



Emerging Trends and Novel Approaches of Quality by Design

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Abstract:-

Quality by Design is a novel concept to pharmaceutical quality. Pharmaceutical Quality by Design (QbD) is described in this paper, along with how it is used to ensure pharmaceutical quality. The Quality by Design concept is explained, and some of its components are listed. For and unit operation, process parameters and quality attributes are defined. It is impossible to evaluate quality. Quality cannot be measured into products; rather, it should be designed into them. Throughout the design and production of a product, it is essential to define the desired product performance profile [Target product profile (TPP), Target product Quality profile (TPQP), and identify Critical quality attributed (CQA) to the product under the QbD definition. We can design the product formulation and process to meet the product attributes based on this. These results in the recognition of the effect of raw material. [Critical material attributes (CMA), Critical process parameter (CPP)] on the CQAs, as well as the identification of uncertainty sources. This paper's application of the quality by design (QbD) aligns with the concepts of the ICH Q8, Q9, and Q10 guidelines.

Key words: Quality by Design (QbD), Quality target product profile (QTPP), Critical process parameter (CPP), critical quality attribute (CQA), Target product profile (TPP), and Critical material attributes (CMA).

Introduction:-

The purpose of pharmaceutical manufacturing is to establish a high-quality product and manufacturing process that consistently produces the desired results. Pharmaceutical development studies and manufacturing experience provide scientific insight into the design space, requirements, and manufacturing controls that can help establish the design space, requirements, and manufacturing controls. Pharmaceutical development studies will provide a foundation for quality risk management. It is important to understand that quality cannot be tested into products; i.e., quality should be built in by design. Working within the design space isn't regarded as a change. Exiting the design space is called a transition, which will usually trigger a regulatory post-approval change process. The overall goal is to move away from the quality by testing (QbT) model that was historically used in the pharmaceutical industry and toward a development that focuses on improving understanding of processes and products, thus improving product quality, process performance, and regulatory flexibility. Pharmaceutical production research and experience provide scientific knowledge that aids in determining the design space, specifications, and manufacturing controls.

The term "quality" refers to a product's ability to perform as expected. Pharmaceutical quality is described as a product that is free of contaminants and consistently provides the therapeutic benefit promised on the label to the consumer. Performance tests may be used to assess the quality of a pharmaceutical product in vivo or in vitro. "As a result, product performance is linked to quality by design." Although QbD can improve design forecasts, it is widely acknowledged that industrial scale-up and commercial manufacturing experience

provide fresh and vital information about the process and the raw materials used. The FDA understands that expertise does not remain stagnant and evolves over time in the manufacturing process. (T. Anusha 2020)

