ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

An Outline of Quality by Design in Pharmaceutical Development

K Ramya sri [1], K Bhavani, [1] T Sri Teja, [1] P Srinivasa Babu [1], Pallavi Kurra[1*]
Department of pharmaceutics
1. Vignan Pharmacy College, Vadlamudi [522213], AP, India
*pallavi1203phd@gmail.com

Abstract:
Quality by design (QBD) is a modern approach that began with predefined objects like safety efficacy of the product widely using in the pharmaceutical development. The main aim of QBD in pharmaceutical development is to provide safety, efficacy of the product. QBD focus to impart quality in the design itself. Food and Drug administration introduced QBD to understand the manufacturing process. This paper gives an idea about International council for Harmonization (ICH) guidelines for pharmaceutical development, quality risk management and pharmaceutical quality system, to maintain the quality of the product. A brief discussion on tools used in QBD, regulatory-industry views and scientifically based QBD was given. An emphasis on drug substances, excipients, container closure systems, manufacturing process development was portrayed. Incorporation of QBD in manufacturing process development is increasing day by day quality in the development of product. Elements of various pharmaceutical developments like Quality target product profile, critical quality attributes process analytical techniques, critical process parameters control strategy and design space were mentioned. A mention on the role of QBD in processing of bio therapeutics with relevant examples using process analytical techniques, role of QBD in food processing using the process analytical techniques, QBD on herbal products was presented.

Key Words: ICH Guidelines, Quality by design, QBD on processing of bio therapeutics, QBD on herbal products, QBD for food processing.

1. INTRODUCTION

Quality by design (QBD) is an organized approach to product development that begins with predefined objects and emphasizes product and process understanding and controls based on sound science and quality risk management safety and efficacy of the product. Quality by design (QBD) is first developed by Quality expert Joseph Moses Juan was born in America. In pharmaceutical science QBD was proposed by Food and Drug Administration (FDA). Generally QBD is a scientific approach it is mainly approached by the ICH (International council of harmonization) it follows three ICH guidelines [1]

During the drug development process, many conflicts will occurs like drug substances, excipients, container closure systems, manufacturing processes and quality control tests are critical to identify product quality. To overcome all these conflicts QBD was introduced.

The three approaches include the following ICH guidelines.

Q_8: Pharmaceutical development
Q_9: Quality risk management
Q_{10}: Pharmaceutical quality system

Now a days as improving a high technology pharmaceutical industries are using this to improve the overall quality of the products and to improve some qualities like placed on the market , regulatory compliance decreasing the cost and saving the time and to provide desired pharmacotherapeutic effects mostly to gain knowledge. [2]

Quality was achieved final by the product testing and not by the process design QBD with knowledge of process and varying with the formulation variables.

Predefined objectives make up the Quality target product profile (QTPP). According to the ICH Q_8 guideline, QTPP is a prospective summary of quality characteristics of a drug product to ensure the desired quality, taking into account safety and efficacy of a drug. Through the process development some parameters involve in it they are critical process parameters (CPP) and Critical quality attributes (CQA) of drug product are identified. [3]

2. ICH Q_8 PHARMACEUTICAL DEVELOPMENT

Pharmaceutical development will discuss various elements of Quality by designed strictly regulated for quality of the products. The ICH Q8 guideline is for good practices of the product development. Information from pharmaceutical development studies can be a based on quality risk management. It is important to recognize that quality of the product with good manufacturing process.

ICH Q8 primarily aims for Pharmaceutical Development to design a quality product and its manufacturing process to deliver the product performance and control strategy is designed to product quality. [4]

Drug substances, container closure systems, excipients, and manufacturing processes that are crucial to product quality it should be determined and control by this process. Crucial formulation attributes and process parameters are identified through an estimation of the extent their variation can have effect on the quality of the drug product.

2.1 DRUG SUBSTANCE

The physicochemical and biological properties of the drug substance can affect the presence of the drug product and its manufacturability, especially planned into the drug substances like solid state properties should be identified and discussed. Physicochemical and biological properties might need to be examined including solubility, particle size water content, biological activity crystal properties,

and permeability. These properties could be interrelated and might need to be considered in combination.

