QUALITY BY DESIGN APPROACH: REGULATORY GUIDELINES AND CURRENT STATUS

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***Abstract*: Quality by design (QbD) is a strategic Process for development and manufacturing. Recently the concept "Quality by Design" gaining much attention among pharmaceutical industries for maintaining quality. The advantage of QbD benefits both the consumer and manufacturer. Some of the QbD elements include quality target product profile (QTPP), CQAs, designing product and manufacturing process, Process parameter and sources of variability. QbD widely promoted by Food and Drug Administration (FDA) and International Conference on Harmonization (ICH). The aim of QbD is to design a quality product and manufacturing process to consistently deliver the intended performance of the product. QbD helps to serve the progressive manufacturing processes, decreases the amount of batch failure, gives more effective control of change and also provide a higher return on investment. In the future, the QbD is going to be accustomed to a far bigger extent. Currently, International Conference on Harmonization is functioning on "ICH- Q13 and ICH- Q14". This new International Conference on Harmonization tips square measure is expected close to the future.**

Keywords*: *Quality by Design, Regulatory Guidelines.

INTRODUCTION

Quality by Design (QbD) is a concept first discovered by quality expert Dr. Joseph M. Juran [1]. Dr. Juran believed that quality could be planned or designed into a product which most quality cries and problems relate to the way in which a product was designed in the first place [2]. The Juran Triology defines the word 'Quality" as having two meanings: 1st the Presence of features that create customer satisfaction; 2nd the reliability of those features. Failures in features create dissatisfactions, so removing failures is the purpose of quality improvement, while creating features is the purpose of QbD [3]. Quality by Design principles have been used to advance product and process quality in industry, and particularly the automotive industry, they have also been adopted by the US-FDA for the discovery, development and manufacture of drugs. The aim of pharmaceutical development is to design a quality product and the manufacturing process to consistently deliver the intended performance of the product.

The concept of QbD was referred in the ICH Q8 guidance, which status that "quality cannot be tested into products, that is, quality should be built in by design". According to International conference on harmonization Q8(R2) QbD is defined 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. [4]

The concept of Quality by Design was mentioned in Food and Drug Administration Process Analytical Technology (FDA PAT) guideline, which status that "A system for designing, analyzing and commanding manufacturing through timely measurements of critical quality and performance attributes of recent and in-process materials and processes to establish the goal of bounding final product safety." The FDA imperative is outlined in its report "Pharmaceutical Quality for the 21st Century: A Risk-Based Approach." [5]

The Pharmaceutical industry is constantly working to ensure and enhance the product safety, quality, and efficacy of the product. Even so, drug recall, manufacturing failure, cost, scale-up issues, and burden in recent are some provocation factors for the industry. In traditional, the finished product quality and performance are mostly ensured by end product testing, with limited understanding of the process and CPP's for that reason, the Regulatory bodies are focused on implementing quality by design. Quality by Design is a science-based approach that reduces process variation and the enabling process-control strategies. The goal of pharmaceutical QbD is to achieve meaningful product quality specification that are based on clinical performance. [6]

BENEFITS OF QUALITY BY DESIGN: - [7,8]

- QbD is economical, agile and versatile system
- Eliminate batch Failures
- Increase manufacturing efficiency, reduce costs and project rejections and waste
- Minimize deviations and costly investigation
- Avoid regulatory compliance problems
- Build scientific knowledge base for all products
- Better interact with industry on science issues
- Empowerment of technical staff
- Ensure consistent information
- Incorporate risk management
- Reduce end-product testing
- Real- time process monitoring and trending (with process Analytical Technology (PAT)) reduces the analysis burden and improves the product quality

Key Elements of Quality by Design: - [9]
ICH Q8: Pharmaceutical development discusses the various elements if QbD.

- Define Quality Target Product Profile (QTPP)
- Identify Critical Quality Attributes (CQAs)
- Perform a Risk (Assessment) Analysis
- Determine the Critical Process Parameter (CPPs)
- Determine the Design Space
- Identify a Control Strategy
- Manage product lifecycle, including continuous improvement

Quality Target Product Profile (QTPP): - [10]
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." The target product profile forms the basis of design for development of the product. Product attributes defining the QTPP for nanostructured lipid carriers includes particle size, polydispersity index, entrapment efficacy and stabilization of nanoparticles. The QTPP is a vital document that allows the rationalization and tracing the evolution of the data no inheritable throughout the lifecycle of the drug. Consideration for the quality target product profile could include: Intended use in clinical setting (patient population), route of administration, dosage form, delivery systems; Dosage strength (s); Container closure system; Therapeutic moiety release or delivery and attributes affecting pharmacokinetics characteristics (e.g., Dissolution, Aerodynamic performance) appropriate to the drug product dosage form being developed; Drug product quality criteria (e.g., Sterility, purity, stability and drug release) appropriate for the intended marketed product.