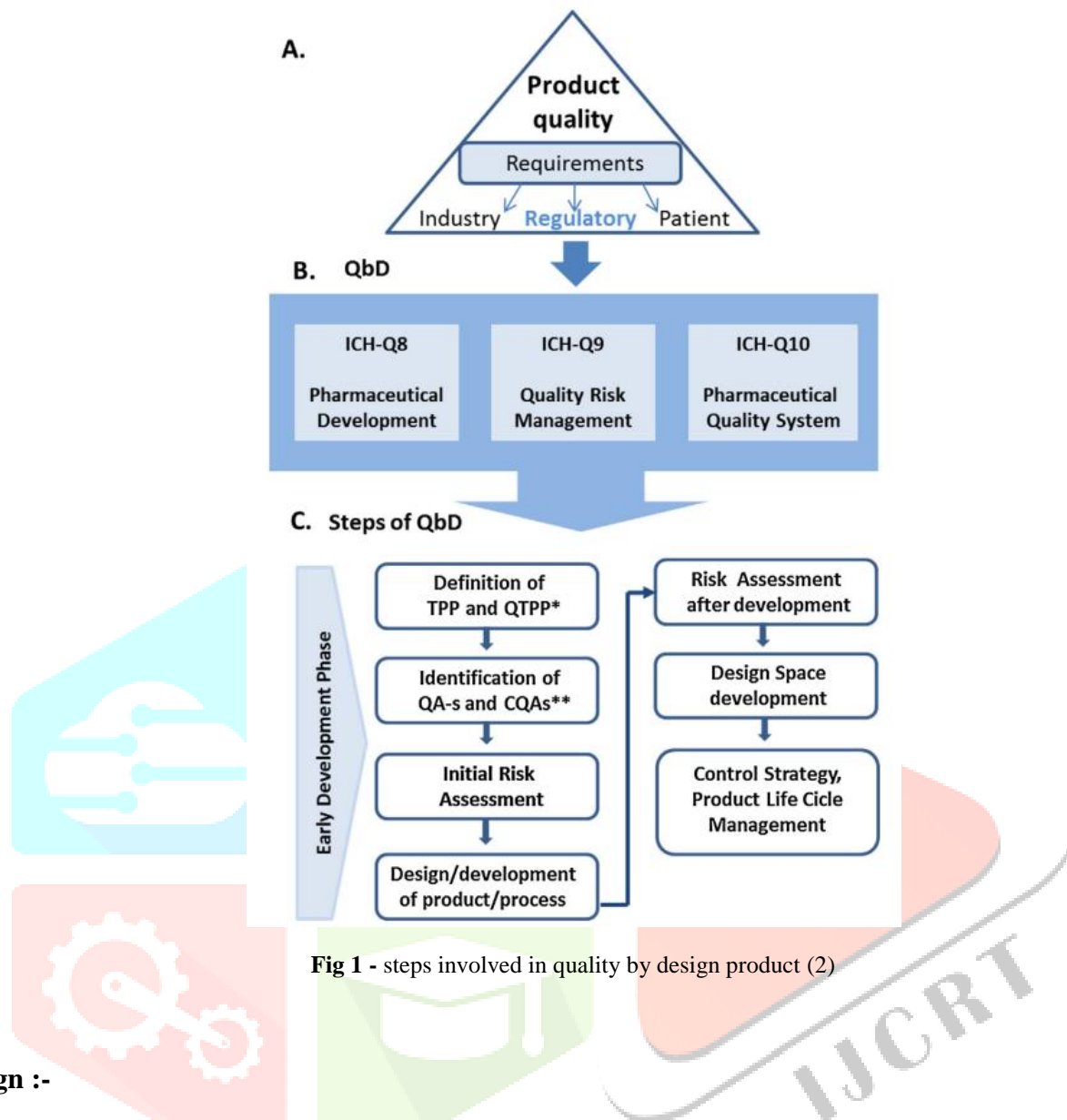


Fig 1 - steps involved in quality by design product (2)

Design :-

Quality by design (QbD) is a term proposed by quality expert Joseph M. Juran, who believed that quality could be designed and that the majority of quality crises and problems stemmed from the way quality was planned. (Nadpara et al. 2012)

US FDA defines QbD as “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”

“Process Analytical Technology (PAT)” is a word that has been used to describe a method for developing and regulating manufacturing using timely measurements. (i.e. during processing) of critical quality and performance attributes for raw and in-process materials and also processes with the goal of ensuring final product safety. (FDA Guidance)

- The product is made to satisfy the needs of the patient as well as the performance criteria.
- The process is structured to ensure that product quality attributes are consistently met.
- The effect of starting raw materials and process parameters on product quality has been identified.
- To maintain consistent quality over time, the process is constantly monitored and updated.
- Define a target product quality profile that formulators and process engineers can use during product development as a quantitative proxy for clinical safety and efficacy.



Fig 2:- Quality By Design (Bhoop BS. et al. 2014)

Pharmaceutical Quality by Design:-

In pharmaceutical development, Quality by Design (QbD) is a systematic approach to development that begins with predefined goals and emphasizes product and process understanding and control, all of which are based on sound science and quality risk management. Quality by Design (QbD) is gaining traction as a way to increase customer confidence in secure, efficient drug delivery while also improving manufacturing quality. (Jadhav JB. et al. 2014)