2.2 EXCIPIENTS

The excipients can chose their concentration and characteristics which can be influence the drug product performance like stability and bioavailability.

2.3 MANUFACTURING PROCESS DEVELOPMENT

The manufacturing process, process improvement programme should identify any crucial process parameters that should be monitored like granulation process at the end point to ensure that the product is of the desired quality. Significant differences between the manufacturing processes used to produce batches for pivotal clinical trials e.g. safety, efficacy, bioavailability, bioequivalence studies. In sequence to provide pliability for forthcoming process improvement, while describing the development of manufacturing process, it is helpful to express measurement systems that allow observing on critical attributes. Group of process monitoring data during the development of the manufacturing process can supply useful knowledge to build-up process understanding. The process control plan of action provides the process adjustment ability to control of all critical attributes should be described. [5]

2.4 CONTAINER CLOSURE SYSTEMS

Pharmaceutical container is a device that grasp the pharmaceutical product and it may or may not be direct exposure with the product mainly selection of container closure system for the product plays important role use of the drug product and the suitability of the container closure system for storage and transportation (shipping), including the storage and shipping container for bulk drug product by checking the stability and storage of the container closure system it will reduce the interactions of the product. The choice of primary packaging materials should consider the choice of materials, protection from moisture and light, .compatibility of the materials of construction with the dosage form including the sorption to container and leaching, safety of materials for construction. Explanation for secondary packaging materials should be included, when it is applicable. Dosing devices like pen injection device, dropper, pipette, and dry powder inhalers plays a vital role for accurate dose of the product for test products.

2.5 ELEMENTS FOR PHARMACEUTICAL DEVELOPMENT

2.5.1 Quality target product profile (QTPP):

QTPP is initially defined based on properties of drug substances, characterization of the reference product and intend patient population and mainly on safety and efficacy.

A drug product designed, developed and manufactured according to Quality Target Product Profile with specification like dissolution or release acceptance criteria steady with the desired in vivo performance of the product. A QTPP for immediate release formulations will include the following requirements assay, content uniformity, dissolution. These all should be in accordance with specifications to assure the safety and efficacy during shelf life. Tablet should be enough hard to transport and handling, suitable in size for ease of compatibility and patient compliance.

2.5.2 Critical quality attribute's (CQAs):

A CQA is a physicochemical and biological or microbiological property that should be within a suitable range, distribution to certify the desired product quality. CQAs are related with the drug substance, excipients, and intermediary in-process materials along with drug product. It can be identified from target product profile and prior knowledge are used to guide the product development, 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 specific aspects, such as aerodynamic properties for inhaled products, sterility for parenteral, and adhesion properties for transdermal patches. For drug substances, raw materials and intermediary, the CQAs as well they include those properties (e.g., particle size distribution, bulk density) that affect drug product CQAs. Potential drug product CQAs obtain from the quality target product profile and. The list of potential CQAs can be modified when the formulation and manufacturing process are selected and as product knowledge and process understanding increase.

Table 1: CQA'S appearance based on dosage forms

For Drug Substance [Chemical]	For Drug Product [Tablet]
Appearance Particle size	Appearance
Particle size	Identification
Morphic forms	Hardness
Water content	Physical form
Residual solvents	Uniformity of dosage
Organic impurities	Dissolution
Heavy metals	Degradation products
Assay	Water content
Residue on ignition	Assay

2.5.3 Critical process parameters (CPP):

A process parameter whose variability has an impact on a critical quality attribute and it should be observation to ensure the process to produces the desired quality.

2.5.4 Process analytical techniques (PAT):

PAT is a system for designing, analysing controlling and manufacturing through the timely measurements of parameters like critical quality and performance attributes of raw materials and in process materials and process with the goal of ensuring final product of the quality. Used in development to gain knowledge about the process understanding. Executed in routine manufacturing to monitor process, control product quality and reduce release testing control. PAT testing can replace additional with laboratory testing. [6]

2.5.5 Design space:
Multidimensional combination and interaction of input variables and process parameters that have been demonstrated to provide a science of quality denoted as design space. ICH Q8 guide line shift pharmaceutical product development in the form of trial and error process to scientifically based process of design space appointment. The relationship between the process inputs, material attributes and process parameters and the critical quality attributes can be designed in design space.
Selection of Variables
Describing a Design Space in a Submission
Unit Operation Design Space(s)
Relationship of Design Space to Scale and Equipment
Design Space versus Proven Acceptable Ranges
Design Space and Edge of Failure.

