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Research Article

Data-Driven Optimization of Pharmaceutical Manufacturing Processes using Quality by Design (QbD) Frameworks

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Abstract

Quality by Design (QbD) is an approach to pharmaceutical quality management that aims to anticipate, mitigate, and respond methodically to potential hazards that may arise during the research and production phases. The work gives a detailed analysis of QbD as a current, scientific method of improving the pharmaceutical development and manufacturing process. It describes the conceptual basis, historical development and regulatory framework of QbD, with emphasis on important ICH guidelines (Q8, Q9, Q10) that could be used to implement quality in a systematic manner. The work compares QbD and the traditional Quality by Testing (QbT) model, and defines the key features of QbD like QTPP, CQA, risk assessment, and control strategy. The paper also looks at the uses of the QbD in formulation development, optimization of processes, and risk-based analysis and looks at its applicability in both upstream and downstream bioprocessing. The barriers to QbD adoption, such as the upfront costs and internal adjustment are mentioned, as well as the new trends, including PAT-based real-time monitoring, AI/ML-assisted analytics, continuous production, and personalized medicine. On the whole, the paper highlights that QbD enhances the quality of merchandise, regulatory issues, and the efficiency of manufacturing, so it an essential paradigm in the further pharmaceutical progress.

Keywords: *Quality by Design (QbD), Pharmaceutical Development, Quality Management, Process Optimization, Continuous Manufacturing.*

Introduction

The rise of personalized and very complicated drug product profiles means that the production and distribution of drugs need to be greatly improved. Efforts to improve manufacturing processes in terms of agility, responsiveness, and reproducibility are being bolstered by digital tools that have the potential to facilitate communication between process units, plants, and distribution locations [1]. The nature of the product greatly determines the level of complexity in pharmaceutical manufacturing and distribution. Biologics and small molecules are the two main categories into which therapeutic medications fall. The first group includes pharmaceuticals that have been chemically produced, whereas the second group includes goods that contain ingredients that have been extracted or created by living organisms. Biologics include things like vaccinations, blood products, monoclonal antibodies (mAbs), and advanced treatment medical products (ATMPs).

A basic requirement for achieving the United Nations' sustainable development goals is the pharmaceutical business [2].

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Producing better and cheaper medications is crucial to achieving the decrease of poverty, a core development aim, and to maintain the health, motivation, and capacities of the population. Promoting parity between the sexes is a by-product of the nutraceutical and functional food industries. As a development goal, ending world hunger requires innovative technology. To save water and energy, new products are essential. An effort to reduce inequities is an effort to make medications more affordable. An important step towards reducing emissions, promoting responsible consumption and production, and slowing the rate of climate change is the "green chemistry" movement's growing influence in the pharmaceutical sector [3]. Some have said that the pharmaceutical sector relies heavily on specialized knowledge. Thus, it is a good case study for studying the connections between R&D spending, intellectual products (patents and publications), and business success.

A common misconception about manufacturing is that it only involves the design and processing of raw materials into finished products [4]. Subtractive manufacturing was the first approach to production [5]. The process starts with acquiring the necessary ingredients and ends with delivering the finished product. When working with blocks of material, the

term "forming" refers to the process of using force to shape them into the final product. When a solid is melted into a liquid, it is poured into a mould and then recovered when the mould cools; this process is called "casting" in manufacturing. Additive manufacturing (AM) is an alternative production approach that entails layer-by-layer component fabrication [6]. Various manufacturing methods that transform digital information into three-dimensional models and prototypes are collectively referred to as AM. First and foremost, additive manufacturing is based on CAD.

QbD was introduced in 2004 and the pharmaceutical research and development industry entered a new era, marking a paradigm shift [7]. By implementing a complex risk-based strategy from the beginning of a product's lifecycle all the way through to its conclusion, this idea increases production flexibility while decreasing manufacturing costs. These days, high-quality pharmaceuticals are made using the QbD technique. Pharmaceutical formulations and manufacturing processes can be designed to meet pre-established product quality requirements using the QbD technique. Simplifying product design and troubleshooting, it is an innovative method. In order to determine the potential impact of different changes on product quality, this idea investigates all aspects associated with the production process and formulation properties. Meeting patients' demands and developing reliable tests are just two of the many objectives of QbD, which necessitates a broad variety of knowledge from various domains.