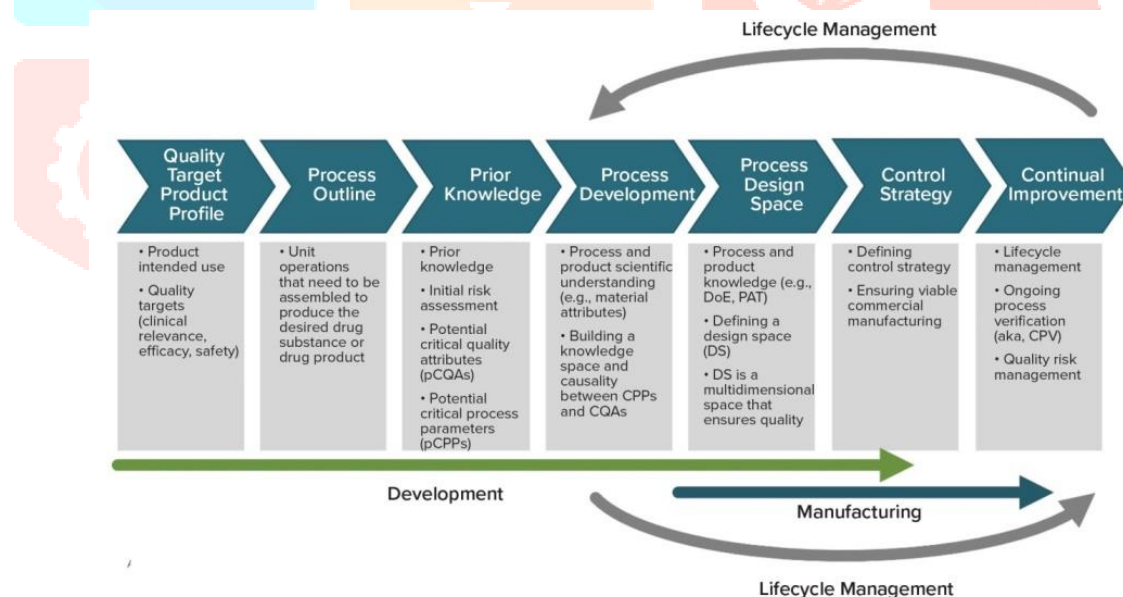


Fig 3- Pharmaceutical Quality by Design From development to Manufacturing.

❖ Quality Target Product Profile (QTPP):-

The quality target product profile (QTPP) is defined as “A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product”. (Jadhav JB. et al. 2014)

(QTPP) is based on the approach of Quality by Design (QbD). “A prospective description of the quality characteristics of a drug product,” according to the ICH Q8 guide (R2) published in 2009. Indications for use in a clinical environment, administration path, dosage type, and delivery systems. Quality requirements for drug products e.g., sterility, purity, safety, and drug release that are suitable for the marketed product. It is

determined by factors such as the active molecule's identification, purity, and stability, which are illustrated throughout the early stages of research and growth, as well as empirical evidence from pharmaco-toxicology, pharmacokinetics, and clinics. The dosage, the design of the packaging, the track, and the delivery system are all justified by QTPP. (Nadpara NP. et al. 2012)

It consists following components:-

- A molecule and impurity characterization are required for the active drug.
- Structure of the drug substance (molecular weight, Conformation)
- Physicochemical properties like pH, Solubility, Appearance, etc.
- Studies of pharmaco-toxicology in vitro and in vivo.
- Basic characteristics can be illustrated in relation to the route of drug administration.
- To ensure product stability and integrity.

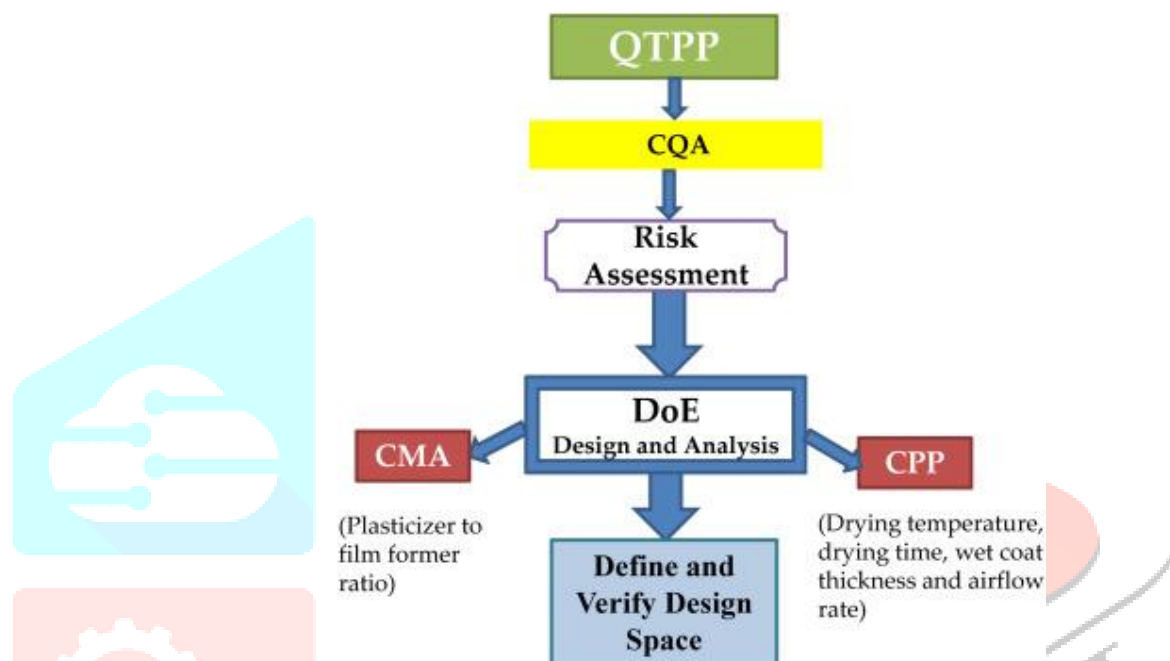


Fig 4 :- Components of Quality Target Product Profile (QTPP)