2.5.6 Control strategy:
Control strategy is defined as it is designed as to make sure that the product of a required quality will be produced. In this control strategy the elements mainly influence the final product is in-process controls, input of the materials, in-process materials, container closure systems and drug products [7]

- Risk based decision
- Continuous Improvement
- Product performance

3. ICHQ9: QUALITY RISK MANAGEMENT

Risk is defined as the combination of possibility and incidence of causing harm and the severity of that harm.
The two principles are involved on the quality risk management

1. The evaluation of the risk to quality should base on scientific knowledge
2. The level of effort, formality and documentation of the quality risk management process.[8]

Quality risk management process
Quality risk management is a planned process for the assessment, control, communication and review of risks to the quality of the drug product across the product lifecycle.
In these given figure 1 decision nodes are not shown in the diagram because decisions can held at any point in the process. Sometimes these decisions might be to return to the previous step and look up for further information, to adjust the risk models or to eliminate the risk management process. [9]

Risk assessment consists of the recognition of hazards and the analysis and evaluation of risks associated with exhibition to those hazards risk assessments begin with a well-defined problem description. Risk management methods are as follows.
Failure Mode Effects Analysis (FMEA)
Failure Mode, Effects and Criticality Analysis (FMECA)

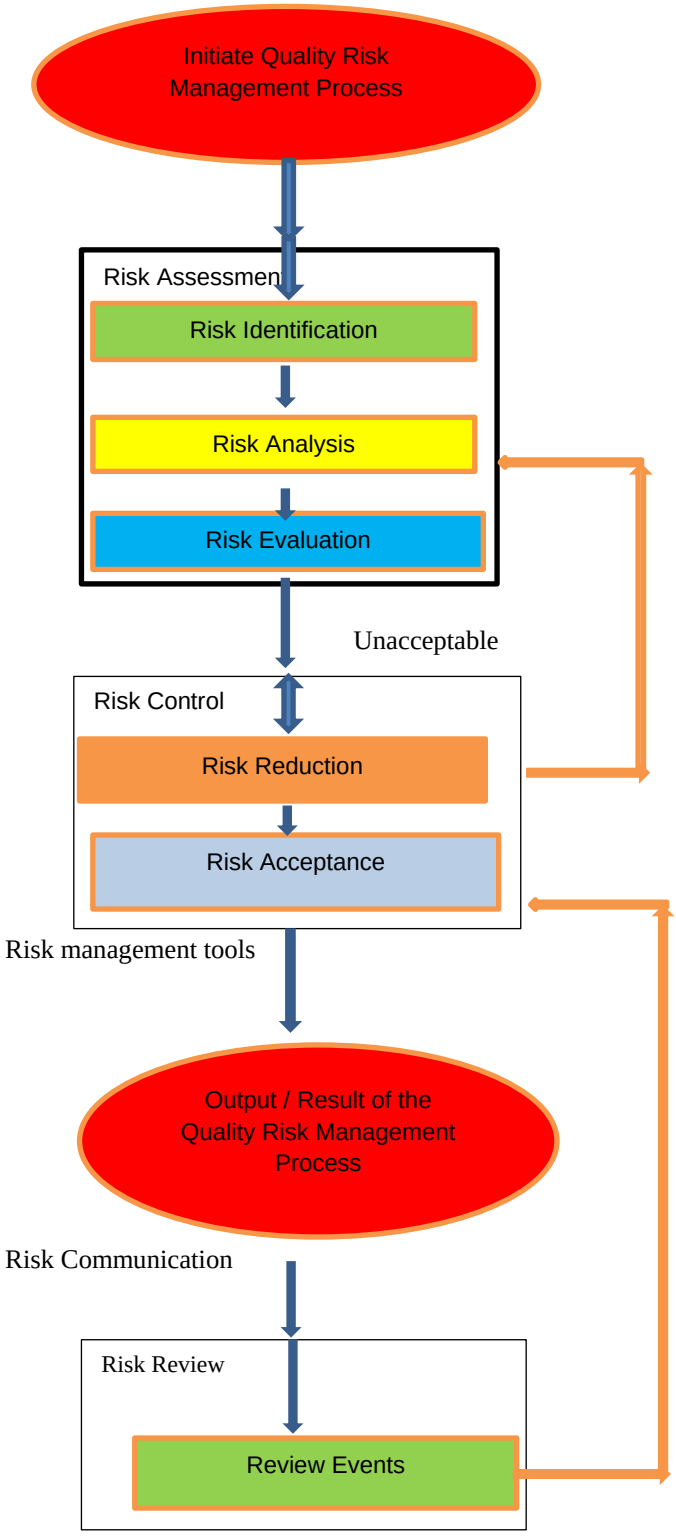

Figure 1: Overview on quality risk management process

4. ICH Q10 PHARMACEUTICAL QUALITY SYSTEM

A control planning usually include input material controls process controls and monitoring, design space around single or multiple unit operations, used to certify steady quality. [10] The finished drug products are tested for quality by estimating if they will meet the specifications.

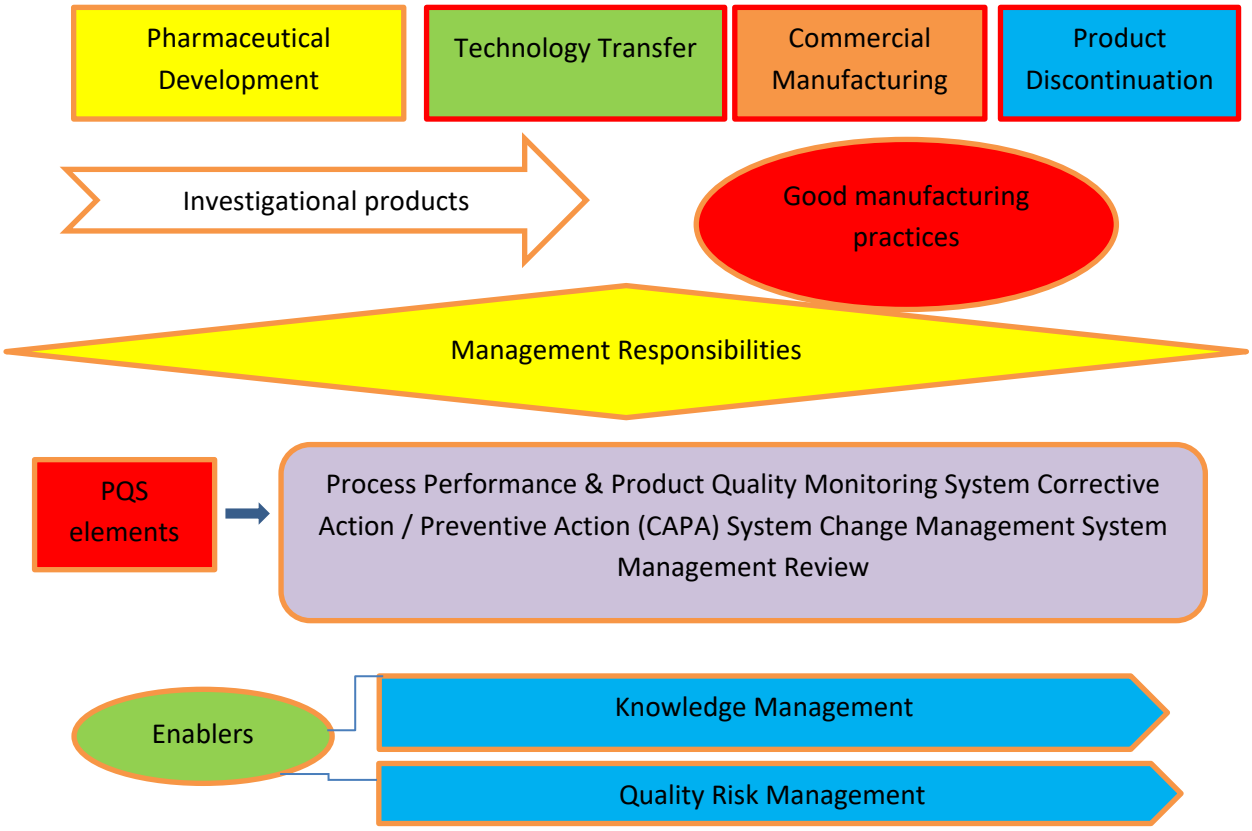

Figure 2: Overview of pharmaceutical Quality system [11]