Critical Quality Attributes (CQAs): - [11,12]
CQAs are physical, chemical, biological or microbiological property or characteristics that should be within an appropriate limit, range or distribution to ensure the desired product quality. CQAs are generally associated with the drug substance, excipients, and drug product. CQAs of solid oral dosage forms are typically those aspects affecting product purity, strength, drug release and stability. CQAs for other delivery systems can additionally include more product aspects, such as aerodynamic properties for inhaled products, sterility for parenteral and transdermal patches. For drug substance, raw materials and intermediates, the CQAs can additionally include those properties (e.g., particle size distribution, bulk density) that affect drug product CQAs. Drug product CQAs are the properties that are important for product performance, that is, the desired quality, safety and efficacy. Identification of CQAs is done through risk assessment as per the ICH guidance Q9. The key of risk assessments includes prior product knowledge, such as the accumulated laboratory, nonclinical and clinical experience with a specific product- quality attribute.

Critical Material Attributes (CMAs): - [13,14]
Critical material attributes (CMAs) are defined as "A material or process whose variability has an impact a critical quality attribute and therefore it should be monitored or controlled to ensure desired drug product quality". A parameter is important once a true modification therein parameter will cause the product to fail to fulfil the QTPP. Thus, whether or not a parameter is important or not depends on the however giant of an amendment one is willing to think about this as well as different properties or characteristic of associate input material. CMAs to be inside associate applicable limit, range or distribution to make sure the required quality of that drug substance, excipient or in-process material.

Critical Process Parameter (CPPs): - [15]
In CPPs pharmaceutical manufacturing are key variables affecting the production process. CPPs are attributes that are monitored to detect deviation in standardized production operation and product output quality or changes in critical quality attributes. The manufacturer should conduct tests to set acceptable range limits of determined CPPs and define acceptable process variable variability. Parameters are monitored before or in processes that influence the looks, impurity, and yield of the ultimate product considerably.

Risk Assessment: - [16]
The FDA defines a Risk Assessment as, "A systematic process of organizing information to support a risk decision to be made within a risk management process." Risk assessment is typically performed early in the pharmaceutical development process and is repeated as more information becomes available and greater knowledge is obtained. Risk assessment tools can be used to identify and rank parameter (e.g., process, equipment, input materials) with potential to have an impact on product quality, based on prior knowledge and initial experimental data. An assessment risk is useful for effective communication between the FDA and trades, research/ development, producing and among multiple producing sites at intervals the corporate. Risk assessment is a valuable science – based process used in ICH guideline Q9 (Quality Risk Management) as follows:

- ✓ Failure Mode Effects Analysis [FMEA]
- ✓ Failure Mode, Effects and Critically Analysis [FMECA]
- ✓ Fault Tree Analysis [FTA]
- ✓ Hazard Analysis and Critical Control Points [HACCP]
- ✓ Hazard Operability Analysis [HAZOP]
- ✓ Preliminary Hazard Analysis [PHA]
- ✓ Risk ranking and filtering

- ✓ Supporting applied mathematics tools

Failure Mode Effects Analysis: - [17,18,19]
FMEA is one of the most commonly used risk-assessment tools in the pharmaceutical industry. FMEA depends on product and process understanding. It is a systematic and proactive method to identify and mitigate the possible failure in the process. Failure modes represent may errors or defects in a process, material, equipment or design. Once failure modes, square measure established, the FMEA tool estimates the result of those failure and prioritizes them consequently. This tool is further advanced with studying critically of the consequence and providing clear indication of situation. Benefits of FMEA include higher reliability, better quality, increased safety and contribution towards cost saving includes decreased development time and reduced waste.

Failures Mode, Effects and Critically Analysis: - [20]
It is extension of earlier said FMEA tool. Extending FMEA to incorporate an investigation of the degree of severity of consequence, their probabilities of occurrence and their detect-ability is failure mode, effects and criticality analysis. In FMECA, each failure mode of the product is identified and then evaluated for criticality. This criticality is then translated into a risk, and if this level of risk isn't acceptable, corrective action should be taken. This could be used for failure and risk related to producing processes. The tool may also be wanted to establish and optimize maintenance plans for repairable systems and/or contributes to regulating plans and different quality assurance procedures.