❖ The Target Product Quality Profile (TPQP):-

TPQP is defined as “prospective and complex description of a drug product's quality characteristics that ideally will be accomplished to ensure that the optimal quality, and therefore the safety and efficacy, of a drug product is realized.” This includes dosage form and route of administration, dosage form strength(s), therapeutic moiety release or delivery, and pharmacokinetic characteristics (e.g., dissolution and aerodynamic performance) relevant to the drug product dosage form being produced, as well as drug product-quality requirements (e.g., sterility and purity) relevant to the intended marketed product.

(TPQP) is a natural extension of TPP, which stands for "total product quality." It is the set of quality characteristics that a drug product must have in order to deliver the therapeutic benefit promised on the label in a consistent manner. The TPQP assists formulation scientists in developing formulation strategies and ensuring that their efforts are focused and efficient. TPQP is associated with identity, assay, dosage form, purity, and label stability. Physical, chemical, and biological properties are all part of the biopharmaceutical properties of a drug substance. (Juran JM. et al. 1992)

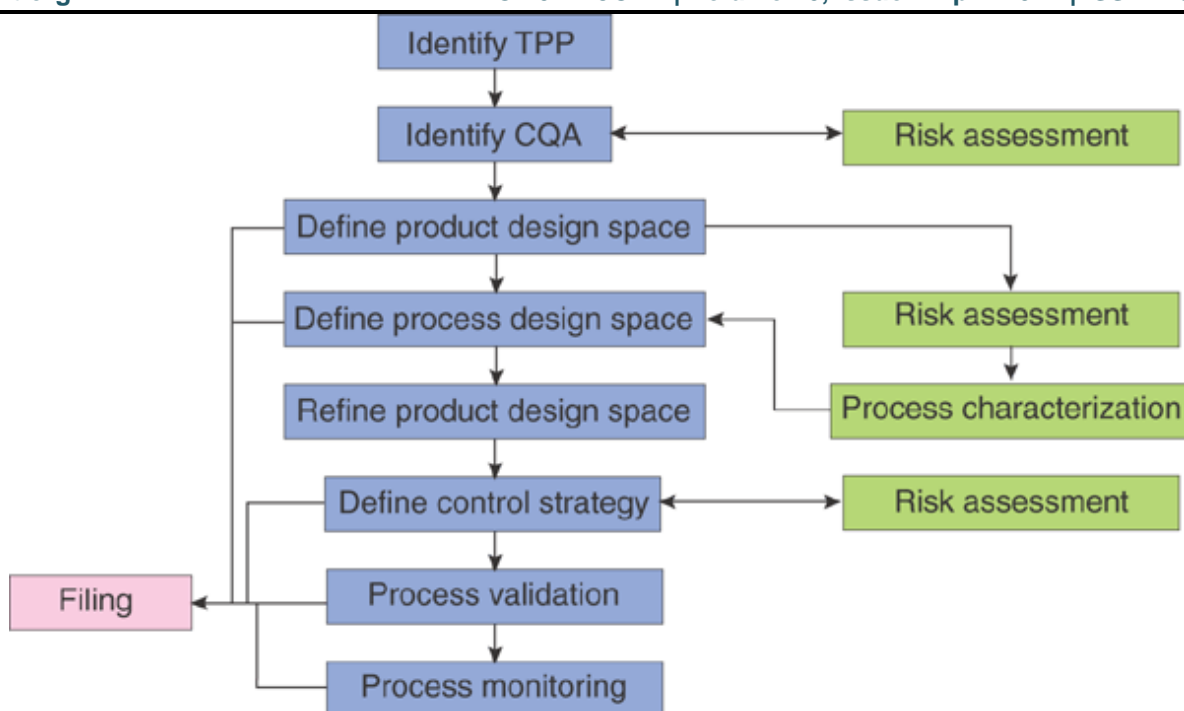


Fig. 5:- Elements of Pharmaceutical Development .

