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Review on Quality by Design Approach (Qbd)

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Abstract:-

In pharma world QbD is one of the utmost influential tactic to confirm quality of the pharmaceuticals. By means of regulatory aspects QbD is based on ICH guidelines Q8, Q9, Q10 (where as Q8 stands for pharmaceutical development, Q9 stands for quality risk management and Q10 stands for pharmaceutical quality systems). In this review it explains how QbD can be achieved, what are the benefits and drawbacks of QbD and the modules, software's and the experiments conducted based on QbD are explained and it also elucidates about the QbD tools (such as risk assessment) in order to lessen the errors in the process to assure the quality of the pharmaceuticals .

Introduction To Qbd:-

The concept was developed by M.Juran in the early's 1970, later QbD concept was instigated into the pharmaceutical industry utterly held up in 2004, hence QbD is not a new concept but old one.

According to [Ich Q 8(R1)]:-

QbD it's 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.

QbD is important in pharmaceutical quality in terms of appropriateness of drug substances or drug product for deliberate use, if quality failures it leads to consequences like lack of therapeutic effect, lack of money and toxic effect.

Why QbD:-

- QbD ensures unfailing product quality.
- QbD is essential to maintain the product eminence by diminishing the sources of deviations completely over the manufacturing process.
- QbD is used to develop a new technique during the product life cycle.
- Enables innovation.
- Facilitates risk based regulation.
- Facilitates lesser amount of product recall which implements profit for the company[1][2].

Advantages of QbD over OFAT (one factor at time):-

Where OFAT experiment is based on varying one independent factor while keeping other factor constant hence in a QbD, designed experiment is more current way to determine the impact of two or more factors on a response than a QbD experiment because..,

- DOE requires fewer resources
- Methodically interaction between the factors can be estimated where in OFAT experiment interactions are not possible.
- Design experiment can elevate the setting of factor whereas OFAT can miss it [3].

Elements of Qbd:-

Fig .1 elements of QbD

Elements of QbD is shown in fig.1

QTPP:- It describes the product profile like unit doses, quantity of active drug constituents to excipient and explains how a drug will enter into body, which will ensures a desired quality of a product by considering the overall overview of characteristic individualities about the drug product which ensures a safety and effectiveness of the manufactured goods[4].

CQA:-

- It governs the criticality associated with the

method like disintegration, dissolution, assay which may affect the physical, chemical, biological property of the product, in which these properties has to be within the limitations to confirm the preferred standard product.

- CQA are interconnected with excipients, drug product, drug constituent, intermediates, unfinished materials.
- Phases of CQA may vary based on dosage form, for example.., in solid oral dosage form CQA's are stereotypically those aspects which affects the product strength, purity, stability, release of drug, while addition of more specific aspects to the product takes place like modernized properties for inhaled products, desolation for parenteral.
- Risk assessment can be used to arrange the grade of prospective CQA's for successive estimation [5].

An example for CQA work is shown in TABLE.1

TABLE .1 an Example for CQA work

DRUG	INFERANCE	TOOL/ MODULE	SOFTWARE	REFERANCE[6]
Ibuprofen	In this study DOE was used as a dominant means to examine the outcome of CPP taking place on a CQA of ibuprofen tablet for establishing a design space by means of a less hazard.	DOE was achieved using unsclambler –X	Norway, CAMO software.	Reference no :6

Risk assessment:-

It is a method used for identifying problems or failure of the product by examination throughout the process, which analyses what can go wrong, what are the possible significances and by using risk assessment tools, it will reduces or eliminates the risk related consequences and it relates a material attributes and method parameter to CQA's[7].

Critical material attribute: -

The critical attributes such as physical, chemical, biological property are allied with the raw materials, starting materials, reagents and inprocess materials. These material attributes can be fixed or sometimes can be changed during processing [8].

Example: - impurity profile, porosity.

Critical process parameter (CPP):-

These are the critical parameters in the ongoing process of product manufacture, which is scrutinized within the limits to get the product of its predetermined strength, purity and safety.

Design space:-

- It is the affiliation between the process parameters, material characteristics and critical attributes that must be demonstrated in multidimensional combination to afford reassurance about quality.
- In design space a change is measured when the movement is outside a design space as of that normally initiates a regulatory post approval changes but occupied inside the design space is not measured to be a variation.
- Design space may be governed as per unit operation (e.g... distribution, purification) and this unit operation will be selected constructed on their impact on CQA's in a design space [9].

