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QUALITY BY DESIGN: CHANGING OUTLOOK OF PHARMACEUTICAL DEVELOPMENT

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Quality by design (QbD), Quality target product profile (QTPP), Critical quality attributes (CQAs), Risk assessment, Pharmaceutical development

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ABSTRACT: The concept of quality by design (QbD) justifies the saying that, quality is not an act, it is a habit. This innovative and systematic approach to pharmaceutical development based on scientific principles has been a breakthrough in developing quality products with a high level of reproducibility. The process of QbD is based on risk management which leads to a better understanding of the product and its manufacturing process, resulting in products with required quality, safety, and efficacy. As the quality and reliability requirements of today's world are constantly increasing, QbD serves as an important tool in outperforming the global competition. This paper comprehensively discusses the concept of pharmaceutical quality by design, elements of QbD; quality target product profile (QTPP), critical quality attributes (CQAs), design space, control strategy, and lifecycle management. Application of QbD across various fields of pharmaceutical development including formulation development, analytical method development, phytopharmaceutical & biopharmaceutical product development are encompassed in the review.

INTRODUCTION: Pharmaceutical industry is rapidly growing, with quality being the most important aspect while developing new products. The goal of pharmaceutical development activities is to design a reproducible high-quality product and efficient manufacturing processes which would fulfill all regulatory and healthcare requirements. Quality by design (QbD) is a new approach in pharmaceutical development which focuses on building quality into the product rather than testing it later.

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ICH Q8 defines QbD as "a systematic approach to development that begins with predefined objectives & emphasizes product and process understanding and process control, based on sound science and quality risk management." QbD essentially involves designing and developing a product and its manufacturing process with predefined quality characteristics. QbD hence establishes an understanding of how material and process variables influence the product quality [1, 2, 3].

Objectives of Quality by Design: Pharmaceutical QbD has the following objectives:

- To establish a better understanding of product and process.
- To achieve a higher degree of assurance of drug product quality.
- To reduce product recall and rejects.

- To accelerate product development and manufacturing activities.
- To make regulatory filings and post-approval changes easier.
- To implement innovative changes throughout the product life cycle.

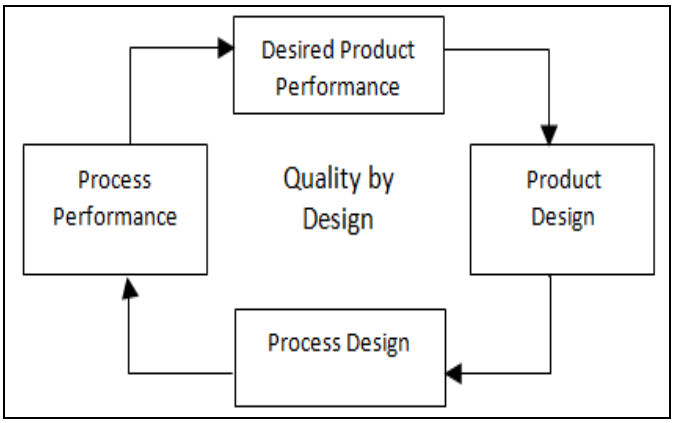

FIG. 1: DIAGRAMMATIC REPRESENTATION OF QbD

History of QbD: Dr. Joseph M. Juran was known as 'Father' of quality, first described the term Quality by Design in 1992 to achieve breakthroughs in new products, services and processes [4]. Later QbD was implemented by automobile, technology, telecommunications, aeronautics, and medical devices industry. Emerge of pharmaceutical quality by design began in 2002, when FDA announced in a concept paper, a new initiative "Pharmaceutical cGMPs for the 21st century". This encouraged pharmaceutical manufacturers to explore QbD [5]. In 2004, the final report on "Pharmaceutical cGMPs for the 21st century-A risk-based approach" was published by FDA and then progress report followed up in May 2007. [6]

Milestone activities that took place after the initiation of Quality by Design approach are:

- Pharmaceutical quality assessment system (PQAS) was established in the FDA's Office of New Drug Quality Assessment (ONDQA) which emphasizes on quality by design in the evaluation of critical aspects of pharmaceutical quality.
- Pharmaceutical manufacturers were encouraged to submit New Drug Applications demonstrating the use of QbD and in 2006 Merck's Januvia became the first product approved based on QbD application.
- International Council for harmonization of technical requirements for pharmaceuticals for Human Use (ICH) described the principles of QbD in its quality guidelines 1.
- On November 1st, 2013 Roche's Gazyva became first QbD approval including design space for a biologic license application.