❖ Critical Quality Attribute (CQA):-

“CQA is a Physical, chemical, biological, microbiological property (or) characteristic that should be within appropriate limit, range or distribution to ensure the desired product quality.” Excipients, drug compounds, and intermediary drug products are all commonly related with CQA. CQAs for pharmaceutical products typically affect product purity, strength, drug release, and stability for solid dosage forms, while sterility and clarity are CQAs for parenterals. CQAs are used to guide the development of new products and processes. (Jadhav JB. et al. 2014)

The product's quality attributes should keep it within its boundaries, and it should perform as intended in terms of safety, efficacy, stability, and performance. It means that all elements affecting ultimate quality and safety must be under control. It Create a link between the CPP and the CQAs: Identification of a characteristic or set of characteristics that can be utilized as a proxy for clinical safety and efficacy (important to patient).

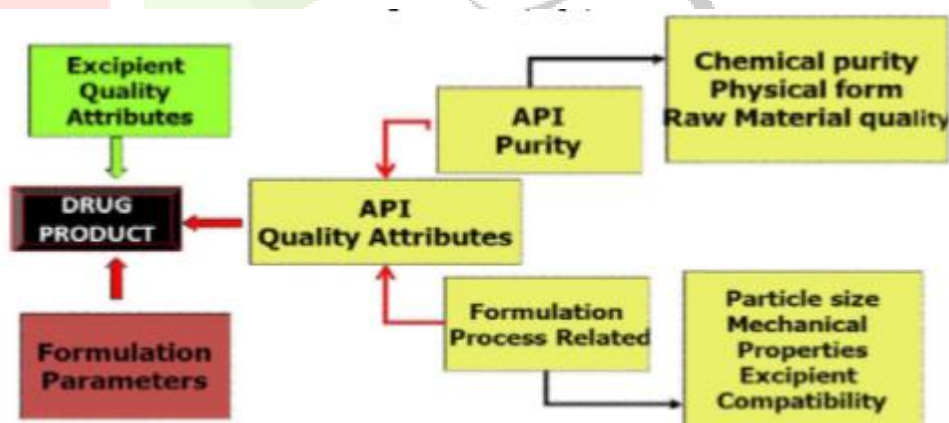


Fig .6:- Role of Critical Quality Attribute. (Jadhav JB. et al. 2014)

❖ Critical Material Attributes:-

Materials: Raw materials, starting materials, reagents, solvents, processing aids, intermediates, packaging, and labeling materials are some of the items used.

In identification of CQAs of drug product, the assessment of linkage between drug substances to drug product is necessary. The majority of excipient functionality is necessary to perform in order to

understand material attributes. The selection of salt, solid forms, particle size and morphology also impact critical quality attributes. (T. Anusha. et.al. 2020)

Material attributes can be quantified and fixed in most cases, but they can also be altered during processing. (Roy S. 2012)

Examples: Impurity profile, porosity, specific volume, sterility.

❖ **Critical process parameters (CPP):-**

Critical process parameter is one whose impact on critical quality attributes. It should be monitored or controlled to ensure the process produces the desired quality. A pharmaceutical manufacturing process usually consists of a series of unit operations (like mixing, milling, granulation, drying etc.) to produce a desired quality product. (FDA 2011)

CPPs are in charge of assuring CQAs, and they are selected via a list of prospective CPPs based on risk assessment.

There are three parameters:-

I. Unclassified parameters:

Unclassified parameters have unknown criticalities. To classify an unclassified metric as critical or non-critical, additional data is required.

II. Critical parameters:

When a reasonable change in a parameter causes the product to fail to receive the QTPP, it is considered critical.

III. Non-critical parameters:

In the prospective working space, there were no QTPP failures and no interactions with other parameters in the specified appropriate range.

Examples for Critical process parameters (CPP):- Temperature, Rate of cooling, Speed of Rotation, pH, etc. (Roy S. 2012)

Risk Assessment:-

Risk is defined as the combination of the likelihood of harm occurring and the severity of harm. It aids in the improvement of method quality. Quality risk management is a systematic process for assessing, controlling, communicating, and reviewing risks to drug (medicinal) product quality throughout the product lifecycle. The initial list of potential parameters that can affect CQAs can be quite long, but quality risk assessment can help to narrow it down and prioritize it (QRA). Risk assessment can have an impact on product quality and preliminary experimental data. The attributes of a drug substance's relative risk were ranked as high, medium, or low. Risk assessment is useful for effective communication between the FDA and industry, as well as for research, development, and manufacturing at multiple locations within a company. Statistical parameters can be used to manage risk for excipients in order to determine shelf-life. As shown in Fig.7, a fault tree analysis is used to link the potentially critical quality attribute "content uniformity" to a potential failure mode and potential causes. Four major causes, namely raw and intermediate material properties, processing parameters, equipment and design parameters, as well as environmental factors, were identified and systematically listed in an Ishikawa diagram (Fig. 8). (Jadhav JB. et al. 2014)

