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A REVIEW ON: QUALITY BY DESIGN (QbD)

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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. It supports both industry and FDA to move towards a more scientific, risk based, holistic and proactive approach to pharmaceutical development. 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 attributed (CQA). The company then designs the product formulation and processes to meet the product attributes. This leads to understanding the impact of raw materials [Critical Material Attributes (CMA)], on the CQAs and identifies and control sources of variability. This systematic approach to product development and manufacturing has received a great deal from the traditional approach, which was extremely empirical. QbD is necessary in regulatory requirement, and to implement new concepts such as design space, International Conference on Harmonization's guidelines i.e. Q8 pharmaceutical development, Q9 quality risk management, and FDAs process analytical technology (PAT).

INTRODUCTION

Quality by Design (QbD) refers to a holistic approach towards drug development. Quality by design is a vital part of the modern approach to pharmaceutical quality. Quality by Design (QbD) was first described by Joseph M. Juran, and applied heavily, particularly in the automotive industry. [1,2,3]

Definition:

A systematic approachto development that beginswith predefined objectives and emphasizes product and process understanding and process control, based onsound science and quality risk management.[4]

Regulatory aspects:

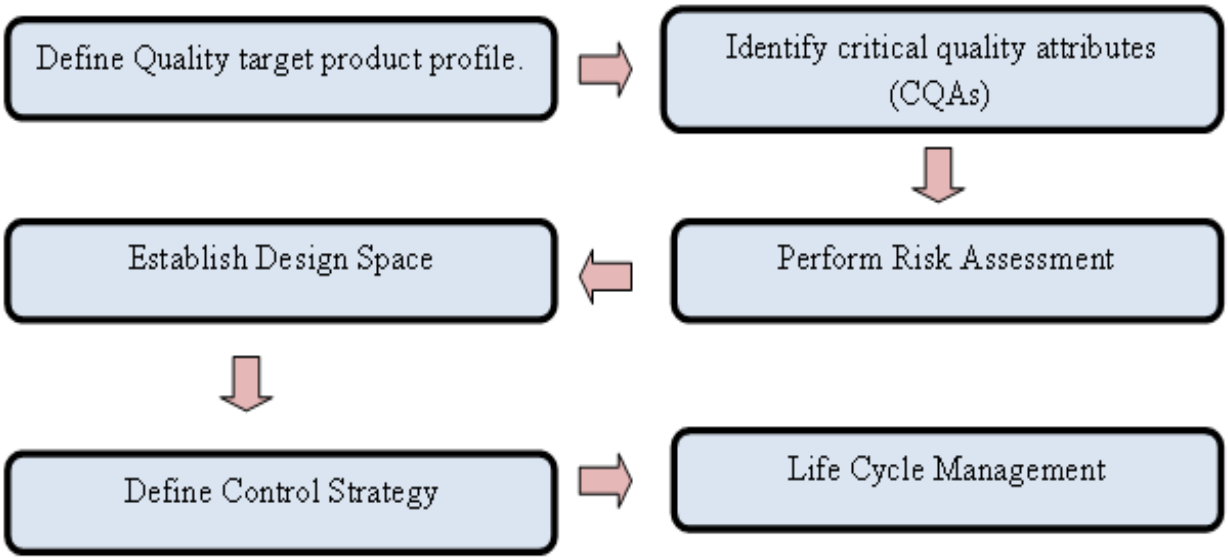
Regulatory authorities consider that incremental and unsystematic improvement in unit operations, in isolation, would only have little effect on overall process performance or quality. To assure the quality of the product, a more holistic approach provided by QbD should be adopted. QbD is defined in the ICH Q8 guideline as "a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management" [5]. In manufacturing of new or marketed products, QbD can help in pre-determining the risk potential of various operation, assuring that suitable control strategies can be applied on time. Since Qbd is a science-based approach, it provides a basis for optimizing and improving the manufacturing operation without facing additional regulatory filings or scrutiny. Furthermore, for technology transfer, QbD generated process understanding can make the transition more efficient [6].

Advantages of QbD:

- It provides a higher level of assurance of drug product quality.
- It offers cost savings and efficiency for the pharmaceutical industry.
- It increases the transparency of the sponsor understands the control strategy for the drug product to obtain approval and ultimately commercialize.
- It makes the scale-up, validation and commercialization transparent, rational and predictable
- It facilitates innovation for unmet medical needs.

