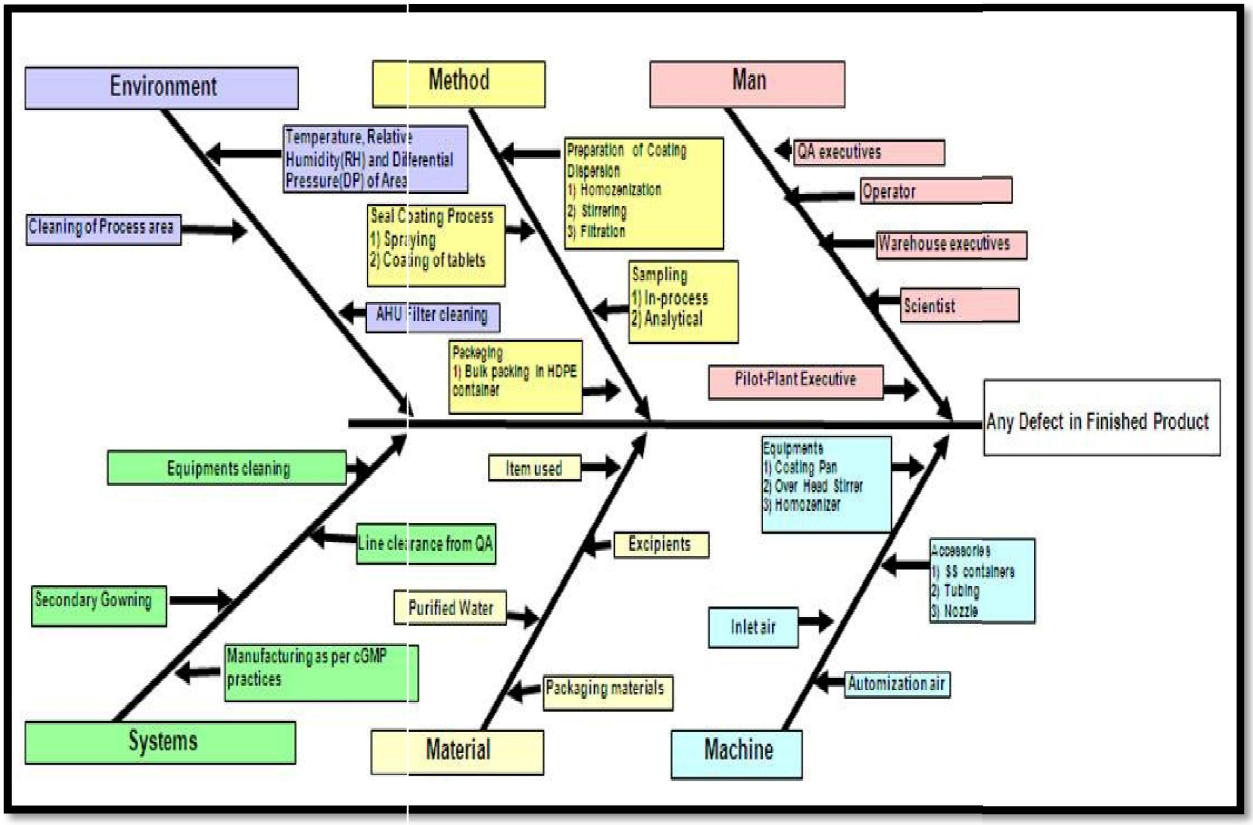

Fig 2 Fishbone Diagram

2.4 Critical Material Attributes (CMAs)

A material attributes can be an excipients raw material, drug substances, reagents, solvents, packaging & labeling materials. A material attributes can be quantified & typically fixed but sometimes can be changed during further processing.E.g. Impurity profile, porosity, specific volume, sterility.[8]

2.5 Critical Process Parameters (CPPs)

Process Parameters includes any input operational parameter of a system or unit operation(eg. mixing speed flow date etc)&Process state variables(eg. Temp, Pressure etc). Must be controlled to achieve the desired product quality and process uniformity.[11]

2.6 Design Space

A Design space is defined as, "Multidimensional combination and interaction of input variables (e.g. material attributes and process parameters) that have been demonstrated to provide assurance of quality."