Control strategy:-

- It is an established method which controls drug substance, equipment operating conditions, inprocess control, specifications which are derived after understanding the process and refining the process performance and its effect.
- The origins of this method will designate and validate how in-process controls, intermediates and manufacturing goods will subsidise to the end marketed product quality and these controls will be constructed on methodology, manufactured goods, method understanding with a slightest rheostat of the critical process parameters and material attribute.
- Progress of control strategy could be done with a blend of methods, exploiting the out-dated approaches for a small number of CQA's or unit operation.

Control strategy compromises of:-

- Control of drug constituent, excipients, 1°packaging materials established on their effect on product stability.
- This method can include product specification.
- When the quality of a product is been effected during manufacturing procedure control strategy can be applied [10].

Modules used in QbD:-/ how can we achieve QbD?

Mainly achieved by:-

TABLE 2: Most commonly used DOE design

Sl.no	Design name	uses
1	Custom design	It creates a design tailored to meet the specific requirements.
2	Augment design	More runs will be added to an existing data table; model items will be added.
3	Definitive screening:- In this method mainly two types of designs will be used... a)Definitive screening design b)Fit definitive screening design	a) It creates a screening design where main effect estimates are unbiased by second –order effects. b) For definitive screening design fitting and mode selection will be performed.
4	Classical design:- Mainly consists of a) Screening design b) Response surface design c) Full factorial design d) Mixture design e) Taguchi arrays	a) It sifts through many factors to find the few that have the most effects. b) It finds the best response allowing quadratic effects c) It generates all possible combinations of the specified factor settings. d) Optimizes a recipe for mixture of several ingredients. e) Makes inner and outer arrays from signal and noise factors.
5	For special purpose these type of designs will be used:- a) Space filling design b) Accelerated life test design c) Non –linear design	a) It designs for computer simulation modelling. b) Designs an accelerated life test experiment. c) Creates an optimal design for models that are non-linear in the parameter [12].

- DOE
- RA
- PAT

Design of experiment:-

it is an a standardised method to regulate relationship amongst the input and output factors of various process or in other words it is about creating an entity of experiment that works together to explore the interesting region[11].

Most commonly used DOE design is shown in TABLE.2

Different software's will be used to perform DOE they are:-

a) Minitab
b) Statistica
c) SAS
d) SPSS
e) Design –Expert
f) Statgraphics
g) Prisma [13]

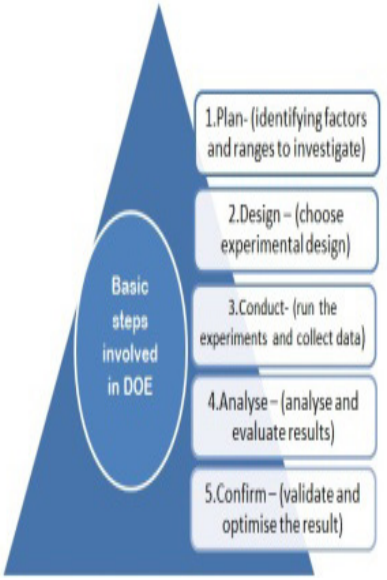

Fig 2: Basic steps involved in DOE

Basic steps involved in DOE are shown in fig.2

Benefits of DOE:-

- Defines the cause and effective relationship by exploiting the non-dependent variable to detect the influence on dependent variable in an experimental design.
- DOE abolishes the unwanted variables in the experimental design.

Risk assessment:-

Is a schematised and sequential process used for detecting, scrutinizing and evaluating risk and also for imparting and evaluation of the hazards to maintain the purity of marketing product.
Steps involved in risk assessment are shown in fig.3

Fig 3: Steps involved in risk assessment

TOOLS UTILISED IN RISK ASSESSMENT:-

a) Failure mode effective analysis :-

- In this process once the potential analysis failure modes are recognised by using risk reduction they can be eliminated, reduced or controlled.
- FMEA may be applied to equipment or facilitates to identify the problems which might affect the method.
- FMEA helps in reducing the progress time and cost with the help of a team, who categorises the potential modes grounded on the earlier practise with comparable problems, empowering the squad to strategy those flops available of the scheme with in the slightest of exertions and resources expenses.
- FMEA prioritizes the risks based on critical failure modes associated with the