- It increases efficiency of pharmaceutical manufacturing processes and reduces manufacturing costs and product rejects.
- It minimizes or eliminates potential compliance actions, costly penalties, and drug recalls.
- It offers opportunities for continual improvement.
- It provides more efficiency for regulatory oversight:
- It streamlines post approval manufacturing changes and regulatory processes.
- It more focused post approval CGMP inspections
- It enhances opportunities for first cycle approval.
- It facilitates continuous improvement and reduces the CMC supplement.
- It enhances the quality of CMC and reduces the CMC review time.[1]

Steps in Quality by design



Quality Target Product Profile

A summary of the drug development program described in terms of labeling concepts and it mainly focus on the safety and efficacy.

- Description
- Clinical Pharmacology
- Indications and Usage
- Contraindications

- Warnings
- Precautions
- Adverse Reactions
- Drug Abuse and Dependence
- Over dosage
- Dosage and Administration
- How Supplied
- Animal Pharmacology and/or Animal Toxicology
- Clinical Studies

A natural extension of Target Product Profile for product quality – Quality characteristics (attributes) that the drug product should possess in order to reproducibly deliverthe therapeutic benefit promised in the label guide to establish formulation strategy and keep the formulation effort focused and efficient .It facilitates identification of what's needed/critical for the patient/consumer in the Quality Target Product Profile (such as Critical Quality Attributes, CQAs)

- Identifies risks and best approaches to manage.
- Uses tools/enablers in an optimized fashion (such asintegration of QbD and biopharmaceutics)
- Generates and enables knowledge sharing.[7]

Critical quality attributes (CQA)

Once QTPP has been identified, the next step is to identify the relevant CQAs. A CQA is defined as "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" [5]. This indicates that CQAs are subsets of QTPP that has a potential to be altered by the change in formulation or process variables [8]. For example, QTPP may include additional quality attributes of the drug product such as strength and dosage form, which are not the part of CQA as it will not change during drug development process. However, QTTP attributes such as assay, content uniformity, dissolution, and permeation flux will also be a part of CQA as they may be altered by formulation or process variables. Identification of CQA can be performed based on prior knowledge and/or quality risk management (QRM).

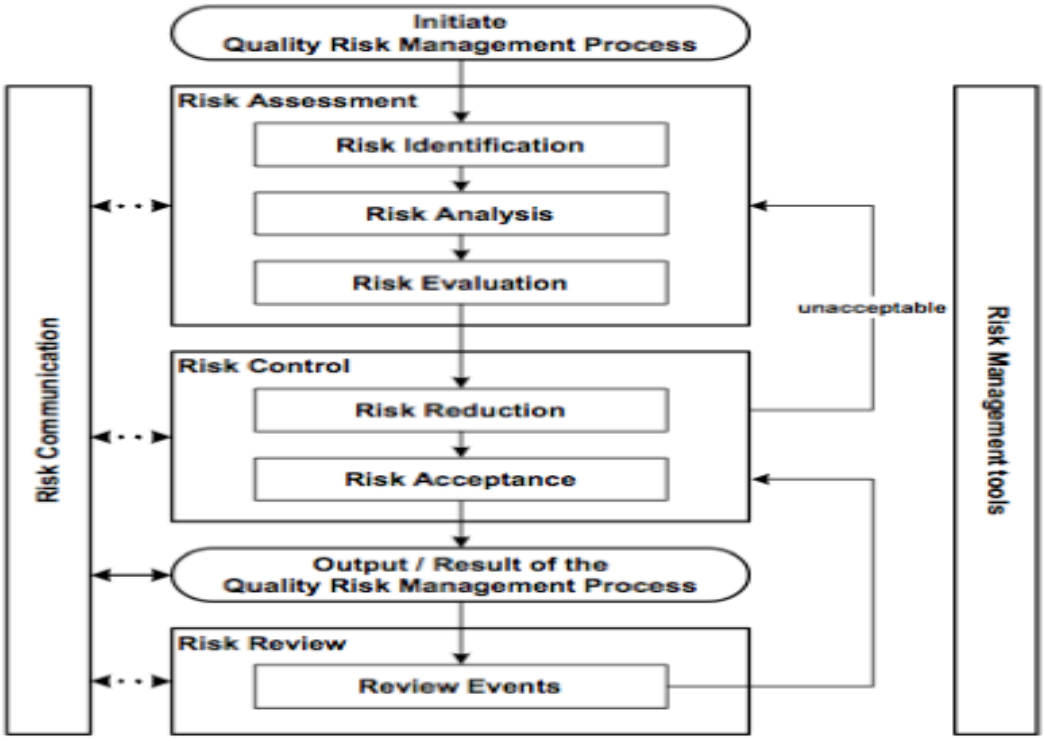
Risk Assessment Method

Quality risk management (QRM)

FDA defines QRM as a systematic process for the assessment, control, communication and review of risks to the quality of the drug product across the product lifecycle. The goal of QRM is therefore to identify risks within a process or event, analyzing the significance of these risks, and take appropriate measures to mitigate such risks if deemed unacceptable [9,10].