Structure of the Paper

Section II addresses the concepts of QbD and regulatory environment, Section III presents the needs regarding pharmaceutical manufacturing and optimization, Section IV looks at QbD applications, challenges and future trends. Section V discusses applicable sources and literature, Section VI concludes the study and presents future work.

Quality by Design (Qbd): Concepts and Regulatory Context

The quality of pharmaceutical products has been prioritised by all regulatory organisations. Customer satisfaction in service, product, and process is what mean when talk about quality. To succeed in today's global market, many organisations are engaging in quality-related operations. Customer expects punctuality, affordability, dependability, and top-notch quality. Two things may be done to ensure that customers are satisfied: having features and making sure that the goods are free from defects. There must not be any flaws in the product, and it must have qualities like reliability, strength, simplicity, and serviceability. The concepts of value, cycle time, cost, productivity, and quality are interdependent. Efforts in quality assurance should aim for early problem detection that allows for action without sacrificing quality, timeliness, or cost.

Qualtiy by Design (QbD): Concepts and Regulatory Context

QbD and other systematic science-based methods have been in high demand by regulatory bodies in recent decades due to the necessity to enhance quality paradigms and the explosive development of the pharmaceutical industry. Due to the enormous expansion of the pharmaceutical industry and the subsequent necessity to fortify quality standards, regulatory authorities were compelled to embrace systematic science-based technologies like QbD in the preceding decades. QRM (Q9), pharmaceutical quality system (Q10), and standards for pharmaceutical development (Q8) were all accepted by the International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, which let QbD run smoothly.

Historical Aspects of QbD Concept

Pharmaceutical quality has been a topic of heated controversy for many years. Ensuring the quality of drug goods is a constant struggle for the pharmaceutical sector in the current regulatory landscape. A lack of understanding regarding the product and process characteristics and insufficient cGMP compliance have emerged as two major issues throughout the years [8]. Scepticism about the quality of pharmaceutical items, particularly generic drugs, is the eventual outcome. Pharmaceutical companies have been using a new approach known as systematic quality by design (QbD) to develop pharmaceutical goods more economically and with better quality. This method replaces the old quality by testing (QbT) approach. Given its pervasiveness throughout the product development lifecycle, QbD has recently been seen as a lifecycle approach.

The contemporary pharmaceutical industry's emphasis on quality implementation is mainly attributable to the tireless efforts of quality development and assurance pioneers such as Joseph M. Juran, W. Edwards Deming, Dr. Kaoru Ishikawa, and Phillip B. Crosby. American innovator and engineer Joseph M. Juran established the principles of Juran's triology as a foundation for process and product quality management. "Juran on Quality by Design," a landmark text from the 1970s by Juran, argued that quality should be planned for, not left to chance. Juran considers "freedom from deficiencies" and "product features that meet customer satisfaction" to be the two most fundamental standards by which to judge a product's quality. Figure 1 illustrates the concept of Juran's triology.

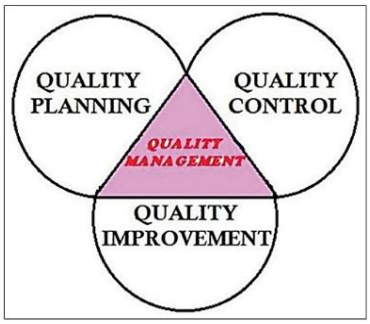

Fig.1 Juran's Quality Triology

The other principle, Six Sigma, was also based on an idea from the past that helped make QbD work. The Six Sigma methodology was developed in 1986 by Motorola employees William Bill Smith and Dr. Mikel J. Harry with the aim of bringing the error rate in a manufacturing system down to 3.4 per million cycles or lower. Figure 2 shows the DMAIC cycle, which stands for "Define, Measure, Analyse, Improve or Design, Control," as a guide for moving forward with the project.