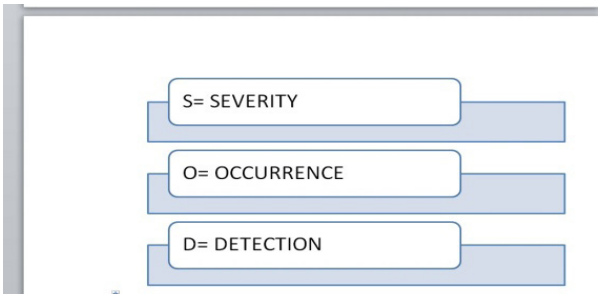

fig .4 : rpn formula

TABLE:3 Example for FMEA work

Tool	Equipment	Inference	Reference [16]
FMEA	C N C grinding machine	Aim of this case study is advance equipment system consistency and enhances safety functioning of CNC grinding machine by adopting the innovative technologies integrated operational aspects.	Ref .no: 16

TABLE: 4 Example for Hazard operability analysis

DRUG	TOOL	SOFTWARE	INFERANCE	REFERANCE[17]
Eprosartan mesylssssate	Design space	Design expert	QbD was implemented in this study to considerate CPP's and CMA's tangled in development of eprosartan mesylate Nanosuspension through sono precipitation procedure. Where QRM was used to identify the critical parameter affecting the design space and particle size which was initiated by utilising design expert software to get Nanosuspension of preferred physicochemical properties which enhances the solubility and dissolution because of a size reduction in a particle and condensed crystallisation as a result upgraded solubility and permeability demonstrated by eprosartan mesylate Nanosuspension explanations for better in-vivo production by complete bioavailability.	Ref.no 17

process or design using RPN to appraisal the risk into three categories.
i.e.. RPN= S×O×D
rpn formula is shown in fig .4

An example for FMEA work is shown in TABLE:3

b) Failure mode, effects and criticality analysis:-

- This method is an allowance of FMEA tool to integrate an exploration of degree of harshness of the consequence, thus probability of occurrence, detectability can become a FMECA.
- FMECA recognises and evaluates the criticality or failure modes related with the product and this criticality will be considered as a risk, if the risk is too high corrective actions must be taken.
- FMECA is exploited in pharmaceutical industry based on disasters and threats allied with the procedure.

C) ***Fault tree analysis:-***

- It's an a process utilised to evaluate how multiple factors affect to issue by representing all the causes or fault modes in the pictorial form of tree in a top down fashion where the expected inadequacy are enlisted at the uppermost as an leading event and the related events are listed down as a succeeding branches till all the root causes are identified.
- FTA is applied while exploring the abnormalities to completely perceive the source or cause in order to certify that improvements will decides issues and not leads to additional issues.

a) ***Hazard analysis and critical control points (HACCP):-***

- Is an organised method which assures product is of quality, safety by categorizing, controlling and preventing the hazard allied with design, development and production and of product or in other words it is utilised to identify and manage hazards related with different types of hazard such as physical, biological chemical risk.
- HACCP reports complete documentation throughout the process by ascertaining the parameters to control and monitor.

It encompasses 7 steps:-

1. Conduct hazard analysis and identify preventive measures for each step of process:-
    - Identify the hazard it may be like physical, chemical, biological hazard that affects the procedure.
    - Recognize the phases that risks expected to happen and choose which threats are important or non- significant and determine the essential measure to govern hazard in order to ensure product safety.
2. Determine critical control points: -it is a point where the preventive measures will be utilised to avoid, eradicate or decrease the hazard to tolerable level.
3. Establish critical limits: - critical limits will be established to a maximum or minimum limit in process, in order to inhibit, exclude or lessen hazard to suitable level.
4. Critical control point monitoring: - is done to direct whether critical control point is within the threat limits in the procedure or not.
5. Establish corrective to be taken when deviation occurs: - it's done to correct and eradicate the source of hazard and bring back critical control point in order to prevent future reoccurrence.
6. Establish verification process:-verification procedure is a step which proves HACCP plan and shows the system is operating accordingly.
7. Establish records keeping system:- to show effective application of HACCP documentation and record keeping will help.
8. Review of HACCP:-
    - Review of HACCP design, plan, structured will be done whenever there is change in operation.
    - The system should be reviewed even when there have been changes.

b) ***Hazard operability analysis :-***

It's a brainstorming technique, which helps to ascertain the probable deviations from regular use or design intent by applying the director words such as no, additional, other than etc...are useful to relevant parameters like adulteration, heat within parts of the process which will be operated by a team who are expertized in design or procedure or marketed product and its application and helps to identify the improvements in process to reduce risk[14][15].