A process of QbD: [7] Pharmaceutical quality by design is a systematic approach in which product specification, manufacturing process, and critical parameters are identified.

The traditional approach for ensuring product quality and performance known as pharmaceutical quality by testing (QbT) includes raw material testing, a fixed drug product manufacturing process, in process material testing and end product testing which significantly differs from QbD.

QbD implements a flexible and robust manufacturing process that is adaptable and yield reproducible results. Knowledge management and quality risk management play a crucial role in the development and implementation of QbD.

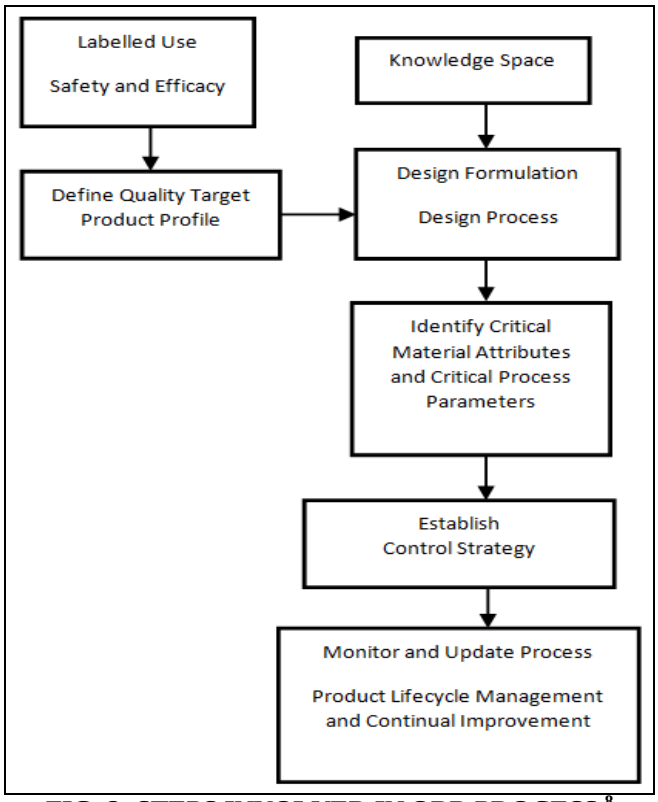

FIG. 2: STEPS INVOLVED IN QBD PROCESS [8]

Elements of Quality by Design: [1, 9] In a QbD approach to product development there is the

identification of characteristics that are critical to quality from the patient's perspective.

QbD consists of the following elements:

1. Defining the quality target product profile (QTPP) which relates to quality, safety, and efficacy.
2. Identifying potential critical quality attributes (CQAs) of the drug product for studying and controlling those product characteristics which have an impact on product quality.
3. Identification of critical material attributes (CMAs) and critical process parameters (CPPs) and linking of CMAs and CPPs to CQAs.
4. Defining a control strategy that includes specifications and controls for each step of the manufacturing process.
5. Product lifecycle management and continual improvement.
6. These elements provide a more systematic approach to pharmaceutical development facilitating innovation.

Quality Target Product Profile: ICH Q8 describes quality target product profile (QTPP) 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." It includes:

- Therapeutic use,
- Dosage form,
- Route of administration,
- Dosage strength,
- Pharmacokinetics,
- The container closure system, *etc*.

Critical Quality Attributes: A critical quality attribute (CQA) is "A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality." It includes but not limited to:

- Assay,
- Dissolution/Drug release,
- Sterility,
- Degradation products,
- Crystallinity.

Risk Assessment: Risk assessment is linking material attributes (Density, particle size distribution, moisture content, *etc*.) and process parameters (Temperature, the rate of drying, mixing speed, *etc*.) to drug product's CQAs. Risk assessment is a scientific process which comes under quality risk management; it facilitates in identifying which material attributes and process parameters potentially affect product CQAs. After parameters are identified mathematical tools are utilized to achieve a higher level of process understanding.