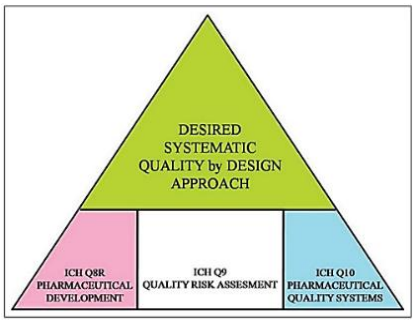

Fig.1 Correlation of ICH guidelines and QbD

ICH Guidelines

The International Council on Harmonisation of Technical Requirements for Medicines for Human Use established a set of interconnected guidelines for pharmaceutical quality systems, QRM, and pharmaceutical development, respectively, which paved the way for the effective application of QbD.

ICH Q8 (R2): Pharmaceutical Development: Quality must be integrated into the product or production process from the beginning, not added on later, as mentioned in ICH Q8 (R2).

ICH Q9: Quality Risk Management: Risk assessments must be grounded in scientific knowledge, and patient safety must always take precedence, according to ICH Q9. The level of formality, depth, and documentation required for a risk management strategy should be proportional to the risk itself.

ICH Q10: Pharmaceutical Quality System: Three basic objectives of ICH Q10 are the following: (3) product realisation; (4) control establishment and maintenance; and (5) drug product continual improvement. The document proposes, using relevant GMPs and an all-encompassing model for an efficient pharmaceutical quality system grounded in ISO quality standards.

Comparison Between Traditional Approach of Quality by Testing (QbT) and Modern QbD

Testing the final product and limiting production process flexibility are two components of the conventional regulatory evaluation system that aim to measure product performance and quality. As a result, the QbT method primarily entails giving low-risk items more review time and reducing resources for high-risk products by treating all product attributes equally. Table I compares the systematic QbD method with the standard QbT method.

Table 1 Comparison between traditional quality by testing approach and systematic quality by design approach

S.No.	Quality by Testing	Quality by Design
1.	Testing and inspection are conducted periodically to ensure quality.	Systematic process design ensures product quality.
2.	Experimental methods based on univariate analysis are used in process development.	Using multivariate experimentation, a systematic process is developed.
3.	The manufacturing process is rigid, making it difficult to incorporate new ideas.	The design space allows for the adjustment of the manufacturing process, with a primary emphasis on the control strategy and continuous verification.
4.	Ignoring variability in favour of process focus on reliability.	Achieving robustness through understanding and regulating variability is the primary focus of the approach.
5.	Reuse and process delays caused by function-based designs.	Easy product commercialisation is enhanced by team-based decisions.

Steps in Quality by Design

The quality of pharmaceutical products has been prioritised by all regulatory organisations. In terms of service, product, and process, quality means that customers are satisfied. The necessity for many of these quality-related endeavours is a direct result of the intense competition that global businesses face. Quality, dependability, affordability, and punctuality are client priorities. The two main strategies to ensure customer pleasure are by providing goods that are both feature-rich and defect-free [9]. When quality is high, it can motivate improvements in other performance metrics. So, in order to prevent future failure, quality must be integrated into products and services through effective planning.

Quality target product profile (QTPP): The new drug discovery and development method depends on the drug development program, or QTPP. When

formulating a strategy, it is important to think about how the product administered, the dosage form, bioavailability, strength, and stability, all of which affect the substance's efficacy, safety, and quality. Organisations with regulatory power can also benefit from this for the efficient optimisation of drug candidates and decision making. Risk management, development, planning [10], clinical decision-making, interactions between regulatory agencies, and commercial decision-making are some of the most recent areas to make use of QTPP.

Critical quality attributes (CQA): Once the QTPP is known, the next step is to find the appropriate CQAs. A CQA is a feature or trait that must be maintained within a suitable limit, range, or distribution to assure the intended product quality. It can be physical, chemical, biological, or microbiological. CQA for materials are known as critical materials attributes (CMAs), and for processes, they are known as critical process parameters (CPPs). Compounds, Methods, and Accessories (CMA) are used in the pharmaceutical business to describe the components, including the active ingredient and any relevant excipients.

Risk assessment: The term "risk" refers to the potential for harm as well as the likelihood and severity of that harm occurring. The goal of any good risk assessment is to catalogue all of the possible threats to a situation and rank them from most danger to least. Updated ICH Q9 The production and administration of pharmaceuticals are subject to quality risk management. involves a level of danger. Scientists should use their expertise to assess potential risks to quality. Critical criteria were identified in this study and can be used to establish a control approach for in-process, row material, and final testing.