An example for hazard operability analysis is

shown in TABLE: 4

PAT-process analytical technology:-

- PAT is constructed on the premise that "Quality cannot be tested into product; it should be built –in or should be by design.
- Hence PAT is an agenda for planning, scrutinizing and governing manufacturing method through appropriate quantities.
- It's about a processing of CQA and CPA of raw and in-process material and process with aim of "Build quality into marketed product" by reducing variation in manufacturing.
- According to this guideline, in PAT the term analytical is broadly viewed as physical, chemical, microbiological and risk scrutiny accompanied in an incorporated manner.

Quality benefits of PAT:-

To build quality into products: -

- Correlates the effects and variables in the preparation process which directly affects the quality of the product. Variables include environmental, process and material variables.
- Develops an effective risk management strategy in process understanding.
- Manufacturing process is improved throughout the product life cycle by applying the PAT.

Advantages of PAT: -

- Lessens production cycle times.
- Prevents rejects or re-processing.
- Provides detailed control strategy on actual release.
- Process automation leads to safety by reducing human interface which is mainly responsible for contamination.
- Helps in bulk manufacturing.
- Reduces burden for validating/revalidating

Process analytical technology: -

- For scientific, manufacture, quality assurance, risk-managed pharmaceutical development many tools are available which enables the process understanding.
- Process analytical tools helps in effective knowledge gaining by understanding the process and helps in risk control approaches [21].

Tools categorised in PAT framework are : -

i. **Multivariate tools for design, data acquisition and analysis: -**
   - These are multivariate mathematical tools used for process simulation, design of experiments which are based on the statistical data and recognition of patterns.
   - Methodological experiments give effective understanding and identification of variables interfering with product and the process; this is purely based on the statistical ideologies. Reference and indiscrimination of one factor at time experimentations will not show any interaction amongst the manufacturing variables.
   - These multivariate tools particularly identify and analyse the factors which directly disturb the stability of the product.
   - Based on the effects of these variables, potential failure modes of the product can be quantified.

ii. ***Process analyser: -***
These are the tools and techniques typically used in the univariate measurement of process factors such as temperature, pH and pressure which are the attributes of physical, chemical and environmental variables.

Measurements can be of three types as follows: -
- In-line
- At-line
- On-line

In-line: - In this type, the sample is analysed in the real time process.

On -line: - In this type, the sample is side-tracked from the process and analysed; if the sample is within the controlled limits then it is returned to the process if not discarded.

At-line: -In this type, sample is isolated and analysed; analysis should be in the process environment.

iii. ***Process control tools:*** These tools provide strong control over the critical quality attributes of the marketed product by analysing the interaction between the developed process and designed product.

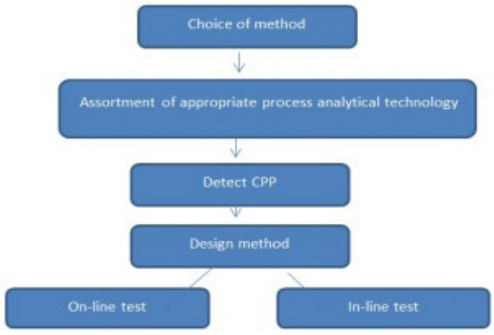

Fig.5 Mechanism of PAT

Mechanism Of Pat: -

Mechanism of PAT is shown in fig.5

- Designing the process controls to ensure the control over the critical attributes of the product.
- Mathematical relationship is established amongst the method and material measures with the quality characteristics of the product.

iv. Continuous improvement and knowledge management: -

- Comprehensive understanding by accumulating and evaluating the records overall the development of a product will be helpful to rationalize the post approval changes.
- The required information essential to be acknowledged throughout regulatory judgment making this information more useful, if it is relevant to scientific base knowledge.
- They should have multidimensional relationships between factors (e.g. between formulation products) and it also benefits to appraise the applicability knowledge in different scenarios [18] [19] [20].

TABLE: 5 an example for PHA work

Sl.no	QbD tool	Inference	Reference [22]
1	PAT	In this study NIR tool was used to precisely extent distinct coating thickness and sheathing variation throughout process.	Ref.no.22

An example for PHA work is shown in TABLE: 5

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