PHARMACEUTICAL QUALITY BY DESIGN - A REVIEW

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ABSTRACT

Pharmaceutical QbD is a systematic approach of development that begins with predefined objectives and emphasizes product and process understanding and control based on sound science and quality risk management. Here the quality is planned and incorporated in the process as well as product considering and having a good knowledge of the risk involved and their management in the process. Once the knowledge of risks involved in the production of a product is gained, it is easier to eliminate the quality flaws and hence the product failure. This ultimately reduces the cost of the product and increases the confidence in and acceptability of the product

KEYWORDS: Quality Risk Management, Quality Risk Management, Quality Assurance

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The principle QbD concepts are:

a. Detailed knowledge of risks and decisions made on their basis
b. Systematic process is developed
c. Continuous improvement
d. Capable process for a reliable product

NECESSITY OF QbD

Quality by design helps industrialists, pharmacists and the patients magnificently as:

Increased Industrial Savings and Reduced Product Cost

As the quality is planned and incorporated by design prior to the process started, it streamlined the manufacturing process which minimizes the possible hurdles that may arise during the process. Also it reduces the tedious frequent quality testing and hence product complaints and recalls. This increases the efficiency of industry and reduces the cost of the product. Hence, QbD increases process capability and reduces product variability and defects by enhancing product and process design, understanding, and control.

Improvement and Innovation

By QbD there are continuous improvements of the manufacturing process from raw material to the marketed product is possible and easier as well. If some new innovative measures have to be taken, their incorporation is also facilitated.

Approval from Regulatory Bodies

Going through QbD it is easier to get approval from the regulatory agencies in first cycle only as chances of error have already been considered and minimized and/or eliminated when the process was designed. This system (i.e QbD) is more focussed on the pre approval inspections (PAI) and post approval cGMP inspections.

Product Quality can be Assured in Better Way

Processes developed by QbD gives the products with consistent and desired product with predefined specifications and thus gives better Quality Assurance and increases product reliability and product acceptance.

MATERIALS AND METHODS

Components of QbD

To improve formulation product compatibility according to critical quality attribute of drug and excipients

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components, the following key components are required for the implementation of QbD.

1. Defining and designing the quality targeted product profile (QTPP) including the critical quality attributes (CQAs).
2. Consideration of critical process parameters (CPPs) required in designing the product.
3. Designing the process considering the identified CPPs and risk management.
4. A well designed control strategy including each and every step of process capability and control of specifications for active and not active ingredients.
5. Continuous improvement of process.

QTPP

It is the summarized predetermined standards of the products that must be achieved for the desired product considering the safety and efficacy of the product. It forms the basis for the development of process and sets the desired development goals. QTPP includes considerations of all steps from manufacturing to clinical use like dosage form and strength, packaging, ADME, quality control parameters etc.

The next step to QTPP is CQAs which includes all the physico-chemical to microbiological parameters of the raw material as well as the finished and marketed product. These parameters must be sufficiently controlled to comply with the regulatory guidelines as well as the safety of the patients.

Product- Designing and Understanding

Since earlier the QbD was concentrated on the process design only. But it is felt that without the knowledge of product it is not possible to give the quality to a product. Before designing the product it also important to understand the product (i.e. in which environmental condition the product will going to be used, its stability study etc.). In product design the priority is given to the needs of ultimate user of the product i.e. patients. The product designed must be easily acceptable to and fulfil clinical requirements of the patients. The delivery of the medicament must be maintained throughout the shelf life of the product. These are some examples which indicate that the product designing is must.

The main parameters of product designing and understanding are listed below.

1. Physico-chemical and biological understanding of the APIs and additives.
2. Drug interactions between the APIs and additives and the APIs-additives.
3. Assortment and knowledge of additives.
4. Considerations of CMAs for APIs and additives.