Control Strategy: Quality and efficient process execution are ensured by a predetermined set of controls that are based on existing knowledge about the product and the process. Controls include processing controls, final product specifications, parameters and qualities of drug substances and drug products, components and ingredients, and the methods and frequency of monitoring and control associated with all of the aforementioned. They also include the conditions in which facilities and equipment are used.

Regulatory Guidance

Initially, there may be a long list of possible factors; but, as research progresses, this list can be refined and ranked (for example, by using a mix of experimental design and mechanistic models). In order to narrow down the options, experiments can show how important each component is and how they may interact with one another. If the important parameters are already known, learn more about the process by studying them in depth (e.g., using a mix of experimental design and mathematical models, or research that leads to a mechanistic understanding). Below, go over the fundamental regulatory rules:

Feature mode effects analysis (FMEA): The pharmaceutical sector makes frequent use of FMEA, among other risk assessment methodologies. The process's possible sites of failure have been identified and mitigated in a systematic and preventative manner. Any time anything goes wrong with a process, material, design, or piece of equipment, it is called a failure mode. The FMEA tool ranks the failure modes in order of severity after the failure modes have been defined [11]. This opens the door to taking precautions against potential risks that could lead to such failures. A thorough familiarity with the FMEA method is essential because the results depend on a clear understanding of cause and effect.

Fault tree analysis (FTA): FTA is a popular tool for analysing system safety, maintainability, and dependability; it was initially developed by Bell Laboratories. Finding the causes of an undesirable event from the top down is the goal of FTA, a deductive analysis technique. It is common practice to start with an anticipated failure at the top of the list and work down the list to identify all of the related system parts that could trigger the event.

Pharmaceutical Manufacturing Processes and Optimization Needs

There are two major steps in making pharmaceuticals: the first step is to make the active pharmaceutical ingredient (API) or drug substance. The second step is to make the product ready to be given to patients. Common process steps typically involve different types of drugs since they are formulation-specific. Granulation, compression, coating, and packing are the subsequent steps in the secondary manufacturing process that follow the API and excipient blend. One typical way to make tiny molecules is by chemical synthesis and purification. The use of living organisms in the synthesis of API or drug product components is characteristic of biologics [12]. Meeting the worldwide demand for pharmaceuticals requires producers to prioritise the delivery of safe and effective medicines in sufficient numbers. Moreover, standardization of processes and products among the key objectives because they need to minimize the variability between batches. Simultaneously, the production processes should be economically viable, which complicates finding the optimal candidate design.

Upstream Manufacturing Process (USP)

The present state of antibody production technology can be categorised into two main areas: DSP and USP development and optimisation. The possibility of constructing technological platforms was made possible by the development of processes and, consequently, production. Using a process of hazard identification and solution development, QbD integrates product quality into the production process. Better and more efficient methods of producing mAbs

with higher clinical efficacy developed as a result of implementing QbD.

Process Development in Upstream Processing

Process optimisation and development in USP includes engineering and developing cell lines, selecting cell clones, developing medium and feed, creating bioprocesses, and scaling up. Analyses pertaining to cell harvesting, process control, optimisation, and reactor design are all within the realm of possibility. When optimised independently, these factors contribute to a high product level, high productivity, and defined quality. Figure 3, which also displays the different optimisation regions, lists and schematically illustrates the most significant parameters.

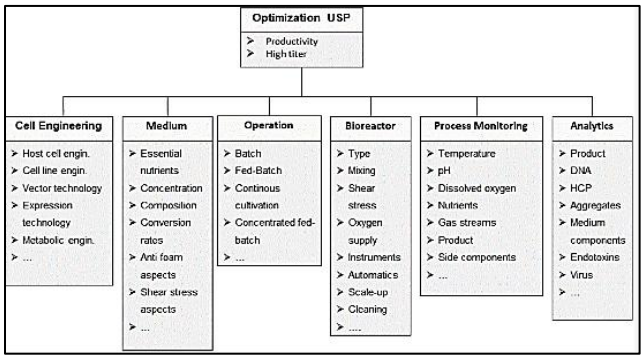

Fig.3 Optimization Areas and Parameters in Upstream Processing

Cell Line Development and Clone Selection: Cell lines are generated by starting with host cells, expression vectors, transfection techniques, and selection processes [13]. The expression system that best guarantees high production while meeting predetermined quality standards is chosen.