There are various methods for determination of risks is as follows.

1. Failure Mode Effect Analysis
2. Failure Mode Effect And Criticality Analysis
3. Fault Tree Analysis
4. Hazards Analysis & Critical Control Point
5. Hazard Operability Analysis
6. Preliminary Hazard Analysis
7. Risk ranking & Filtering



Overview of typical quality risk assessment process

1. **Failure mode effects analysis (FMEA)**

FMEA is one of the most commonly used risk-assessment tools in the pharmaceutical industry. It is a systematic and proactive method to identify and mitigate the possible failure in the process. Failure modes represent any errors or defects in a process, material, design, or equipment. Once failure modes are established, FMEA tool evaluates the effect of these failures and prioritizes them accordingly [11]. Risk control activities can then be performed to avoid such failures modes. Since FMEAs require a good understanding of cause and effects, a thorough process understanding is essential [12]

2. **Fault tree analysis (FTA)**

The fault tree analysis (FTA) was first introduced by Bell Laboratories and is one of the most widely used methods in system reliability, maintainability and safety analysis [12, 13]. FTA is a deductive analysis approach for resolving an undesired event into its causes in a top down fashion [11]. Typically, assumed failures are listed at the top as main event and all of the associated elements in that system that could cause the event are listed as subsequent branches till the root condition or cause is identified [11, 12]. The results are represented pictorially in the form of a tree of fault modes and their relationship are described with logical operators like "AND","OR", etc. [11]

3. **Hazard analysis and critical control points (HACCP)**

HACCP provides detailed documentation to show process or product understanding through identifying parameters to control and monitor [12]. The definition of hazard includes both safety and quality concern in a process or product. Examples of hazards within the pharmaceutical setting include environmental aspects of the facility (environmental conditions, hygiene aspects); material flow; manufacturing steps; personnel hygiene and gowning; and technical aspects relating to process design.HACCP consists of the following seven steps: (i) conduct a hazard analysis and identify preventive measures for each step of the process, (ii) determine the critical control points, (iii) establish critical limits, (iv) establish a system to monitor the critical control points, (v) establish the corrective action to be taken when monitoring indicates that the critical control points are not in a state of control, (vi) establish system to verify that the HACCP system is working effectively, (vii) establish a record-keeping system [11]

Design of Experiment

The design of experiment (DOE) approach, process variables are first 'screened' to determine which are important to the outcome (excipients type, percentage, disintegration time (DT) etc. Second step is the 'optimization', when the best settings for the important variables are determined. It involves the use of 'mixture designs' for changing mixture composition and exploring how such changes will affect the properties of the mixture.[15,16,17,18,19]

Advantages

- Better innovation due to the ability to improve processes.
- More efficient technology transfer to manufacturing.
- Less batch failures.
- Greater regulator confidence of robust products.
- Risk- based approach and identification.
- Innovative process validation approaches.
- For the consumer, greater product consistency.[14]

Design Space

The design space is the established range of process parameters that has been demonstrated to provide assurance of quality. In some cases design space can also be applicable to formulation attributes. Working within the design space is not generally considered as a change of the approved ranges for process parameters and formulation attributes. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. The design space is the established range of process parameters and formulation attributes that have been demonstrated to provide assurance of quality. It forms the linkage between development and manufacturing design.[14]

Design of experiments (DOE) is an efficient procedure for planning experiments so that the data obtained can be analyzed to yield valid and objective conclusions. A structured, organized method for determine the relationship between factors affecting a process and the output of that process is known as "Design of experiment". In experiments, we deliberately change one or more process variables (or factors) in order to observe the effects the change will have on one more response variables. The (Statistical) design of experiments (DOE) is an efficient procedure for planning experiments so that the data obtained can be analyzed to yield valid & objective

conclusions. DOE begins with determining the objective of an experiments & selecting the process factors for the study. A experiments design is the laying out of a detailed experiments plan in advance of doing the experiment will chose experimental designs Maximize the amount of "Information" that can be obtained for a given amount of experimental effect.