Fault Tree Analysis (FTA): - [21]
This tool assumes failure of the functionality of a product or process. The results are represented pictorially in the form of a tree of fault modes. This can be used to investigate complaints or deviation in order to fully understand their root cause and ensure that intended improvement will resolve the issues and not cause any other different problems.

Hazard Analysis and Critical Control Points (HACCP): - [22]
HACCP is a systematic, proactive and preventive tool for assuring quality, reliability and safety. It involves hazard analysis, determining critical control point, establishing critical limits, establishing a system to monitor critical control point and establishing a record keeping system. This is used to identify and manage risk associated with physical, chemical and biological hazards.

Hazard Operability Analysis (HAZOP): -
HAZOP is a highly structured hazards identification tool. This is based on assumption that events are caused by deviation from the design or operating intention.

Preliminary Hazard Analysis (PHA): -
It is based on applying prior experience or knowledge of hazard to identify future hazards, hazardous situation. This can be used for product, process and facility design. This can be used in early development of a project where there is little information on detail is available. Preliminary hazard analysis (PHA) is a semi-quantitative analysis that is performed to identify all potential hazards and accidental events that may lead to an accident, Rank the identified accidental events according to their severity and identify required hazards controls.

Design Space: - [23]
ICH Q8 (R2) defines design space as "the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval.'' Design space may be constructed for a single unit operation, multiple unit operation or for the entire process. Methods for determining design space included: one variable at a time experiments, statistically designed experiments, and modelling approaches. Methods for presenting design space included graphs (surface-response curves and contour plots), linear combination of parameter ranges, equations and models. Alternatively, the design space can be explained mathematically through equations describing relationships between parameters for successful operation.

Control Strategy: - [24]
ICH Q10 defines a control strategy as "a planned set of controls derived from current product and process understanding that assures process performance and product quality. The control can include parameter and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in process controls, finished product specifications and the associated methods and frequency of monitoring and control. "Control strategy, including Continuous Quality Overall Summary (CQOS), is also a critical element of QbD and should include starting materials, intermediates and finished products. The strategy should include every aspect known to potentially impact the product.

Elements of Effective Strategy:
- ✓ Procedural controls
- ✓ In-process controls

- ✓ Batch release testing
- ✓ Method observation characterization testing
- ✓ Comparability testing
- ✓ Constancy testing

Product Lifecycle Management and Continual Improvement:
Product quality is often improved throughout the product lifecycle; firms have opportunities to choose creative approaches to boost quality. Method performance is often monitored to form certain consistency in quality. Extra expertise and information are gained throughout routine manufacture that contributes to method development. The QbD approach avails the continual improvement throughout the products lifecycle this can be a characteristics purpose of the traditional technique that is the way frozen method.

Process Analytical Technology: - [25,26,27]
Process analytical technology (PAT) is defined by the FDA as a mechanism to design, analyse, and control pharmaceutical manufacturing process through the measurement of critical process parameters that affect critical quality attributes of an active pharmaceutical ingredients (API). PAT could be a term used for describing a broader amendment in pharmaceutical production from static batch producing to a lot of dynamic approaches. It involves process the CPPs of the instrumentation accustomed, create the product, that have an effect on the COA's of the product and so dominant these CPPs at intervals outlined limits. PAT is a system for Designing, analyzing and controlling manufacturing processes.

PAT tools:
In order to implement a successful PAT project, a combination of three main PAT tools is essential:

- Multivariate data acquisition and data analysis tools: usually advanced software packages which aid in design of experiments, collection of raw data and statistically analysing this data in order to determine what parameter are CPP.
- Process analytical chemistry (PAC) tools: in-line and on-line analytical instruments used to measure those parameters that have been defined as CPP. These include mainly near infrared spectroscopy (NIRS); but also include biosensors, Raman spectroscopy, and others.
- Continuous improvement and/or knowledge management tools: paper systems or software packages which accumulate quality control data acquired over time for specific processes with the aim of defining process weakness and implementing and monitoring process improvement initiatives.

Regulatory Perspective: - [28]
Quality suggests that client satisfaction in terms of service, product and method. Client demands the perfection in quality, reliability, low value, and timely performance. Client satisfaction is achieved by two ways in which, that is, options and free from deficiencies within the product. There are recent regulative developments that will cause a better want for the integrated use of QbD and quality. Regulative agencies, today, emphasize not just on "Quality by Testing" or "Quality by Chance" but solely on QbD.