5. QUALITY BY DESIGN TOOLS

Design of experiment (DOE) tools is used in QBD. Some of the tools are listed below.

- Statistical design of experiments
- Factorial designs
- Full factorial designs
- Fractional factorial designs
- Two- level factorial designs
- Three – level factorial designs
- Optimized designs
- Placket-Burman Designs (PB)
- Central Composite Design (CCD)
- Box-Behnken Designs (BBD)
- Multivariate Data Analysis (MVDA).[12]

6. QBD ON PROCESSING OF BIO THERAPEUTICS

Now a days Biotechnology based products have become expanding more important in recent years in treatment of chronic diseases like cancer and arthritis. In biopharmaceutical manufacturing process, there are numerous batch processing unit operations samples are taken to make sure that the process is in control and gain the quality of the product. [13]

Table 1: QBD implementation for processing of Bio therapeutics [15, 16]

PAT processing in bio therapeutics	
Application	**Output**
Estimating product concentration and affinity using Surface Plasmon Resonance [SPR]	For detecting the antigen and antibody complexes
Estimating product concentration and affinity using High performance liquid chromatography	For detecting the metabolites
Biomass Determination using dielectric spectroscopy	Closed-loop control of medium feed rate in fluidized bed fermenters
Characterization of cell population using microscopy with processing image and computer control	Specific growth rate used to control product formation in agitated cell broth cultivation
Detection of media components, metabolic end products, sensing metabolic process failure using Near infrared [NIR] spectroscopy	Monitoring and control of a Staphylococcus xylosus

This may be achieved by employing the real-time measurements, open and closed-loop controls, and monitoring to achieve the good quality of the product. In order to identify, monitor and control variability in materials and in the process new technology was introduced, such as advanced process analytical technologies can be incorporated in the process development.

Multivariate data analysis (MVDA) approaches like Principal Components Analysis (PCA) and Partial Least Squares (PLS) have been used to hold the complexity of bioprocess data such as the large collinearity, large number of variables and missing data. [14]

7. QBD FOR FOOD PROCESSING

In recent days determining and predicting the quality, safety and nutritional values in both raw and processed foods is becoming more valuable information because of attacking severe diseases which leads to life threatening [17]. Food quality will be identified based on the following criteria

Authenticity: Foods which comes naturally or traditionally that are synthesizes during production, storage

Function: Quality of food based on the function like storage capacity and cooks well

Biological activity: Food interaction on the body both positively and negatively.

Nutrition: Nutrition food interactions on both positive and negative aspects.

Sensual: supply of the food to the senses like smell, taste, texture of the food. [18]

Table 2: QBD implementation in food processing [20, 21]

PAT in food processing	
Application	**Output**
For milk NIR spectroscopy was used to determine coagulation	Real time predictive kinetic is observed
For meat online Infrared spectroscopy [IV] was used to measure fatty acid unsaturation	A new tool for carcass-grading not only based on metric measures of fat but also on true fat quality characteristics.
For Oranges, peaches, strawberries checked physical parameters using various techniques	Parameters are successfully identified
For Onions , peas Wheat, barley, fava beans and potatoes Inductively Coupled Plasma-Mass Spectrometry [ICP-MS] to measure trace elements and analysis	Clear separation between organic and conventional samples was obtained
For Wheat grains Wheat ears and grains to Gas Chromatography Mass Spectrometry (GC/MS) to measure metabolites	Differences in metabolite concentrations detected