Use of Design of experiment:

Design of experiments is used to determine the causes of variation in the response, the find conditions under which the optimal (maximum or minimum) response is achieved, to compare responses at different levels of controlled variables & to develop a Model for predicting response.

Design of experiments (DOE) is an efficient procedure for planning experiments so that the data obtained can be analyzed to yield valid and objective conclusions. A structured, organized method for determine the relationship between factors affecting a process and the output of that process is known as "Design of experiment". In experiments, we deliberately change one or more process variables (or factors) in order to observe the effects the change will have on one more response variables. The (Statistical) design of experiments (DOE) is an efficient procedure for planning experiments so that the data obtained can be analyzed to yield valid & objective conclusions. DOE begins with determining the objective of an experiments & selecting the process factors for the study. A experiments design is the laying out of a detailed experiments plan in advance of doing the experiment will chose experimental designs Maximize the amount of "Information" that can be obtained for a given amount of experimental effect [20]

Key steps for Design of experiments

Obtaining good results from a Design of experiments involves those seven steps.

- Set objective
- Select process variables
- Select an experimental design
- Execute the design
- Check that the data are consistent with the experimental assumptions.
- Analyze and interpret the results.

Related definitions:

Some of the related definitions are stated below

- **Treatment:** Different combinations of conditions for rest.
- **Treatment levels:** The relative intensities at which a treatment will be set during the experiments.
- **Treatment factors (variables):** One of the controlled conditions of the experiments.
- **Experimental unit:** Subject on which a treatment will be applied & from which a response will be elicited also called measurement or response units.
- **Responses:** Outcomes that will be elicited from experimental units after treatments have been applied eq. hardness, friability (release of drug from a formulation).
- **Experimental design:** Rule for assigning treatment levels to experimental units.
- **Analysis variance (ANOVA):** Principal statically means for evaluating potential sources of variation in the responses.
- **Replication:** Observing individual response of multiple experimental units' under identical experimental conditions. It is use to detect Noise
- **Randomization:** Non- systematic assignment of experimental units to treatments.
- **Confounding:** Design situation in which the effect of one factor or treatment can't be distinguished from another factor or treatment. [19]

Screening Design (S.D)	Screening designs are effective way to identified significant main effects. The term "Screening design" refers to an experimental plan i.e. indented to find a few significant factors from a list of many potential ones.
Response Screening Design	Response screening design involves just the main effects & interactions or they may also have quadratic & possibly cubic terms to account for curvature model which may be appropriate to described a response
Fractional Factorial Design	Full factorial experiments can requires may runs. The solution to this problem is to use only a fraction of the runs specified by the full factorial design. In general, we pick a fraction such ½, ¼ etc. of the runs called for by the full factorial.

Placket – Burmam Design	These designs have run numbers that are in multiple of 4.placket Burmam (PB) designs are used for screening experiments because in PB designs, main effects are, heavenly confounded with two – factor interactions.
Box- Behnken Design	The Box- Behnken Design is an independent quadratic design which does not contain an embedded factorial or fractional factorial design. These designs are rotatable (or near rotatable) & requires 3 levels of each factors.

Type of design experiment commonly used

Control Strategy

Control strategy is defined as "a planned set of controls, derived from current product and process understanding that assures process performance and product quality". The control strategy in the QbD paradigm is established via risk assessment that takes into account the criticality of the CQA and process capability.

The control strategy can include the following elements: procedural controls, in process controls, lot release testing, process monitoring, characterization testing, comparability testing and stability testing. It is worth noting that the use of risk assessment in creating the control strategy is unique to the QbD approach [21].

A control strategy may include input material controls, process controls and monitoring, design spaces around individual or multiple unit operations, and/or final product specifications used to ensure consistent quality. A control strategy is what a generic sponsor uses to ensure consistent quality as they scale up their process from the exhibit batch presented in the ANDA to commercial production. Every process has a control strategy right now. The finished drug products are tested for quality by assessing if they meet specifications. In addition, manufacturers are usually expected to conduct extensive in process tests, such as blend uniformity or tablet hardness. Manufacturer are also not permitted to make changes to the operating parameters (a large number of UPPs) specified in the batch record or other process changes without filling supplements with the FDA [22]

Life Cycle Management

Life cycle approach differs from that of the traditional approach of method development.

According to Elaine Morefield (Deputy director USFDA) it includes continuous improvement of method performance and the design space allows flexibility for continuous improvement in analytical method can be done without prior regulatory approval because of design space made previously. Knowledge gained from risk assessment & data collected from design of experiment can be used as the repository of knowledge to make justified change whenever required.[23]

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