Design Space: Design space is an essential element of QbD, it describes the relationship between the process inputs (material attributes and process parameters) and the critical quality attributes.

- A design space is either described in terms of ranges of material attributes and process parameters or using complex mathematical relationships.
- A design space is a better way to represent the established process of understanding.
- Operations within the design space results in products with desired quality characteristics.

Control Strategy: The role of the control strategy is to ensure that the products of the required quality are developed consistently. It consists of:

- Input material controls (Drug substance, excipients, packaging material, *etc*.)
- Control for maintaining the predefined product specifications.
- Control for critical process parameters.
- Real-time release testing.
- Overall monitoring program.

Product Lifecycle Management and Continual Improvement: Continual improvement is the essence of the QbD process. Over the lifecycle of a product, certain process changes are required for further improvisation. It is necessary that the improvisation is being carried within the design space. With the help of data collected throughout

the product lifecycle, innovative approaches can be applied to improve product quality.

Quality by Design in Formulation: When QbD principles are applied, it results in a better understanding of the process which ultimately leads to a robust formulation with predefined quality characteristics. QbD is applied to various aspects of formulation development which are described below:

Novel Drug Delivery System: Developing new dosage forms is a challenging process, and huge money is invested in R & D. Using QbD ensures a quality product right from the beginning which saves time and effort in developing the desired formulation. A case study carried out by Kan *et al*., described the preparation of Naproxen enteric coated pellets by fluidized bed coating using the QbD principle. Acid resistance and cumulative drug release were identified CQAs, based on which design space was established. Confirmation tests showed that the predicted and the response values of the formulations with different variables were similar, thus the validity of the model was established and all the parameters were robust within design space [10].

TABLE 1: RECENTLY DEVELOPED NOVEL DRUG DELIVERY SYSTEM BASED ON QbD [13-22]

Year	Author(s)	Area of study	Parameters evaluated	Outcome
2018	Leng *et al*.,	Engineering of budesonide-loaded lipid-polymer hybrid nanoparticles using a QbD approach	Hydrodynamic particle diameter, polydispersity index, zeta potential, and budesonide encapsulation efficiency	Systematic formulation the design is achieved by identifying optimal operation space (OOS) by QbD
2018	Bakonyi *et al*.,	Application of quality by design in the development and evaluation of drug carrier systems for the transdermal delivery of lidocaine	Solubility and homogeneity of API, *in-vitro* drug release, moisturizing effect, and viscosity	QbD initial risk assessment and evaluation lead to the conclusion that nanostructured lipid carrier is an efficient vehicle for topical delivery of lidocaine
2018	Chudiwal *et al*.,	Development of sustained release gastro-retentive (SRGR) tablet of nicardipine hydrochloride by QbD approach	Assay, drug release and floating-lag time	Development of SRGR tablet with reduced development time, cost and manpower
2017	Gavan *et al*.,	Formulation of quetiapine fumarate sustained release matrix tablets using a QbD approach	Dissolution release profile and kinetic drug release	Fast development of sustained release quetiapine tablets
2017	Hales *et al*.,	Pharmaceutical development of enoxaparin sodium loaded polymeric microspheres for colon-specific delivery	Particle size, encapsulation efficiency, and percentages of drug released	Optimum formulation is prepared with close to ideal *in-vitro* release profile
2017	Kovacs *et al*.,	QbD based development of n and structured lipid carriers of salicylic acid for dermal use	Particle size, particle size distribution, dissolution efficiency, lipid solubility, surfactant concentration and ultra-sonification time	Significantly high *in-vitro* drug release is achieved through optimization by QbD
2016	Bansal *et al*.,	Development and characterization of effervescent floating-bio adhesive tablets of cefuroxime axetil by quality by design	The concentration of release control polymers, *in-vitro* buoyancy, *ex-vivo* mucoadhesion strength, and drug release	Successful development of once a day gastroretentive tablet of cefuroxime axetil having controlled drug release profile
2016	Bansal *et al*.,	Development of gastroretentive multiple unit micro balloons of itopride hydrochloride by QbD	Percentage yield, entrapment efficiency, buoyancy, stirring temperature, stirring speed and the drug-polymer ratio	Hollow and spherical shaped microspheres are achieved by evaluating factors affecting drug CQAs
2015	Pallagi *et al*.,	Adaptation of the quality by design concept in the pharmaceutical development of an intranasal nanosized formulation	Surface area, excipients, dissolution, permeability and rotation time	The study confirmed the QbD based method reduces the development time, needs fewer human resources and effective target orientation is achieved
2015	Ahmed *et al*.,	QbD based formulation of transdermal glimepiride liposomal films	Drug, cholesterol and phosphatidylserine concentrations, pH of hydration medium, plasticizer and polymer percentages	Liposomes of effective entrapment capacity and drug release is developed by thorough understanding of the process