Modelling techniques used in food processing is Design expert. In QBD mechanistic modelling is used for food processing organic products will be examined using the fingerprinting approaches. PAT approaches within the manufacturing of food processes to enhance process economics and compliance with the standards, quality, and safe food supply chains. To minimize the risk and increase the safety, quality of the food products various techniques are develops in food manufacturing process. PAT using different approaches in food processing and CAQ and CPP these are involved in the food processing for best quality of the food. [19]

8. QBD FOR HERBAL PRODUCTS

Herbal medicinal system is developed in olden days. In ancient days these herbal medicines used to treat various diseases. These Herbal products have played an important role in world health and make an important contribution to health care in spite of the great advances observed in modern medicine in recent decades [22]

According to an estimate of the World Health Organization (WHO), about 80 % of the world population uses herbs and other traditional medicines. They are known for their safety, efficacy, cultural acceptability and lesser side effects. This has led to phenomenal increase in the demand for herbal supplements in the last two decades and a need has been felt for ensuring the quality, safety and efficacy of herbal drugs. [23]

Since Quality and safety is considered to be a major issue with the use of herbal supplements, it becomes imperative, that appropriate quality assessment measures should be put in place to protect public health by ensuring that all herbal medicines are safe and of suitable quality. The need of this to evolve an organized approach and to develop well-designed methodologies for the development herbal products. [24]

9. REGULATORY AND INDUSTRY VIEWS ON QBD

The application of QBD has permeated and practice of several industrial environs. The regulatory agencies and the pharmaceutical Design industry across the globe are striving hard to implement the QBD paradigms for improving the quality of drug products for patients benefit and for safety.

QBD has proved to be an organized approach applicable in all the areas of pharmaceutical development areas.

AS defined as an FDA official, the QBD concept represents the product and process performances, characteristics scientifically designed to meet specific objectives, not simply seen, derived from performance of the test batches.

FDA representative states that introduction of QBD concept leads to cost savings and efficiency improvements for both regulatory and industry basis.

10. SCIENTIFICALLY BASED QBD –EXAMPLE OF APPLICATION

Quality built into product and process by design is based on scientific understanding

A combined QBD and Discrete element model (DEM) was used to identify a blending unit operation by evaluating the effect of formulation parameters and process variables on the blending quality and the blending end point.

QBD was used to establish content uniformity as CQA and link to blend homogeneity to identify crucial factors that affect blending operation quality and risk rank of these factors to define activities for process characterization. Results obtained were used to draw a 3D knowledge space providing parameters to define design space and set upon an appropriative control strategy. [25]

11. CONCLUSION

QBD process is plays an important in pharmaceutical industries for product safety and efficacy. ICH guideline maintains the product safer, and able to detect the risk during the manufacturing process. The QBD process on an active association of analytical scientists at both the development and operational laboratories as methods are established as factors that lead to potential method failures are identified and controlled. QBD for bio therapeutics products plays a important role for safety and cost reduction. A QBD approach for analytical methods that include risk assessment, robustness testing, and ruggedness testing is much more important for the ICH validation. Quality cannot be tested into products but should be built-in or should be by design. Benefits of QBD application for both regulatory and manufactures have been proven. It is clear that QBD has become a necessity therefore the entire stake holders should adopt to its implementation. Overall QBD is very important for developing the best Quality products.

REFERENCES

[1]. Nishendu P., Nadpara, Rakshit V., Thumar, Vidhi, Kalola N., Parula and Patel B. *Quality by design (QBD) a complete review*. International Journal of Pharmaceutical Sciences Review and Research. 2012, *17*, 20-28.

[2]. Vemuri Pavan Kumar, Vishal Gupta N. *A Review on quality by design approach (QBD) for Pharmaceutical.* International journal of drug development and research. 2015, *7*, 35-60.

[3]. Anuj M., Gourab Gochhayat, Shamshir A., Manish Kumar, Preeti P., Raj S and Vipin S. *Quality by Design: A new practice for production of pharmaceutical products*. Journal of Drug Delivery and Therapeutics. 2019, *9*, 416-424.

[4]. Q8 (R1): Pharmaceutical Development, Revision 1. ICH Harmonized Tripartite Guidelines, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. 2007.

[5]. Lawrence X Yu., Pharmaceutical Quality by design: *Product and process development, Understanding and control.* National library of medicine (PubMed). 2008, *25*, 781-791.