The linkage between the process inputs and critical quality attributes can be described in the design space. A design space is a way to represent the process understanding that has been established. Design space is the direct outcome of the analysis of the DoE data& validated models such as first-principle models.[16]

2.7 Control Strategy

Control strategy is defined as, "A designed set of control, derived from current product and process understanding that assures process performance and product quality." A control strategy is designed to ensured that product of required

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quality will be produce consistently. Once sufficient level of process understanding is achieved, a control strategy should be developed that assures the process will remain in control within normal variation in material attributes & process operating ranges.

A control strategy may include input material controls, process controls, and monitoring, design spaces around individual or multiple unit operations, and final product specifications used to ensure consistent quality.[13]

III. PHARMACEUTICAL QUALITY BY DESIGN TOOLS

3.1 Risk Assessment

FDA define a Risk Management as, a strategic safety program designed to decrease product risk by using one or more interventions or tools. It is comprehensive process for the assessment, control, communication and review of risks to the quality of the drug product across the product lifecycle.

Fig 3. Risk Assessment

The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient and the level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk.

The purpose of ICH Q9 is to offer a systematic approach to quality risk management and does not specifically address risk assessment in product development. However, the risk assessment tools identified in ICH Q9 are applicable to risk assessment in product development also. The purpose of risk assessment prior to development studies is to identify potentially high-risk formulation and process variables that could impact the quality of the drug product. It helps to prioritize which studies need to be conducted and is often driven by knowledge gaps or uncertainty. Study results determine which variables are critical and which are not, which facilitates the establishment of a control strategy. The outcome of the risk assessment is to identify the variables to be experimentally investigated. ICH Q9 provides a nonexhaustive list of common risk assessment tools as follows: Basic risk management facilitation methods (flowcharts, check sheets, etc.) Fault tree analysis, Risk ranking, filtering, Preliminary hazard analysis, Hazard analysis, critical control points, Failure mode effects analysis, Failure mode, effects, and criticality analysis, Hazard operability analysis & Supporting statistical tools. It might be appropriate to adapt these tools for use in specific areas pertaining to drug substance and drug product quality.[7]

3.2 Design of Experiments (DOE)

Is concerned with the planning and conduct of experiments to analyse the resulting data so that we obtain valid and objective conclusions.This tool is very effective in identifying all the factors that together impact the output responses.

Role of DOE-

- Gain maximum information from a minimum number of experiments
- Study effects individually by varying all operating parameters simultaneously
- Take account of variability in experiments, operators, raw materials, or processes themselves
- Identify interactions among process parameters[14]

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3.3. Process Analytical Technology (PAT)

A system for designing, analysing and controlling manufacturing through timely measurements of critical quality and performance attributes for raw and in-process material and process with the goal of ensuring product quality.[10]

PAT Goals:

1) Building quality
2) To enhance understanding and Control.
3) To reduce variation in process.
4) To enhance process safety.

PAT tools:

- Multivariate tools for design.
- Process Analysis (At-line, in-line, online)
- Continuous improvement and knowledge management
- Process control tool[13]

IV. ADVANTAGES

4.1 Continuous Improvement

QbD can ensure a safe and effective drug supply, while also significantly improving the quality of manufacturing performance. It is based on the principle of continuous improvement and the growing need for manufacturing organizations to increase their understanding of products and benefit from the growing knowledge base that develops as a product moves through its lifecycle. During the development phase, for example, design of experiments (DOE) are useful to identify the impact of important factors and interactions.

4.2 Change Control

Improved capabilities to support change is where the QbD approach comes into its own. If quality is built inside a product development process, the updating of regulatory documentation following any manufacturing process adaptations may only require minor variations to be made. This is because a deep knowledge of the process and its parameters has already been established and data has been collected to support any updates. This differs from the old approach, where change was avoided due to the potential of product quality being negatively impacted.