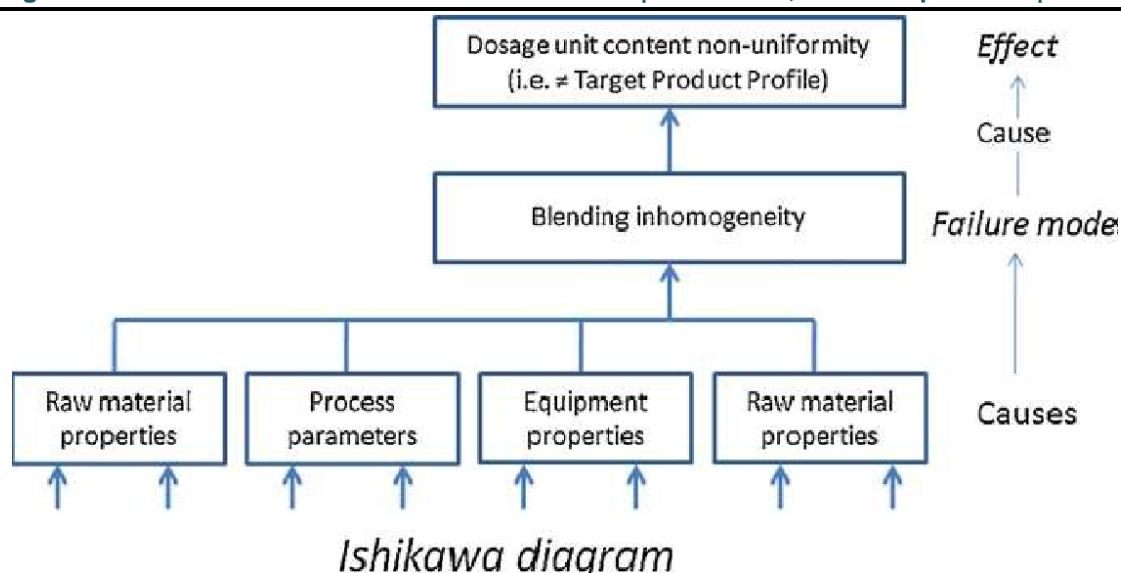


Fig 7:- Risk identification: fault tree analysis of variable content uniformity

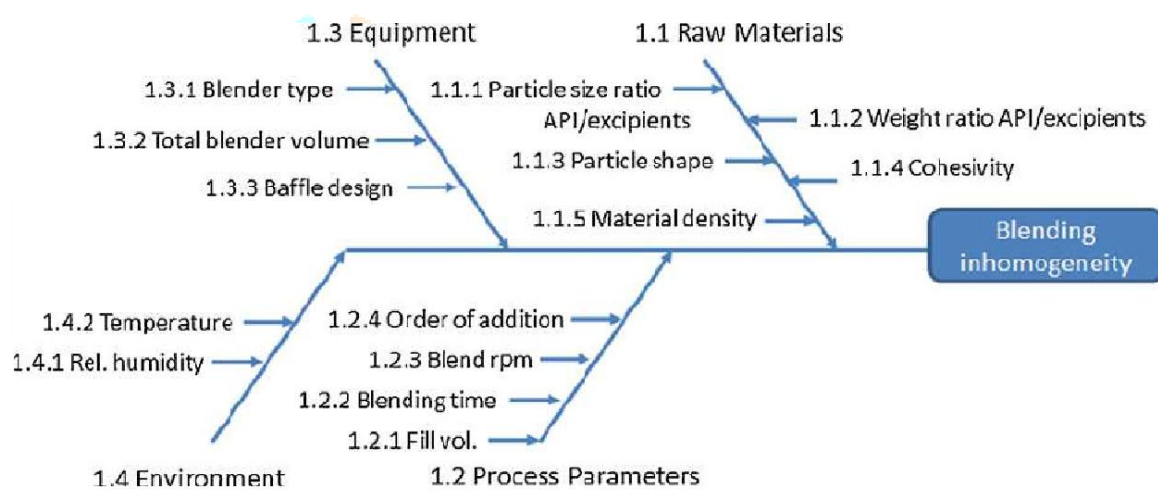


Fig. 8:- Risk identification: Ishikawa diagram for the blending unit operation (Adam S. et al. 2011)

Methods for Risk assessment: (T. Anusha et. al. 2020)