Media Development and Optimization: There has been advancement in commercially available media thanks to media optimisation processes in the previous several decades. Blood serum supplements were the basis of early cell culture medium such as Ham's F10 and Dulbecco's Modified Eagle medium. Included in this is a plethora of mysterious substances. The development of media has a significant impact on cell growth behaviour and productivity, as well as product quality [14]. Successful media development relies on using appropriate optimising tools. It is common practice to use automated screening, component titration, media blending, and analysis of spent media.

Downstream Manufacturing Process (DSP)

The physical laws that control separation ensure that downstream capacity grows at least linearly with costs, even though increasing upstream capacity does not always increase expenses. While upstream manufacturing is more expensive than downstream processing at low product levels, the main manufacturing expenses shift from upstream processing to downstream processing as titers increase, causing a non-linear rise in the overall manufacturing process costs [15].

Process Development in Downstream Processing

Digital signal processor research and development focusses on enhancing process capacity, purity, productivity, and yield. Process optimisation, new process development, and facility expansion can increase the separation efficiency of individual unit operations. Investigations into different methods for developing processes are still underway. Platform technologies, high-throughput methods grounded in QbD research, and experimental optimisations grounded in the theory of constraints (DoE) are all within reach. In addition to using unit operation modelling and simulation, process development makes use of mini-plant facilities (see Figure 4).

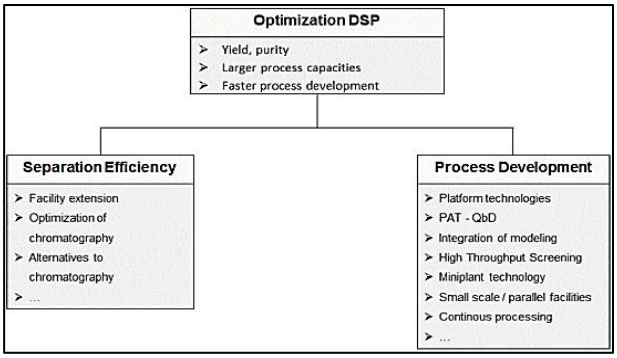

Fig.4 Optimization Fields in Downstream Processing

Chromatography Separations: A chromatographic separation equipment is used to isolate the antibodies present in the fermentation broth, and centrifuging or filtering the cells enhances their collection. Antibody trapping relies heavily on protein chromatography. Apart from its capacity and fast flow rate, it has extraordinary selectivity for IgG-type antibodies. The precise value of the dynamic binding capacity often varies with the antibody, flow velocity, and adsorbent, although it can range from 15 to 100 g mAb/L resin. Consistently over 95% purity. So, contaminants from the process, including as HCP, DNA, medium components, and viral particles, are removed. A significant step forward in process development over the past few years has been the improvement of chromatography's integration into the production process as a whole [16]. Immobilising viruses or starting ion exchange chromatography needs changing the elution conditions of the first Protein A capture phase to match the next unit operation. This is an example of the successful integration of single separation processes in recent decades, as it eliminates the requirement for buffer exchange between these unit activities.

Non-Chromatography Separations: DSP also incorporates ideas for procedures that do not involve chromatography, such as those involving membranes, ATPE, precipitation, and crystallisation [17], or affinity choices. Chromatographic procedures are being sought after for elimination or at least reduction. Processes outside of the pharmaceutical industry often use substantially larger feed quantities to demonstrate the viability of non-chromatographic separations. Since higher level are involved and more buffer is needed, they are especially helpful for DSP. Quickly extracting a volume of liquid, these low-tech separation techniques work well with big supply volumes. Possible savings in process time, money, and yield losses might result from this innovation.

Applications, Challenges and Future Trends of Qbd in the Pharmaceutical Industry

QbD is a current, organized method of pharmaceutical development that aims at integrating quality in products at its very early developmental phases. As compared to the traditional approaches, where it is commonly done through testing the end product to be sure that it is quality, QbD focuses on the determination of the communication between the processes, raw materials, and the product characteristics. QbD seeks to enhance process understanding and control by thoroughly investigating the impact of various process variables on product quality. With this information, a Design Space could be created where changes to manufacturing parameters could be made without compromising product quality. This understanding allows for creating a Design Space within which changes to manufacturing parameters can occur without negatively impacting product quality. Pharmaceutical firms can enhance the reliability and robustness of their products by incorporating statistical analysis, DOE, and risk management strategies. QbD makes production processes more efficient and compliant with regulations [18], which in turn saves time and money while delivering high-quality products to patients.