4.3 Failure Prevention

The QbD approach can provide manufacturing teams with a better understanding of the parameters of the development process. It has a deep understanding of how the process parameters work and are interlinked may also make it less likely for batch failure to occur as a result of unexpected reasons, as all possible interactions have already been evaluated and are already known. This may have the added benefit of reducing overall costs.

4.4 Consistency

Designing quality inside the process will ensure greater batch-to-batch consistency. This proven consistency will help instill better regulatory confidence in the robustness of both the process and product. This may allow for less intense regulatory oversight during registration, as well as less post-approval submissions and requests.

4.5 Right First Time

One of the goals of the QbD approach is to increase the chances of product registration being “right first time.” QbD ensures that all sources of variability affecting a process are identified, explained and managed by appropriate measures. This ensures that products consistently meet predefined characteristics and are “right first time.” Success first time not only means lean asset management for organizations but ensures that efforts are concentrated in the right areas.

4.6 Reduced Control

Possessing an extensive understanding of the processes provides a good indication of the quality of manufactured products prior to even testing them as the assurance of quality has already been built in. This reduces the need for

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controls over the intermediates and final products because real-time controls exist within the process itself. For both manufacturing organizations and their customers, this reduces time for manufacturing, testing and release, while also reducing costs.[18]

V. SOFTWARES

1. Design of Expert®(DOE)
2. MODDE®
3. Unscramble ®
4. JMP®
5. Statistica ®
6. Minitab ®[12]

VI. CASE STUDY

6.1 Capsule Development

Comparison study with traditional and QbD approaches on two products:

Tradium and Qbidium they were in the same capsule dosage form and had the same manufacturing process, but QbD was implemented only in Qbidium

Tradium studies began with making a general product description and poorly defined manufacturing process also missed critical factor in manufacturing process and reflection came as extended regulatory review time for Qbidium, QbD principles were properly implemented also risk assessment studies performed property anduse of softwares to understand critical factors

The time spent in the early development of Qbidium seems longer but gained knowledge faster and a more robust processing.

6.2 Formulation Development of Orally Dispersible Tablets

Charoo et al. studied on the development of diclofenac orally dispersible tablets through a QbD approach. QTPP was made clear. Active pharmaceutical ingredients, excipient and process attributes were determined based on QTPP, preformulation studies and previous experience. Severity of hazards and probability of occurrence were scored and risk ranking was performed. Determined CQAs such as appearance, hardness, friability, dissolution, content uniformity and disintegration time were further studied with a number of factorial design studies. The control strategy was developed after the estimation of residual risk and an assessment for its acceptability. The disintegrate amount and the compression pressure were found to be CPPs in their effects on the disintegration time and the dissolution of tablets. With various combinations of hardness and disintegrants, desired disintegration time was achievable in the larger area of design space. For the blend homogeneity, a combination of blend time, blender speed and drug particle size was selected as CPPs. With less than 7.6 kN compression force, tablets showed acceptable disintegration time and content uniformity. Adherence to design space provided the flexibility for real-time batch releasing. [17]

VII. CONCLUSION

Quality by design is an essential part of modern approach pharmaceutical quality. Quality by Design is intended to enhance process knowledge and is based on existing guidance and reference documents. QbD is a quality system that builds on past and sets future regulatory expectations; the QbD can be viewed as a process defined by series of document requirements. These documents organize and demonstrate process knowledge and understanding. QbD can be applied to legacy and new products, but the supporting document package may differ. The QbD suite of documents is “alive”. They can and should be revised as the knowledge base changes. It ensures robust commercial manufacturing methods for consistent production of quality drugs. It ensures the consumers that therapeutic equivalent generics are manufactured every single time. QbD methodology helps in identifying and justifying target product profiles, product and process understanding. There is a need for vigorous and well funded research programs to develop new pharmaceutical manufacturing platforms. The QbD process offers the chance for much greater regulatory flexibility within the future. the tactic performance criteria could potentially be registered instead of the tactic itself. the tactic used

might be referred to as an example of the way to attain the specified method performance criteria. Any changes to the present method would be covered by internal change control procedures.

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