A recent paper by Porfire *et al*. illustrates the use of a QbD approach for the development of lyophilized liposomes of simvastatin. Formulation factors mainly PEG proportion, cholesterol concentration, cryoprotectant to phospholipids molar ratio are identified. Two process parameters, the no. of extrusions through 100 nm polycarbonate membranes and freezing conditions prior lyophilization are also taken into account. Among the formulation factors, the cholesterol concentration had a significant effect on the CQAs of the product, and hence lyophilized liposomes with predictable quality were developed [11]. Recently developed novel drug delivery system based upon QbD are summarised in **Table 1**.

Coating Process Optimization: Variability in the coating thickness is a common problem during tablet coating; it alters the aesthetics and taste masking properties. QbD approach can be applied to optimize the coating process thus reducing coating variability. The approach consists of achieving an optimal set of operating conditions which includes the amount of coating material, pan rotation speed, spray rate, and spray temperature. Appropriate CQAs are identified, and the optimum ranges of these parameters are established which leads to improved coating process, examples of which are given in **Table 2**.

Enhanced Manufacturing Process: QbD provides a thorough understanding of the manufacturing process; all critical factors of variability are identified and explained. QbD emphasizes on controlling process output using real-time release testing which enables continuous tracking of the process. QbD is encouraging the use of new technologies to improve manufacturing processes like the use of morphologically directed imaging, in which imaging technology and spectroscopy are combined to provide chemical identification and physical measurements of the material under process [12]. **Table 3** describes how QbD resulted in designing an efficient manufacturing process.

TABLE 2: APPLICATION OF QbD IN COATING PROCESS OPTIMIZATION [23-27]

Year	Author(s)	Area of study	Parameters evaluated	Outcome
2018	Thapa *et al*.,	Effects of pharmaceutical processes on the quality of ethylcellulose coated pellets by QbD	Drug release at different intervals, content uniformity, appearance, and pellet density	Smooth and homogenous film is formed
2017	Nayak *et al*.,	QbD approach for coating process parameter optimization	Pan pressure, pan speed, spray rate, inlet air temperature and atomization air pressure	Effective coating process and coating formulation resulted in predicted weight gain and surface roughness
2017	Kim *et al*.,	Design of experiments for the coating process of a fixed-dose combination tablet	Spray rate, pan speed, inlet temperature, disintegration time and dissolution	Successful implementation of QbD to obtain a wide range of CQAs for fixed-dose combination tablets
2013	Teckoe *et al*.,	Process optimization of an immediate release film coating system using QbD	Coating time, gloss, bed temperature, air flow and spray rate	High-quality tablet appearance is achieved with consistent disintegration and dissolution
2010	Prpich *et al*.,	A QbD approach for scale-up of tablet film coating	Atomization air pressure, Upper and lower inlet air temperature and upper and lower spray rate condition	No. of required trial runs are minimized and the process focuses optimization rather than validation

TABLE 3: QbD APPROACH IN ENHANCING MANUFACTURING PROCESS [28-32]

Year	Author(s)	Area of study	Parameters evaluated	Outcome
2018	Santos *et al*.,	QbD approach in understanding pharmaceutical excipients properties and screw feeder performance	Bulk density, powder flow properties, hopper volume and screw speed	Continuous stable feed rate can be obtained by identifying critical sources of variability of powder excipients
2018	Jin Ko *et al*.,	Granulation development in batch and continuous processes from a QbD perspective	Blend uniformity, dissolution rate, flowability, moisture content, compressibility, and granule brittleness	No significant difference between batch and continuous processing of granules by QbD
2017	Grymonpre *et al*.,	Downstream process from hot-melt extrusion	Barrel temperature, screw speed, throughput	Amorphous glassy solutions are obtained with minimal impact of

		towards tablets by QbD approach	and drug load	process parameters on extrudate and tablet properties
2017	Maniruzzaman *et al*.,	A QbD approach for processing water insoluble drugs	Binder amount, excipient composition, liquid to solid ratio, surface area, particle size, and drug dissolution rates	Dissolution rates are enhanced with increase in water absorption for granules
2015	Freeman *et al*.,	Quality by design in continuous tablet manufacture	Screw speed, water content and powder feed rate	Specific tablet properties can be generated by using different combinations of process conditions