FDA Perspective: - [29]
Based on the applying of product and method understanding, the FDA's office of new Drug Quality Assessment, was established a brand-new risk based pharmaceutical quality assessment system. QbD help to implement Q8 and Q9. FDA's read of QbD is "QbD may be a systematic approach to product and method style and development." This idea was accepted by the office in 2004 and careful description was given in pharmaceutical. CGMP for the 21st century – a risk based mostly approach. In shell, product quality and performance are assured by coming up with economical producing processes. Connected regulative policies and measure area unit changed to accommodate the important time knowledge base. Quality assurance may be a continuous method.

ICH Guidelines and QbD: - [30]
The basic principles of Quality by Design, i.e., Science- and risk-based product development, risk assessment, lifecycle approach, and method design are explained within the quality guidelines of International Conference on Harmonization (ICH). The ICH guideline Q8 (R2) to provide guidance for drug product development; ICH Q9 is to focus the behaviours of industry and regulatory authorities on the principle of Quality Risk Management; and ICH Q10 to provide a harmonized model for a Pharmaceutical Quality System.

Regulatory Challenges: -
The majority of pharmaceutical companies feel that there is a need for an easier guidance on how to actually implement QbD. Companies wanted clarification from FDA on QbD terminologies, acceptable methods, criteria to select and deselect critical quality attributes, standards by which to judge adequacy of controls, and criteria for analytical method substitution. Ten key challenges are the foremost problematic for QbD adoption. These challenges are evaluated by their relevancy against different drug type as well as different levels of adoption.
The first four challenges occur within companies:

- Internal misalignment (Disconnect between cross functional areas, e.g., R&D and manufacturing or quality and regulatory)
- Lack of belief in business case i.e., there is a lot of uncertainty over timing of and investment for QbD implementation.
- Lack of technology to execute (e.g., Difficulty managing data, limited understanding of Critical Quality Attributes (CQA) implication)

- Alignment with third parties (i.e., How to implement QbD with increasing reliance on suppliers and contract manufacturers?)

The next six challenges are directly related to the regulatory authority:

- Inconsistency of treatment of QbD across regulatory authority
- Lack of tangible steering for business
- Regulators not prepared to handle QbD applications
- The way promised regulatory benefits are currently being shared does not inspire confidence
- Misalignment of international regulatory bodies
- Current interaction with companies is not conductive to QbD

It is accepted that the challenges and issues related to implementation of QbD will solely be resolved if there is efficient communication between the industry and therefore regulative bodies.

Future Perspective: -

"Quality by Design does not necessarily mean less analytical testing" certainly it means the right analysis at the right time and is based on science and risk assessment. Implementation of quality by design helps to develop rough and robust method which helps to comply with ICH guideline hence for the reason pharmaceutical industries are adopting this concept of QbD. It suggests that approaches applicable like target profile, CQA, design space and risk assessment are applicable to analytical method also. Though it is not adopted by all pharmaceutical industries it has future perspective because it may become obligatory by regulatory bodies. Voluntary adoption of this concept by industries is possible because of its various benefits and ease of compliance with regulatory authorities.

In the future, quality by design is going to be customary to a far bigger extent. Together it will be additionally applied within the production space, as a result of currently, its often used within the development space, wherever we tend to use the event approaches within the method. If we can keep the present production inside the instrumentation limits that we have then it's fine. Howbeit, after we have gotten toward the additional advanced and impactful a part of the standard intentionally approaches to process analytical technology (PAT) following controlled methods, this is often truly wherever we tend to square measure introduced to quite important resistance.

Some regulative Agencies Conjointly initiate the QbD ideas about parallel implementation like pharmaceutical research and manufactures of America (PhRMA), Analytical Technical Group (ATG) and European Medicines Agency (EMA). The European Medicines Agency is showing partial interest in the application that primarily support the idea of quality intentionally (QbD). Quality intentionally is exactly an abstract approach that aims to make sure the standard of medicines using applied mathematics, analytical and risk-management methodology severally within the style, development, and production of medicines. U.S. authority/EMA refers to International Conference on Harmonization guidelines Q8 [Pharmaceutical Development]; Q9 [QRM]; Q10 [Pharmaceutical Quality System]; Q11 [Development and Manufacture of Drug Substance] and Q12 [Lifecycle Management] for QbD implementation. Presently, ICH functioning on Q13- "Continuous Manufacturing of Drug Substances and Drug Products" and Q14- "Analytical Technique Development". These new international conference on harmonization tips square measures are expected close to the future.

