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QbD- AN INTRODUCTIVE APPROACH

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ABSTRACT

In the stage of the development of different innovative methods, quality is a prime factor of importance. The principles of quality have been described by the International Conference on Harmonization (ICH) guidelines: Q8 Pharmaceutical development, Q9 Pharmaceutical quality risk management and Q10 Pharmaceutical quality system. Quality-by-design (QbD) is a recent attribute which has been added as an annex to ICH Q8. It is a scientific approach that helps to build in quality into the product rather than testing of the final product. For the implementation of QbD various tools are needed to be used which have been described briefly. Risk assessment approaches, process analytical technology tools and mathematical, statistical and continuous improvement tools are important elements of quality by design, which mainly focus on the identification of critical parameters and defining a design space statistically. The basic principles of these three ICH guidelines with regard to quality of pharmaceutical products have been briefly discussed.

Keywords: ICH, QbD, Pharmaceutical Development, Risk Assessment.

INTRODUCTION

Quality by design is a systematized approach for the development of a product from the beginning with predetermined objectives and process perspective and process standard based on sound knowledge and product quality risk management [1].

The aim of development of a pharmaceutical product is to develop a design for the product with quality and the manufacturing process to produce predetermined performance of the product [2]. The performance of the product is gained by product development studies and manufacturing experience that are implemented for the scientific understanding to establish design space, specifications and processing controls [3].

The pharmaceutical development study is constructed on the quality risk management to recognize that quality that cannot be tested in the products and therefore quality should be intensified by design. Quality risk management is the key element for the development and implementation of Quality by design that enables resources to focus on the perceived condemnatory areas that influence product and process [4].

The objective of the pharmaceutical development of a product is to design the quality and processing methods to produce an intended performance of the product. The knowledge of a pharmaceutical product development renders the type of dosage form selected and the proposed formulations are acceptable for the intended use [1,5]. The pharmaceutical development of the products is dependent on the aspects of drug substances, excipients, container closure systems and manufacturing processes are gained to obtain critical quality product be determined and rationalize control strategies. Parameters like critical formulation attributes and process parameters are to be identified via an assessment of the stretch to which their variation can possess impact on the drug product quality[1]. Pharmaceutical development of a product leads to intensify/ strengthen the knowledge of product performance to manifest the higher degree of knowledge of material characteristics, manufacturing processes and their

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controls. Due to the facilitation by scientific understanding design space are expanded to situations, opportunities for development of more flexible regulatory approaches like

- Risk based regulatory resolution (reviews and inspections).
- Advancements in manufacturing process, that are within approved design space reported in dossier, without any extent of regulatory review.
- Minimization of post approval
- Real time quality control, essential to a reduced finished product release testing.

By understanding the attributes for the procurement by formal experimental design, process analytical technology (PAT) and/or preceding knowledge. Quality risk management principles are used to prioritize as suitable use for additional pharmaceutical development studies intended for scientific purpose to be compatible. The level of knowledge procured that is recognized, are based on the development of product but not on the volume of data acquired that contribute to the basis for science based submissions and its regulatory evaluation[1].

The pharmaceutical development Q8 is annexed with quality by design to show how concepts and tools (e.g. design space) are outlined instead to establish new regulatory requirements or to initiate new standards. The quality by design approach establishes the key model for developing the quality based product by use of quality risk management tools associated with appropriate pharmaceutical quality system, to strengthen knowledge and risk built regulatory requirements [6].

Pharmceutical Developmetal Approaches

The product is designed to meet the patient's requirement and intended product performance. Product development strategies vary from company to company and from product to product. The development of product is chosen either by a feasible approach or a more systematic approach or a combination of both.

More systematized approach is incorporated for the development of the product by prior knowledge that results in studies by use of design of experiments, use of quality risk management and use of knowledge management throughout the lifecycle of the product. To enhance desired product quality, it is achieved by systematic approach and help the regulators to better knowledge of a company strategy.

Elements are favorable for the pharmaceutical development namely:

- Defining Quality Target Product Profile (QTTP) associated to product quality, safety and efficacy accordance to the dosage form, route of administration, strength, bioavailability and stability.
- Identifying prospective critical quality attributes (CQA) of the drug product, so as to possess impact on the product quality by product characteristics are to be considered and controlled.
- Establishing the critical quality aspects of the API, excipients to drug delivery of desired quality.
- Selection of process of manufacturing.
- Defining control strategy.