Quality by Design in Phytopharmaceuticals: Quality by Design for the development of herbal products is comparatively new but has expanded over a few years. Quality of phytopharmaceuticals is a concern not only for the safety of patients but also for the standardization of herbal products. It plays a significant role in increasing the confidence of patients in the quality of plant-based products. The main challenge of applying QbD approach in herbal products is the natural variation in the plant species due to the genetic and environmental factors. Thus, well-defined quality standards and process knowledge are essential in developing a robust, reproducible phytopharmaceutical products. Development in the field of quality by design in phytopharmaceuticals is summarized in **Table 4**.

TABLE 4: SIGNIFICANT ADVANCES IN APPLICATION OF QBD APPROACH TO PHYTO-PHARMACEUTICALS [33-36]

Year	Author(s)	Area of study	Parameters evaluated	Outcome
2017	Uhlenbrock *et al*.,	QbD process evaluation for phytopharmaceuticals from Yew	Raw material variation, vaporization, load, and flow rate	Maximum yield is obtained with less experimental effort and time during development
2014	Yan *et al*.,	Designing a control strategy and defining acceptable ranges of CQAs for herbal drugs	Total solid, the concentration of constituents and solvent flow rate	Proposed control strategy and acceptable ranges for CQAspromoted implementation of QbD in herbal drugs
2013	Zhang *et al*.,	Application of QbD to the process development of botanical drug products	A density of concentrate, ethanol consumption, and temperature	Enhanced understanding of the performance of ethanol precipitation is achieved
2012	Khan *et al*.,	Implementing a QbD approach for assuring safety and integrity of botanical dietary supplements	NA	Described several techniques for authentication of plant material

Analytical Quality by Design: Quality by design finds great application in analytical method development, the aim of analytical QbD (AQbD) is to develop a robust method which is applicable throughout the life cycle of the drug product and on similar products containing the same active ingredient. Analytical QbD provides flexibility in the analysis of API, drug impurities and biological metabolites. **Table 5** summarizes recent applications of AQbD.

Analytical Target Profile (ATP): Analytical target profile is parallel to QTPP, defining the goal of the analytical method development process. The Pharmaceutical Research and Manufacturers of America (PhRMA) and European Federation of Pharmaceutical Industries and Associations (EFPIA) define ATP as "A statement that defines the method's purpose which is used to drive method selection, design and development activities." ATP consists of identifying target analytes and selecting the suitable analytical technique for carrying out process [37].

Method Operable Design Region (MODR): MODR is the analog of "design space" in analytical QbD. It describes the operating range for critical input variables to achieve the ATP [37]. Working in MODR provides flexibility in changing the method input variables without any post-approval changes.

The process of Analytical QbD: [38] Process of analytical QbD broadly consists of:

- Defining the objectives of method development, laying emphasis on product and process understanding and establishing an analytical target profile (ATP).

- Performing experimental design which consists of a selection of analytical technique, obtaining method understanding and performance optimization and designing MODR.
- Finally, risk assessment and method verification are performed to prove that method is applicable throughout the product lifecycle with robustness and ruggedness.