[6]. Dispas, Avohou A., Lebrun H T., Hubert P., and Hubert C. *Quality by Design approaches for the analysis of impurities in pharmaceutical drug products and drug substances.* TrAC Trends in Analytical Chemistry. 2017,*101*, 24–33.

[7]. James Munson, Freeman Stanfield C and Gujral B. *A review of process analytical technology (PAT) in the U.S. pharmaceutical Industry.* Current pharmaceutical analysis. 2006, *2*, 405-415.

[8]. Q9: Quality Risk Management. ICH Harmonized Tripartite Guidelines. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. 2006.

[9]. Patwardhan D M., Amrutkar S S., Kotwal T S. and Wagh M. A*pplication of quality by design to different aspects of pharmaceutical technologies.* International Journal of Pharmaceutical sciences and journal. 2017, 3649-3662.

[10]. Q10: Pharmaceutical Quality System. ICH Tripartite Guidelines. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. 2007.

[11]. Janet Wood cock. *The concept of pharmaceutical Quality.* A Journal of American pharmaceuticals review. 2004, *7*, 10-15.

[12]. Deepika P., Manisha S., Parijat P., Swagat T. and Harish D. *Implementation of Quality by Design: A Review.* Applied drug research, clinical trials and regulatory affairs journal. 2019, *6*, 99-111.

[13]. Noll T., Biselli M. *Dielectric spectroscopy in the cultivation of suspended and immobilized hybridoma cells.* Journal of Biotechnology. 1998, *63*, 187-198.

[14]. Cenk Undey., Mistretta T., Sinem Ertunc and Bryan Looze. *Applied advanced process Analytics in Biopharmaceutical Manufacturing: Challenges and prospects in real-time monitoring and control.* Journal of process control. 2010, *20*, 1009-1018.

[15]. Sitton G., Srienc F. *Mammalian cell culture scale-up and feed-batch control using automated flow cytometry.* Journal of Biotechnology. 2008, *135*, 174-180.

[16]. Silvia G., Lorenzo S., Ernestina C. and Cristina A. *Control and monitoring of milk renneting using FT-NIR Spectroscopy as a process analytical tool.* Asian Journal of Pharmaceutical Sciences. 2018, *12*, 1-10.

[17]. Cubero-Leon E., Olivier De Rudder and Alain Maquet. *Metabolomics for organic food authentication: Results from a long term field study in Carrots.* Journal of Biotechnology. 2018, 760-770.

[18]. Zhang L. & Mao S. *Application of quality by design in the current drug development.* Asian Journal of Pharmaceutical Sciences. 2017, *12*, 1-8.

[19]. Jaiprakash N., Sangshetti, Mrinmayee D., Rohidas A., *Zahid Zaheer and Devanand B. Shinde. Quality by design approach: Regulatory need.* Arabian Journal of Chemistry.2014, 22-34.

[20]. Vogt F G. & Kord A S. *Development of Quality-By-Design Analytical Methods.* Journal of Pharmaceutical Sciences. 2011, *100*,797–812.

[21]. Marique A. and Marnus M. *The physical stability of drugs linked to quality-by-design (QBD) and in-process technology (PAT) perspectives.* European Journal of Pharmaceutical Sciences. 2019, *139*, 12-32.

[22]. Calixto J B. *Efficacy, Safety, Quality Control, Marketing and regulatory guidelines for herbal medicines (Phototherapeutic Agents).* National library of medicine (PubMed). 2000, *33*, 179-189.

[23]. Dnyaneshwar W., Bhushan, Patwardhan K. *Botanicals: Quality and Regulatory Issues*. Journal of Scientific and industrial Research. 2005, *64*, 83-92.

[24]. Kritika K. and Rajiv G. *Bioavailability enhancers of herbal origin: An overview.* Asian pacific journal of tropical Bio medicine. 2013, *3*, 253-266.

[25]. Helena B G., Claudia S., Sergio Paulo S. and Marcoreis S. *Quality by Design in Pharmaceutical Manufacturing a systematic review of current status, challenges and future perspectives.* European journal of pharmaceutics and Biopharmaceutics. 2020, *147*, 19-37.