Quality by design concept for an enhanced product development include the following elements:

- Manufacturing process with systematized evaluation, understanding and improvisation of the formulation includes:
- Identifying CQA's of an approach with prior knowledge, experimentation and risk assessment to have effective material aspects and process parameters.
- Determining function relationships to associate material aspects and process parameters to produce product CQA's.

Use of process understanding with enhanced produced development to establish selective control strategy for proposed design space and or real time release testing[1].

Pharmaceutical Development Elements

The elements are favored based on the approaches to gain a more systematic enhanced knowledge of the product during processing development.

Quality Target Product Profile

The QTPP acts as the fundamental aspect to propose the development of product. They are produced by considerations like pharmaceutical use in clinical ambience, dosage form and route of administration, delivering systems, dosage strength, container and closure system. Drug product is based on the therapeutic affiliation for release or delivery that affects the pharmacokinetic characteristics with appropriate dosage form developed. Quality criteria of drug product is intended for market product to ensure sterility, purity, drug release and stability [7-9].

Critical Quality Attributes

A CQA designs the product from its physical, chemical, biological or microbiological property or characteristics should meet its limit or specification, range or distribution to ensure desired product quality. CQA's are affiliated with the drug excipients, materials for in process and drug product.

The aspects of solid dosage form CQA's are typically which affect the purity, concentration, drug release and stability. CQA's for alternative delivery systems include more definite aspects, such as aerodynamic properties for parenteral with inhalation stability and adhesion properties for transdermal patches.

CQA's are additionally included for API's, raw materials and intermediates those properties like bulk density, particle size distribution that affect drug product CQA's. CQA's derived from quality target product profile and preceding knowledge are used to escort the process and product development for potential drug product.

The CQA's of potential product are to be modified for the increase in formulation and process of manufacturing are selected based on the product knowledge and perspective of a process.Quality risk management are used to compute the list of probable CQA's for consecutive evaluation.Repetitive process of quality risk management and analysis to assess the extent at which their variation impacts on the drug product quality by relevant CQA's [10-13].

Risk Assessment: Associating Material Attributes And Process Parameters To Drug Product CQA's

Risk assessment is an important science based process used in quality risk management are used for the assistance in identifying material attributes and process parameters potentially affect the product CQA's.

Risk assessment are consistently performed before in the development of pharmaceutical process and is reproduced as more information develops into accessible and superlative knowledge is obtained. Schematic diagram of risk management tools is given in Fig. 1.

Tools of risk assessment are developed to identify and parameters for process, equipment, input materials that impact on product quality based on preceding knowledge and initial experimental data. The introductory list of parameters are quite extensive that can be altered and computed by more consideration like combination of design of experiments, mechanistic models. When the significant parameters are identified they are studied to achieve higher level of process perspective.

Identification of hazards, analysis and evaluation of risks which are related to the exposure of those hazards are called risk assessment. Quality based risk assessments commence with a well-defined problem characterization or risk investigation.

As the risk in question explicated, an appropriate risk management tool and the types of knowledge that will approach the risk question that are more identifiable. The aid of defining the risk for assessment purpose, three fundamental questions are helpful: What might go wrong? What is the probability it will go wrong? What are the severity?

Risk identification is a systematized use of information to identify hazards attributing to the risk question or problem characterization. Information includes historical data, theoretical analysis, informed opinions and the concerns of stakeholders. Risk identification approaches "what might go wrong?" question, including identifying the possible consequences. This contributes the basis for future steps in the quality risk management process.

Risk analysis is the evaluation of risk associated with the identified hazards. It is one of the qualitative and quantitative process of associating the probability of occurrence and severity of harms. In some of the risk management tools, the qualification to detect the detectability or harm also affects in the estimation of risk.

Risk evaluation correlates the identified and analyzed risk against given specification risk criteria. Risk evaluations scrutinize the strength of confirmation for all three fundamental questions. In the accomplishment of an effective risk assessment, the robustness of the data is important as it determines the quality of the product. Revealing expectations and acceptable sources of uncertainty enhance confidence in its output or help identify its limitations. Uncertainty is occurred due to combination of inadequate knowledge about a process and its expected or unexpected variability. Uncertainty typical sources include inconsistency in knowledge, inconsistency in pharmaceutical science and process perceptive, sources of harm (failure of a process or source of variability) and detection of probability problems. The output of a risk assessment is either a qualitative description or a quantitative estimate of risk with respect to the range of risk. The risk is expressed qualitatively by descriptors such as "high," "medium," or "low" that as to be detailed. The quantitative risk is expressed by numerical probability used. Consistently a risk score is used for descriptors to define in risk ranking. Quantitative risk assessments, a risk estimate provides the probability of a specific consequence provided by a set of risk-generating occurrences. Quantitative risk estimation is thus useful for a particular consequence at a time. Some of the risk management tools are alternatively used for a relative risk measure to combine multiple levels of severity and probability to an overall estimation of relative risk. Quantitative risk estimation employs intermediate steps within scoring process.