Applications of QbD in Modern Pharmaceutical Analysis

QbD has a far-reaching influence on the pharmaceutical analysis of the modern day as the method boosts the effectiveness and dependability of the formulation progression, optimization procedures and risk monitoring. QbD guarantees the high quality of pharmaceutical products, which is methodically science-based and enhances the scaling and minimizes risks of development and production. Table II displays the pharmaceutical analytical applications of QbD.

Table 3 Application of QbD in pharmaceutical analysis

Application	Description
Formulation Development	Optimizes the interactions between ingredients to ensure the product's CQAs (e.g., stability, dissolution, and bioavailability).
Process Optimization	Develops robust and scalable manufacturing processes by controlling CPPs and ensuring flexibility within the design space.
Risk-Based Approach	Uses risk assessments to identify critical areas, prioritize resources, and implement controls to minimize product variability.

Formulation Development: QbD is a great way to make formulations better because it helps to see how the different parts work together to affect the CQAs of the final product. For instance, in a pill formulation, the bioavailability, stability, and dissolving rate of the medicine can be greatly affected by the kind and quantity of binders, lubricants, and excipients. QbD enables formulators to determine the most desirable formulation by systematically investigating these interactions using Design of Experiments (DOE) and other approaches [19]. This reduces chances of failures during later stages of development and makes sure that the product is up to the regulatory and therapeutic standards even before it is developed.

Process Optimization: Quality by Design also has a significant role in process optimization within the pharmaceutical industry. QbD assists in coming up with manufacturing processes that are scalable and flexible without compromising the quality of the products. QbD identifies and manages CPPs including mixing time, temperature, and drying conditions, to maintain the strength of the manufacturing process as it increases in scale, between pilot and full-scale production [20]. The concept of Design space in QbD is used to make small changes in CPPs without compromising the quality of a product, which has flexibility in manufacturing. The method improves efficiency and complies with regulations because product quality is verified during the process rather than after the fact.

Risk-Based Approach: QbD uses risk-based approach to give priority to the resources and concentrate on most important areas of drug development and analysis. Risk evaluations are done by means of FMEA to determine possible quality risks of the product at every phase of its development [21]. Due to its concentration on risky zones, QbD can be used to introduce the necessary levels of control and mitigation measures at the initial stages of the process and eliminate the chances of failures or recalls. This organized risk management methodology would mean that the most significant elements of the product and process are prioritized thereby increasing the safety and reliability of the product.

Challenges in Implementing QbD

QbD face several challenges while implementing to the pharmaceutical industries. These challenges are outlines in Table III and IV. Table III describes about the high initial investment challenges whereas Table IV discusses about the organizational adaptation challenges.

Table 3 High Initial Investment Challenges

Challenge	Description
Technical Expertise	Requires skilled personnel with knowledge in advanced data analysis, risk management, and statistical tools.
Advanced Analytical Tools	Investment in sophisticated tools such as PAT and DOE is necessary for thorough process understanding.
Extensive Data Collection	Gathering large volumes of data to map relationships between CPPs and CQAs is resource-intensive.
High Costs for Small Companies	Smaller pharmaceutical companies may struggle to afford the upfront costs of QbD implementation.

Table 4 Organizational Adaptation Challenges

Challenge	Description
Cultural Shift	Requires moving from a reactive, testing-based approach to a proactive, quality-focused mindset.
Cross-Functional Collaboration	Demands greater teamwork across R&D, manufacturing, and quality control to optimize processes.
New Workflows	Development of new, integrated workflows to build quality into the product from the start.
Employee Resistance	Resistance from staff used to traditional methods; requires training and leadership to foster QbD adoption.