1. Failure mode effects analysis (FMEA)
2. Failure mode effect and criticality analysis (FMECA)
3. Fault tree analysis (FTA)
4. Hazard analysis and critical control points (HACCP)
5. Risk ranking and filtering (PHA)
6. Supporting statistical tools. (Chavan SD. et al. 2016)

Control Strategy :-

The ability to evaluate and maintain the quality of an in-process or finished product based on process data, which usually includes a valid combination of measured material attributes and process controls. (ICH Q8(R2) 2005). "A designed set of controls derived from current product and process understanding that assures process performance and product quality," according to the definition of control strategy. To ensure that the material and process are within the expected lower and upper limits, a control strategy is required. It aids in the prevention of defects and the maintenance of desired quality. (FDA 2011). To ensure consistent quality, control strategies may include input material control, process controls, and monitoring, as well as design space to final product specification. (Yu LX. 2008)

Control strategy includes :- (Lawrence XY. 2009)

- Control of raw material attributes (excipients, packaging material, etc.)
- Procedural Control
- Product specifications
- In-process controls
- Process monitoring
- Batch release testing
- Comparability testing

Life Cycle Management:-

Process changes within the design space will not require review or approval in the QbD paradigm. As a result, process improvements in terms of process consistency and throughput could occur during the product life cycle with fewer post-approval submissions. In addition to regulatory flexibility, a better understanding of the manufacturing process, as defined by ICH Q9, would allow for more informed risk assessment of the effects of process changes and manufacturing deviations (excursions) on product quality. (Purohit PJ. et al. 2013)

TOOLS OF QUALITY BY DESIGN:-

I. Design of Experiments (DOE) :-

The design of experiments (DOE) method is a structured and organized method for determining the relationship between factors that influence process outputs. DOE is said to be able to provide returns that are four to eight times greater than the cost of running the experiments in a fraction of the time. The design of experiments (DOE) method is a structured and organized method for determining the relationship between factors that influence process outputs. (Shah RB. et.al. 2009) DOE is said to be able to provide returns that are four to eight times greater than the cost of running the experiments in a fraction of the time. Because each unit operation has a large number of input and output variables, as well as process parameters, it is impossible to investigate all of them experimentally. (Bhasin. et al. 2012)

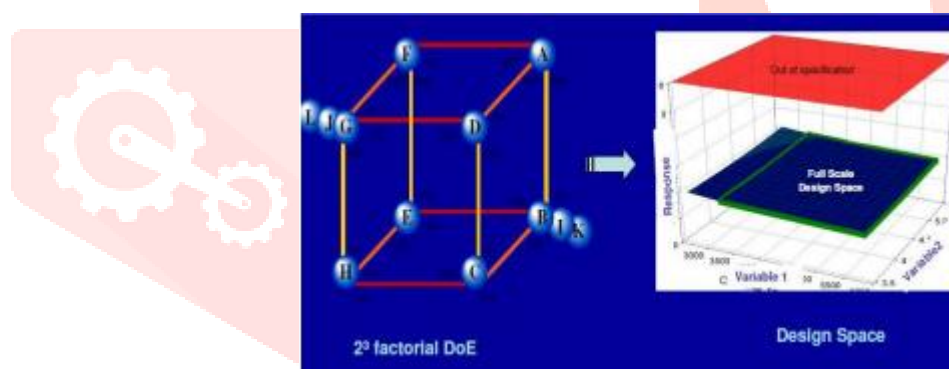


Fig. 9:- Design of experiment (DOE) (Jadhav JB. et al. 2014)

II. Process Analytical Technology (PAT):-

PAT is defined as "a system for designing, analyzing, and controlling manufacturing through measurements of critical quality and performance attributes of raw and in-process materials and processes during processing, with the goal of ensuring final product quality." PAT's goal is to "improve understanding and control of the manufacturing process, which is consistent with our current drug quality system: quality cannot be tested into products; it must be built-in or by design." The key and critical process parameters identified from process characterization studies, as well as their acceptable ranges, define the design space. On-, in-, and at-line PAT applications are primarily concerned with these parameters. In theory, real-time PAT assessments could serve as the foundation for continuous feedback, resulting in increased process robustness. NIR serves as a tool for PAT and is useful in RTRT (Real Time Release Testing) because it monitors particle size, blend uniformity, granulation, content uniformity, polymorphism, dissolution, and monitoring the process online, on the line, and offline, thereby reducing product release testing. (US FDA 2004)