The understanding of physical and chemical properties along with their biological properties must be considered for designing and developing a product. In physical property, their melting point, colour, texture etc are taken. While in chemical studies their solubility, interactions, pH, dissolution rate, stability etc are considered. Biological understanding is required for their ADME, bioavailability, half life, adverse effects etc.

Before the manufacturing of product, CQAs should be considered. Drug Interactions between the two or more additives like binders, glidants, lubricants, colours, preservatives etc are to be considered. Besides this the interaction in between the two APIs (active pharmaceutical ingredients) and between the APIs and additives must also be considered. As the interactions could spoil the product and harm the patient as well.

Additives are identified and selected based on the final formulation which is going to be designed. Their properties like lubrication, binding, coating etc give vast effect on the product formulation. It should be noted that the additives are selected based on their role in the pharmaceutical formulation. A list of functional additives has given in USP/NF. The safety limits of additives are also given by the FDA.

Additives or excipients are the parts of the formulation other than the API. They can be a major source of variability. They effect the stability, bioavailability, appearance etc of the product greatly. But then also the basis of selection is not well defined. Perhaps they are selected without any solid reason. This may cause loss of raw material, labour and time, which are most important for an industrialist. To facilitate the early prediction of the additive-API compatibility studies are recommended in ICH Q8 (R2). Great advantages can be gained by systematic compatibility study of additives. These advantages can be:

a. Stability failures which can delay the production time and cost, can be reduced.
b. Increased shelf life of the product.
c. Increased stability of a product formulation.

Formulation standardization studies are essential for developing a standard formulation which is failure free. Without optimization studies, a formulation is more likely to be high risk because it is unknown whether any changes in the formulation itself or in the raw material properties would significantly impact the quality and performance of the drug product . Here the quality is planned and incorporated in the process as well as product considering and having a good knowledge of the risk involved and their management in the process. Once the knowledge of risks involved in the production of a product is gained, it is easier to eliminate the quality flaws and hence the product failure. This ultimately reduces the cost of the product and increases the confidence in and acceptability of the product.

Process Designing and Understanding

For manufacturing a pharmaceutical product of desired quality, a systematic sequential series of unit operations are required. When all the sources of variability in a product are identified, and pre-established PQAs are considered to manage them, than only the process is said to be well understood and is under QbD.

Operating parameters (e.g., speed and flow rate) or process state variables (e.g., temperature and pressure) of a process step or unit operation are referred as the Critical Process Parameters. A process parameter is critical when the variability which has been produced impacts on the critical quality attributes and hence should be controlled to ensure the process produces the product of desired quality. Under this definition, the state of a process depends on its CPPs and the CMAs of the input materials.

Risk Assessment

ICH Q9 quality risk management indicates that "the manufacturing and use of a drug product, including its components, necessarily entail some degree of risk.… 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.

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 non-exhaustive list of common risk assessment tools as follows:

- Methods of risk management at the base and facilitation methods (check sheets, flow-charts etc.)
- Fault or error tree analysis
- Ranking and filtering the risks
- Preliminary hazard analysis
- Hazard analysis and critical control points
- Effect of failure mode on analysis
- Failure mode, its effects, and their criticality analysis
- Hazard operability analysis
- Supporting statistical tools

CONCLUSION

This review is based on implementing pharmaceutical QbD which reduces the product variability and defects, and improves the development and manufacturing effectiveness and the change management of the product after the approval is granted. It is achieved by designing a robust formulation and manufacturing process and establishing clinically relevant specifications. QTPP, product design and understanding, process design and understanding, scale up, control strategy, and continual improvement are the key parameters of implementing QbD. Prior knowledge, risk assessment, DoE, and PAT are also other factors which facilitate QbD implementation. Finally, assessment of product and process capability and continually improved product lifecycle after approval is also reviewed. Multivariate data acquisition and analysis, process analytical techniques, process monitoring and control continuous process optimization and knowledge management. For the formulations which are on high risk

and the other process variables which could effect the quality of the product, risk assessment is mandatory.

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