Future Trends of QbD in Pharmaceutical Sectors

The future trends if the QbD implementation to the pharmaceutical industries are as follows:

Integration of Advanced Technologies: Quality by design (QbD) is changing in the pharmaceutical industry due to the introduction of cutting-edge technologies including PAT, AI, and ML. PAT allows for the control and monitoring of manufacturing processes in real-time, which helps to keep CQAs within the appropriate range while production is underway. Collecting data in real-time allows for finer-grained process modifications, which in turn reduces variability and ensures consistent product quality [22]. The use of AI and ML allows for more efficient processing of massive amounts of data generated by QbD. These technologies have the ability to detect advanced patterns and correlations between CPPs and CQAs to make predictive modelling and automate decisions.

Continuous Manufacturing: QbD is essential in easing the shift from conventional batch manufacturing to continuous manufacturing, which is a major challenge in contemporary pharmaceutical production. Continuous manufacturing is used in contrast to batch manufacturing, which means that during the production process, products and materials run through continuously, without interruption [23]. QbD allows one to gain a profound insight into the process variables making sure that CQAs are regulated all through the ongoing process.

Personalized Medicine: QbD is essential in the new area of personalized medicine and biologics in the provision of quality and consistency of products. Personalized medicine refers to the process of customizing medical interventions to specific patients through genetic, biomarker or environmental factors. Any variation could impact the patient outcomes, hence extreme rigour in controlling the production processes is required to guarantee high-quality products. QbD assists in the development of solid processes to take into account the unique requirements of tailored therapies and obtain that every batch is uniform, even at the point of small or highly personalized dosing. In biologics, consisting of complex molecules such as proteins or antibodies, QbD makes sure that the biological variation that is present in these products is highly regulated.

Literature Review

This section presents earlier studies on Data-Driven approaches in Pharmaceutical Manufacturing. Table V presents a tabular comparison of past studies, in terms of Tools/Techniques Used, Pharma Context, Concept Category, Tech Area, Benefits on Pharma Manufacturing.

Mehta et al. (2023) displayed an innovative method for pharmaceutical manufacturing predictive maintenance using models derived from RNNs and long-term memory. By implementing lean management principles—which are renowned for reducing waste and increasing value—in pharmaceutical production processes, operations can be streamlined and resources can be better utilised. The pharmaceutical sector is very important, and meeting their demanding quality requirements requires a great deal of efficiency and accuracy in their manufacturing processes. A powerful approach to improving pharmaceutical production processes has emerged with the incorporation of AI and lean management principles [24].

Bastogne et al. (2023) suggested that empirical models frequently rely solely on numerical data. Prediction quality is also negatively impacted in practice by datasets that are either too small or contain missing data. A case study is presented that focusses on the production of Cationic Nano-Lipid Structures for siRNA transfection. This paper presents and evaluates a Bayesian approach that encompasses parameter estimation, variable selection, and model quality assessment. For response variables that can be expressed as either a binary or percentage, two unique model structures are also provided. Using a Bayesian

approach, the results validate the usefulness and practicality of the QbD analysis [25].

Copot, (2022) advised that pharmaceutical companies should focus on moving from batch to continuous manufacturing as a top priority. Using the end-to-end continuous manufacturing process, tablets can be made on demand with a substantial reduction in prices, quality, and time. Aim is to create state-of-the-art technology that lead to the most efficient manufacturing process and highest quality products. Nevertheless, due to the intricate nature of these production lines, extensive testing and analysis must precede the implementation of the control strategy, initially in a lab-scale facility and then at an industrial level [26].

Meyliana et al. (2021) carried out with the use of a qualitative methodology, specifically the User Centre Design (UCD). One of Indonesia's biggest pharmaceutical firms employs a team of five specialists from different domains to verify the efficacy of a blockchain-based business strategy. Discussions within a forum group serve as the validation mechanism. The FGD concluded that the pharmaceutical industry can benefit from a business model that incorporates blockchain technology into the medication production process. Owners of businesses in the pharmaceutical industry may rest easy knowing that their data is securely stored and processed using this blockchain system, which also offers great data integration for all parties involved in a transaction [27].