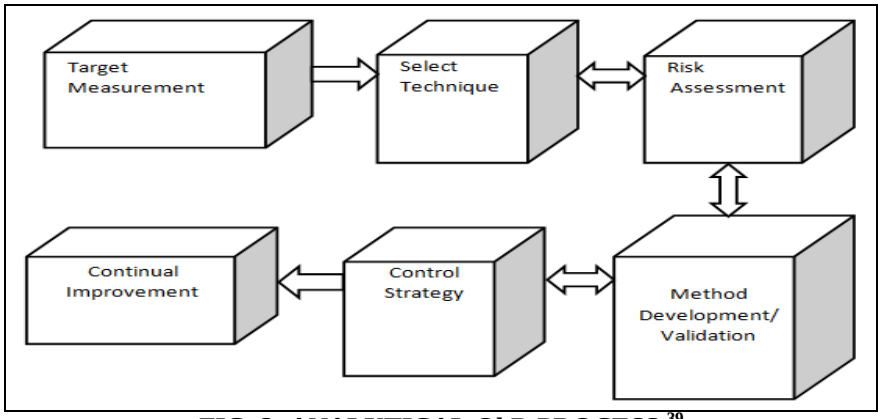

FIG. 3: ANALYTICAL QbD PROCESS [39]

TABLE 5: RECENT APPLICATIONS OF ANALYTICAL QUALITY BY DESIGN [40-44]

Year	Author(s)	Area of study	Parameters evaluated	Outcome
2018	Shao *et al*.,	QbD based development of the HPLC method to analyze herbal extracts	Retention time, initial and final solvent content in the mobile phase, flow rate, gradient run time, column temperature	An accurate and precise method is developed by using AQbD for the identification of critical variables
2018	Zacharis *et al*.,	Application of AQbD for determination of alkyl sulfonates impurities	Peak efficiencies of analytes, analysis time, flow rate, gradient slope, and acetonitrile content	Optimum separation conditions are estimated leading to a simple and robust method
2017	Bossunia *et al*.,	Development of stability indicating RP-HPLC method for estimation of canagliflozin by QbD	Mobile phase composition, diluents, λ_{max}, and column composition	A consistent and reliable method for routine analysis of canagliflozin in quality control labs is developed
2016	Terzic *et al*.,	Application of AQbD for bilastine and its degradation impurities determination	Ammonium acetate concentration in the aqueous phase, acetonitrile content in the mobile phase, pH of the aqueous phase and retention factor of impurities	Optimal and robust chromatographic conditions are established with applicability for real samples of bilastine
2016	Yao *et al*.,	Analytical quality by design for the development of L-asparaginase activity method	The ratio of potassium iodide to mercuric iodide, sodium hydroxide to mercuric iodide and final mercuric iodide concentration, reaction temperature, pH, and L-asparaginase concentration	Efficient determination of activity of unstressed and partially denatured L-asparaginase by defining the design space

Quality by Design in Biopharmaceuticals: A biopharmaceutical also known as a biologic or biological is a pharmaceutical product that originated from biological sources. In September 2004, the United States Food and drug administration published process analytical technology (PAT) Guidance, PAT-A framework for innovative pharmaceutical development, manufacturing, and quality assurance [45]. These publications encouraged the use of QbD for biological products. QbD principles are being adopted by the biotechnology industry to develop safe and effective biologics [46]. QbD provides a systematic way of development of biologicals to prevent lot failures and to reduce variability in product quality. As cost is an important factor while developing biologicals, thorough product, and process understanding, proves to be more efficient and cost-effective.

Challenges in implementing QbD to Biologics: [47]

- Biologics are complex, and there is a limited understanding of CQAs and CPPs
- Biotechnological processes consist of many process variables and a large number of raw materials

- Scale-up and technology transfer is difficult to predict
- Lack of harmonization and clarity across different regulatory bodies

Steps to Overcome Challenges:

- Increased understanding of the impact of quality attributes on safety and efficacy is required.
- Regulatory bodies have to work more towards framing clear-cut guidelines on QbD for Biologics.
- Use of advanced statistical and analytical tools to achieve results in less time.
- Encourage manufacturers to develop QbD based biologics by simplifying the application process.
- More pilot programmes are needed to demonstrate the significant benefits of QbD.

CONCLUSION: Quality by design approach leads to the development of efficient and cost-effective product and its manufacturing process in a shorter period. Reproducible products with required quality attributes are achieved through QbD. Though the concept of QbD is in a growing phase and still requires worldwide harmonization; the Pharmaceutical industry is embracing QbD concepts and implementing this approach in the product development process due to its significant benefits. It is also pivotal to comply with emerging technologies & upcoming regulatory requirements. Thus, QbD has a promising future in the development of quality pharmaceuticals.

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