APPLICATION OF QUALITY BY DESIGN: - [31 TO 36]

1. Quality by Design can be applied for various analytical methods which include,

- Chromatographic techniques like High Performance Liquid Chromatography for stability studies, method development and determination of impurities in pharmaceuticals.
- Hyphenated technique like LC-MS.
- Advanced techniques like mass spectroscopy and capillary electrophoresis.

2. QbD has been applied to Pharmaceuticals; The delivery of medicine at the appropriate purity, potency and delivery rate, is expected from the pharmaceutical products. While pharmaceutical regulations have undoubtedly protected the human beings from any of unwanted harms which occurred early in the 20th century. Hence recent guidelines in Q8 for pharmaceutical development are milestone in the way of making quality products. Application of QbD to various pharmaceutical dosage forms reported in the literature are explained below.

- A Quality by Design study for a Roller Compactor. Immediate Release Tablet is used to examine the impact of inconsistency in excipient material properties on the quality attributes (Joseph et al., 2011).
- A current review on 'Overall impact of the regulatory requirements for genotoxic impurities on the drug development process' discusses analytical assessment of genotoxic impurities and the regulations in the toxicological background for establishing limits. Its overall light on genotoxic impurities concerns during the development of new drug substance (Antonia et al., 2011).
- In gel manufacturing: QbD Approach of a Pharmaceutical Gel producing method, by close to infrared watching of Composition and Physical Parameters gel by exploitation the near-infrared spectroscopy (NIRS) technique with multivariate geometric tools.

3. QbD has also been applied to biopharmaceuticals. It is a fast-growing industry parallel to pharmaceutical. High expectation of regulatory bodies is the one of the reasons for adoption of QbD by industries. Manufacturing of biopharmaceuticals involves number of complex processes, chromatography is also the most important unit operation in downstream processing of biomolecules, many of the times it is the primary step for purification. Hence, it is beneficial to apply QbD to biopharmaceutical products. Recently QbD has been successfully applied by determining design space for HPLC method for analysis of water-soluble vitamins (Wagdy et l., 2013).

4. According to Cook (2012) it may be possible to establish relationships between CQAs and Pharmacokinetic parameters in healthy volunteer trials and then also to establish relationships between pharmacokinetics and safety and efficacy. But cost involved does not make it feasible.

5. In Nanomedicine: QbD on a rational development of a stable liquid formulation of Nanomedicine product.

6. Quality by Design was applied to Drug substance development (ICH Q11); Drug Product (ICH Q8 R2); Analytical method development. The office powerfully recommends incorporating QbD components in ANDA submissions since Jan 2013. It will be enforced in Biopharmaceuticals products too.

7. US office has already reveled two qualities by design implementation case studies;

1) Quality by choice for Abbreviate New Drug Application an Example for Immediate-Release Tablets April 2012.
2) Quality by choice for Abbreviate New Drug Application (ANDA's) An Example for change unleash Tablets Gregorian calendar month 2011.

8. Application of Pharmaceutical QbD for the solubility improvement and Dissolution of sophistication II BCS Drug , exploitation chemical compound, surfactants, and Crystallization Inhibitors: Development of Controlled-release Tablets.

CONCLUSION

Pharmaceutical industry is fast moving with quality being the most important aspect while developing new products. The intention of pharmaceutical industry is based on manufacturing processes and innovation a quality product and healthcare requirement. Implementing quality by design conceptualization in product development provide quality medicines to patients, production enrichment to operator with significantly reduced batch failures and drug regulative bodies can have greater confidence within the robust quality of products. Quality by design helps in characteristics and justifying quality target product profile and helps in continuous improvement. Quality by design has gain important in the space of pharmaceutical processes such as drug development, formulations, analytical method and biopharmaceuticals. The pharmaceutical industry needs a regulatory compliance so as to get their product approved for promoting. QbD is intended to improve the knowledge and is based on existing guidance and reference document. Nevertheless, quality by design is a cost and time efficient approach in manufacturing, with risk assessment and PAT as its tools to accomplish a better understanding on the materials which make the QbD accessible and feasible to the pharmaceutical field.

CONFLICT OF INTEREST

The Author(s) declares "**NO CONFLICT OF INTEREST**"

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