Risk control includes decision making to reduce or accept risks. The need of risk control is to minimize the risk to an acceptable level. The extent of effort implied for risk control should be proportional to the influence of risk. Decision makers use different processes, including benefit-cost analysis, for perceptive the optimal level of risk control. Risk control focuses on the following questions: Is the risk above an acceptable level? What to be done to reduce or eliminate risks? What is the appropriate balance among benefits, risks and resources? Are any new risks introduced as a result of the identified risks being controlled?

Risk reduction focuses on processes for mitigation and avoidance of quality risk that exceeds a specified acceptable level. Risk reduction includes actions to mitigate the severity and probability of harm. Improve processes detectability of hazards and quality risks also be used as part of risk control strategy. Implementation of risk reduction measures introduces new risks into the system or increase the consequences of other existing risks. Hence, it is appropriate to revisit the risk assessment to identify and evaluate any changes in risk after implementing a risk reduction process.

Risk acceptance is a decision to accept risk. Risk acceptance is a formal decision to accept the residual risk or it can be a passive decision in which residual risks are not specified. Few risk harms have best quality risk management practices that not entirely eliminate the risk. In this prospect it is agreed that a convenient quality risk management strategy is applied and that quality risk is reduced to a specified acceptable level. This acceptable level is dependent on many parameters and should be decided on a case-by-case basis.

Risk communication

Risk communication is the information sharing about risk and risk management between the decision makers and others. Parties communicate at any stage of the risk management process. The result of the quality risk management process is communicated and documented appropriately. Communications include interested parties (like regulators and industry; industry and the patient; within a company, industry, or regulatory authority). The information includes to existence, nature, form, probability, severity, acceptability, control, treatment, detectability or other aspects of risks to quality. Communication is not carried out for each and every risk acceptance. The information between and regulatory authorities, communication concerned in quality risk management decisions are effected through existing channels as specified in regulations and guidances.

Risk review

Risk management is an ongoing part of quality management process. Review or monitor events are implemented by mechanism. The results of risk management process are reviewed into account new knowledge and experience. Once quality risk management process is initiated, the process is continued to utilize for events that impact the original quality risk management decision, these events are planned (results of product review, inspections, audits, change control) or unplanned (root cause from failure investigations, recall). The frequency of review is based upon the level of risk. Risk review includes reconsideration of risk acceptance decisions[12,13].

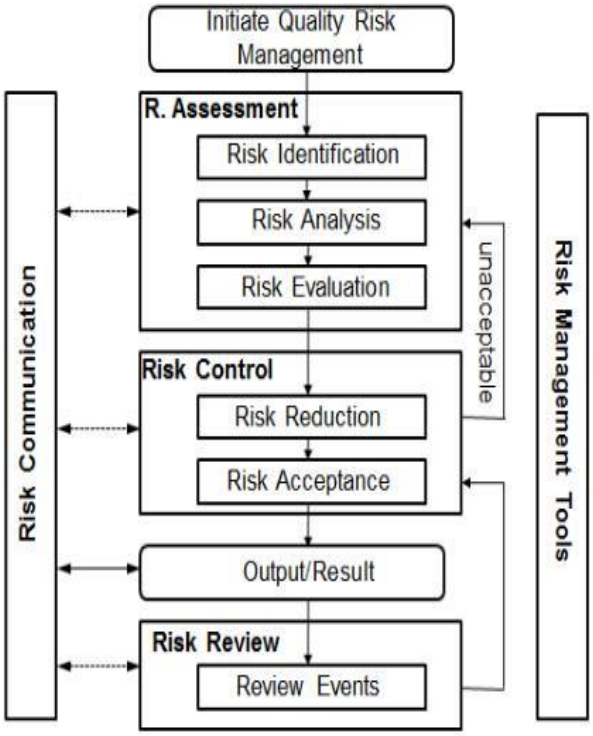

Fig. 1: Schematic diagram showing Risk Management Tools.

Design space

Design space describes the relationship between the process inputs and the critical quality attributes. The design space is based on various factors like:

Selection of variables

The risk assessment and the process development tools help in understanding the linkage and effect of process parameters and material attributes on product CQA's and these also help to identify the variables and their ranges within consistent quality are achieved. In the design space it includes the selection of process parameters and material attributes.