Kocyigit, Sahingoz and Diri (2020) efficiently distributed pharmaceutical products—an essential optimisation problem in times of pandemics—by utilising a well-known evolutionary technique known as a genetic algorithm. Accelerated distribution of pharmaceuticals was achieved by employing the Multiple Travelling Salesman Problem strategy. To acquire the best outcomes in earlier iterations, they also used the 2-Opt method to enhance their proposal method. The accuracy of the results and the amount of time it took to calculate them were evaluated using various datasets taken from a library. When all was said and done, they found that their suggested algorithm produces good results in a reasonable amount of time. A novel mutation notion added to this study in future work [28]

Soliman, Daoud and Amer (2019) the automation community is starting to take an interest in Networked Control Systems (NCS) that employ Ethernet as its communication channel. A wide variety of industries, including aerospace, automotive, and industrial control, can benefit from such a protocol. There is a growing need for innovative designs that can withstand the failure of a single node or a cluster of them. Reduced production downtime and increased profitability are the results of this system design. This study proposes a model for pharmaceutical tablet production based on an NCS fault-tolerant system [29].

Table 5 Summary of Relevant Literature on Digital and Data-Driven Approaches in Pharmaceutical Manufacturing

Reference	Tools/Techniques used	Pharma Context	Concept Category	Tech Area	Benefits on Pharma Manufacturing
Mehta et al. (2023)	LSTM, RNN, Lean Management Principles, Artificial Intelligence	Predictive maintenance & efficiency in pharma production	Predictive Maintenance & Lean Optimization	AI/ML & Operational Excellence	Reduced downtime, minimized waste, improved resource utilization, enhanced efficiency & precision
Bastogne et al. (2023)	Bayesian Modeling, Variable Selection, Parameter Estimation, Model Quality Assessment	QbD-based formulation for nano-lipid structures	Statistical QbD Modeling	Data Analytics & Bayesian Statistics	Handles incomplete datasets, improved prediction quality, enhanced QbD-based decision-making
Copot (2022)	Continuous Manufacturing Models, Control Strategy Testing & Validation	Transition from batch to continuous tablet manufacturing	Continuous Manufacturing & Control	Process Automation & Advanced Control	On-demand production, reduced cost & time, improved product quality, enhanced scalability
Meyliana et al. (2021)	Blockchain, User-Centered Design (UCD), Business Model Validation (FGD)	Blockchain-enabled traceability in drug manufacturing	Digital Traceability & Supply Chain Integrity	Blockchain & Industry 4.0	Better data integration, enhanced traceability, secure transactions, improved trust in production
Kocyigit, Sahingoz & Diri (2020)	Genetic Algorithm (GA), Multiple Traveling Salesman Problem (MTSP), 2-Opt Optimization	Optimized distribution of pharmaceuticals	Logistics Optimization	Evolutionary Computing & Smart Logistics	Faster delivery, optimized routing, efficient pandemic response, acceptable computing time
Soliman, Daoud & Amer (2019)	Ethernet-based Networked Control Systems (NCS), Fault-Tolerant System Architecture	Tablet production automation & fault tolerance	Fault-Tolerant Control Systems	Industrial Automation & Communication Systems	Reduced production downtime, increased system reliability, improved profitability

Conclusion and Future Work

The development of QbD-based medicines is ongoing on a global scale. These drugs aid in the identification of potential dangers and the management of all process steps, from drug design to patient consumption. As a result, patients are able to receive high-quality treatments that are based on their design. Overall, QbD represents a sea change in the pharmaceutical business, doing away with end-product testing in favour of proactive, science-based, process-knowledge-based control. QbD allows the creation of a strong manufacturing process that ensures products of high quality by incorporating tools like risk management, design of experiment and monitoring of the continuous process. The fact that it is consistent with regulatory expectations especially in the form of ICH Q8, Q9 and Q10 further enhances compliance as well as lifecycle management. Its implementation issues, in particular, cost, technical knowledge, and cultural adjustment, still exist, but the long-term benefits of the implementation in terms of efficiency, regulatory flexibility, less variability, and patient safety are significant. With the ongoing rise of new technologies such as PAT, AI/ML, and continuous manufacturing, QbD will remain a key factor in the process design of the modern world and innovation. Finally, QbD offers a framework that supports sustainability that empowers quality, reliability, and competitiveness in a fast-growing pharmaceutical environment.

The further research should be on how to integrate further with QbD artificial intelligence, real-time analytics and continuous manufacturing. By increasing its presence in personalized medicine, in the biologics and in complex dosage forms, precision, regulatory flexibility, and patient-centric quality will be further enhanced and eventually the global pharmaceutical innovation and transformational healthcare solutions.

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