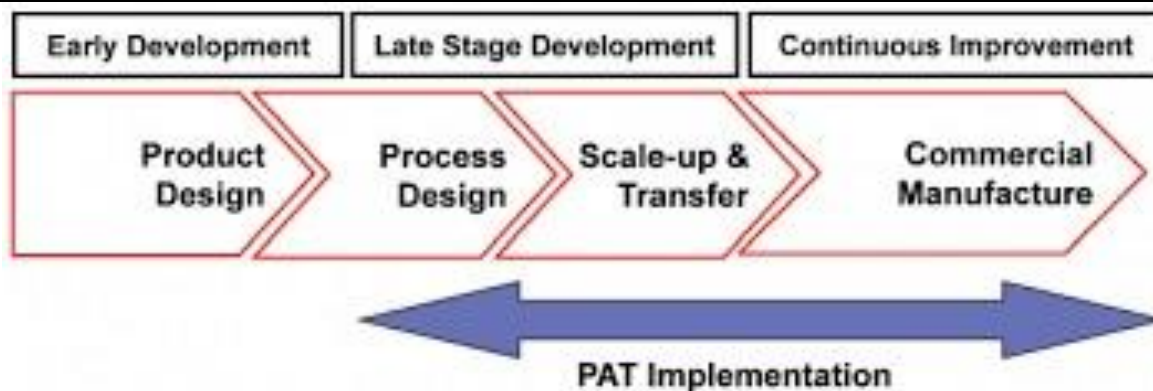


Fig 10:- PAT implementation in product life

III. Risk Management Methodology:-

Quality Risk Management is defined as "a systematic process for assessing, controlling, communicating, and reviewing risks to the quality of the drug (medicinal) product throughout the product lifecycle." Based on prior knowledge and primary experimental data, risk assessment tools can be used to identify and level parameters (e.g., process, equipment, input materials) that have the potential to impact product quality. The initial list of potential parameters may be fairly broad, but it can be modified and prioritised by subsequent studies (e.g., through a combination of design of experiments and mechanistic models). Once the significant parameters have been identified, they can be studied further (e.g., through a combination of design of experiments, mathematical models, or studies that lead to mechanistic understanding) to achieve a higher level of process understanding. (Jadhav JB. et al. 2014)

Risks can be evaluated and managed by the pharmaceutical industry and regulators using well-known risk management tools and/or internal procedures such as,

- Basic risk management facilitation methods (flowcharts, check sheets etc.)
- Failure Mode, Effects and Criticality Analysis (FMECA)
- Failure Mode Effects Analysis (FMEA)
- Fault Tree Analysis (FTA)
- Hazard Analysis and Critical Control Points (HACCP)
- Preliminary Hazard Analysis (PHA) (Jadhav JB. et al. 2014)

Applications:-

The basic concept of QBD is "The quality is tested into the product, but it should be built into it." During development of analytical methods, same QBD principle can be applied to the development of analytical method. Various quality and statistical tools and methods, such as statistical designs and experiments, multivariate statistics, statistical quality control have been comprised in QBD. The major purpose of moving away from quality by testing is to speed up product understanding so that product quality, process efficacy, and regulatory flexibility may be achieved. (T. Anusha et al. 2020)

QBD includes a variety of quality and statistical tools and approaches, including statistical designs and experiments, multivariate statistics, and statistical quality control. The major purpose of moving away from quality by testing is to speed up product understanding so that product quality, process efficacy, and regulatory flexibility may be achieved.

QBD can be used in a variety of processes, including (T. Anusha et al. 2020, M. Deepa et al. 2017, Patwardhan DM. et al. 2017)

- Chromatographic techniques like HPLC (High performance liquid chromatography)
- Hyphenated technique like LC-MS
- Karl-fisher titration for determination of moisture content.
- Analysis of genotoxic impurities.
- To Development of Analytical Separation Methods.
- Enhancement of the Solubility and Dissolution.
- For Formulation Development.

- In Drug Substance Development.
- In Clinical Trials.

Conclusions:-

Quality by design is an important component of today's pharmaceutical quality management strategy. This is an idea that has the potential to replace the old approach and is gaining traction in the industry. If correctly implemented and combined with the existing global harmonization of rules and risk, QbD should be viewed for what it can provide rather than for what it might cause. QBD is becoming increasingly important in pharmaceutical processes such as drug development, formulation, analytical methods, and pharmaceuticals. The main reason for implementing QBD is to meet regulatory requirements. To get their product approved for marketing, the pharmaceutical industry requires regulatory compliance.

This paper discusses the necessity of the Quality Target Product Profile, as well as the discovery of important material qualities that offer a mechanistic relationship between product quality and manufacturing processes. clarification that critical process parameters are operating variables that should be paired with critical material attributes to describe the relationship between inputs and outputs of unit operations.

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