Description should be provided for the application of process parameters and for design space are examined for design space that are included and the effect of their product quality. The effect of inclusion in design space should be conferred. These are helpful that provides how to minimize some parameters that are excluded. Information gained by these studies are describable to submission and the parameters and attributes for process and material are not varied through development should be highlighted.

Describing a Design Space in a Submission:

A design space is characterized by ranges of material attributes and process mathematical relationship. Design space is described as a time dependent function or combination of variables like components of a multivariate model. Design space of intended span multiple operational scales are by scaling factors. Historical data analysis are favored for the establishment of a design space. Nevertheless how design space is developed, the operation expected will result in product with defined quality within the design space.

Unit Operation Design Space:

Establishment of independent design spaces are chosen for one or more unit operations, or to establish a single design space with span multiple operation. Design space with separate design for each unit operation is often simpler to develop, a design space spans the entire process that provide more operation flexibility. In case of a drug product which endures degradation in solution prior to lyophilization, the design space is used to control the extent of degradation are expressed for each unit operation or all unit operations.

Design Space relationship to scale and equipment

Describing a design space, the type of operational are to be considered for flexibility desired. Design space are developed at any scale and justify relevant at small or pilot scale to propose production scale manufacturing process and consider the prospective risks in scale up operation. Design space proposes to multiple operational scales, the design space are described in terms of relevant scale-independent parameters. If a product was determined to be shear sensitive in a mixing operation rate, other than the agitation rate. Dimensionless number or models scaling are included as a part of design space description.

Design space versus proven acceptable range

The characterized range of a process parameter for operation which in range keeping other parameters constant. This range does not constitute design space, however based on univariate range with useful knowledge are processed.

Design Space and Edge of Failure

It is used to determine the edge of failure of a process parameter or a material attributes which are quality relevant attributes are not obtained. Determination of the edge of failure or demonstration of failure modes are not effective parts to determine design space[13].

Control Strategy

The quality of the product produced consistently is designed by the use of control strategy. It describes how in-process controls and controls of input materials, intermediates and container closure system and drug products affect the quality of the final product. The controls are based on product, formulation and process parameter and the controls of the critical process parameters and material attributes to be minimized. An extensive pharmaceutical development access to generate process and product understanding by identify sources of variability.

Sources of variability include identification, understand and controlled to produce quality product. Knowing the sources of variability their downstream processed or processing, in-process materials, quality of drug product are impacted and provide shift controls for upstream and reduce the need for finished product testing.

Process and product development are estimated in combination with quality risk management are compensated for an adaptable to obtain consistent product quality. These process understanding are established for an alternative manufacturing paradigm where the variability of input materials are less constrained. Instead design of an adaptive process step with proper process control are ensured with consistent product quality. The performance of product are justified by the use of alternative approaches that determine the material to meet its quality attributes. The need of alternative method is to produce real time release testing.

E.g.: Disintegration serves as a surrogate for dissolution for fast disintegrating solid forms with highly soluble drug substances. Unit dose uniformity are performed for in-process that is used for real time release testing and to provide quality assurance increased level compared to end product testing by use of compendial uniformity content standards. Real time release testing replaces end product testing and does not replace the review and quality control steps called for GMP to release the batch.

Control strategy includes the following:

- Control of material attributes based on understanding of their impact on process ability or product quality.
- Product standards.
- Controls of unit operations that show impact on downstream processing or product quality.
- In process or real time release testing of end product testing.
- A monitoring for verifying multi variant prediction models.

Control strategy includes different elements. One element of the control strategy relay on end product testing whereas other element depends on real time testing [14].

Product life cycle management and continual improvement

To evaluate innovative approaches to improve product quality throughout the product life cycle management plays a key role for the product

development. Performance of the product are monitored to ensure the working principles are anticipated to deliver quality product attributes as predicted by the design space. Monitoring these could give trend analysis of the manufacturing process and gained during manufacturing process. For preferred design spaces mathematical models, periodic maintenance are used to ensure model's performance. The model maintenance is the activity managed within company's own internal quality system to provide design space unchanged. Expansion, reduction or redefinition of the design space are desired upon gaining beneficial process knowledge. Design space changes could subject to regional requirements [15].

CONCLUSION

QbD has gained importance in the area of pharmaceutical processes like drug development, formulations, analytical method and biopharmaceuticals. Nevertheless QbD approach gives quality product with cost effective procedures and that is the basic need. QbD replaces previously used frizzed approach of process development by providing a design space concept. Identification of critical material attributes that provides a link of the product quality to the manufacturing process. The role of control strategy as the completion of QbD elements into practice.

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