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Review paper

Integration of quality by design with artificial intelligence/machine learning technologies in pharmaceutical manufacturing: A comprehensive review

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Abstract

Background and purpose: Quality by design (QbD) has revolutionized pharmaceutical development by shifting from a conventional quality-by-testing approach to a science-based approach that incorporates quality into products and processes from inception. The integration of artificial intelligence (AI), machine learning (ML), automation, and digital technologies with QbD offers new opportunities to enhance process understanding, optimize critical quality attributes (CQAs) and support the Pharma 4.0 industry framework. **Experimental approach:** A systematic review of studies published between 2016 and 2025 was conducted to evaluate the application of supervised learning algorithms, deep neural networks, reinforcement learning, and digital twin technologies within QbD. Regulatory frameworks, including International Council for Harmonisation (ICH) quality guideline Q8 through Q14, the U.S. Food and Drug Administration's Emerging Technology Program and the European Medicines Agency quality initiative, together with representative industrial case studies, were also examined. **Key results:** This review demonstrates that AI-driven QbD improves process understanding, CQA optimization, batch-to-batch consistency, process robustness, and real-time quality control. Further, advanced computational models enable predictive process monitoring, intelligent decision-making, and in silico experimentation, reducing manufacturing costs, development time and experimental burden. However, challenges related to data quality, model interpretability, validation, and regulatory harmonisation remain a critical barrier to widespread implementation. **Conclusion:** The convergence of AI, ML and QbD provides a robust framework for intelligent pharmaceutical manufacturing (PM). AI-enabled QbD supports the development of high-quality products through predictive, data-driven, and in silico approaches while accelerating development and improving manufacturing efficiency. These technologies offer a practical roadmap toward Pharma 4.0 and the future of digital PM.

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Keywords

Quality by testing; critical quality attributes; deep neural networks; process analytical technology; digital twins; continuous manufacturing

Introduction

The pharmaceutical manufacturing (PM) industry is the most regulated and quality-sensitive sector. To increase product quality, patient safety, and to eliminate alterations to raw materials or marketed products, traditional manufacturing must shift to advanced digital technologies and science-based quality frameworks [1].

The concept of quality by design (QbD) is taken from the International Council for Harmonization (ICH), and according to the ICH Q8 (R2) guideline, it represents a systematic approach to PD [2,3]. The primary goals of pharmaceutical development (PD) focus on product or process quality risk management (QRM) [3]. Conventional quality-by-testing (QbT) methodologies rely on end-product inspection [4]. QbD helps continuously improve the quality and safety standards of pharmaceutical products by developing an understanding of critical process parameters (CPPs) and CQAs [1-5].

In recent years, the global pharmaceutical landscape has undergone rapid transformation through advanced automation technologies such as artificial intelligence (AI) and machine learning (ML) [6]. Since the adoption of AI across all areas of the pharmaceutical sector, it has not only enhanced operational approaches but also unlocked billions of marketed value for companies [7]. These computationally based approaches have demonstrated extraordinary capabilities in predicting complex process outcomes, optimizing formulation parameters, and enabling real-time process control; previously, conventional statistical methods made this impossible [8]. The combination of QbD principles with digital, computational AI/ML technologies has emerged alongside the fourth industrial revolution (Industry 4.0) and its adaptation in the pharmaceutical sector, known as Pharma 4.0, which envisions a manufacturing ecosystem capable of autonomous optimization and continuous improvement [9].

Current regulatory developments have further accelerated the adoption of sophisticated manufacturing technologies [10]. The U.S. Food and Drug Administration's (FDA) Emerging Technology Program (ETP), first launched in 2014 and later evolving into ETP 2.0, provides a framework for early engagement between industry and regulators on novel technologies, including AI/ML implementations [11]. Similarly, the FDA's framework for regulatory advanced manufacturing evaluation (FRAME) program, launched in 2021, specifically addresses AI/ML applications in PM [12,13]. In 2019, ICH adopted product lifecycle management under the Q12 guideline and continuous manufacturing under the Q13 guideline. These guidelines provide regulatory pathways that support innovation and post-approval changes while ensuring quality assurance (QA) [14].

The application of ML within QbD frameworks covers various pharmaceutical operations, including drug discovery, formulation development, process optimization and QC [15]. When modeling the nonlinear relationship between CPPs and CQA, AI showed better prediction accuracy than traditional design of experiments (DoE) approaches [16]. Reinforcement learning, a powerful algorithmic tool, supports process control and enables automatic optimization of continuous manufacturing systems [17]. It relies on deep learning (DL) architectures, such as convolutional neural networks (CNNs) and deep neural networks (DNNs), for spectral data analysis, image-based defect detection and real-time process monitoring applications [18].

Within pharmaceutical development (PD), process analytical technology (PAT) was introduced in 2004 as a key enabler of QbD implementation, enabling accurate measurement of critical quality and performance attributes [19]. Aligning PAT with ML algorithms can drive analysis of changes in quality properties and real-time feedback throughout the production process, resulting in soft sensors, digital twins (DT), and predictive control systems that shift manufacturing from reactive to proactive quality management [20]. These technological advances enable real-time release testing (RTRT) for batch release based on in-process data rather than traditional endpoint testing [21]. This review provides a comprehensive overview of modern applications of automated AI and ML approaches. These articles systematically explore the theoretical foundation of QbD, the scope of AI and ML technology in PM, regulatory aspects and strategies for industry implementation.

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Fundamental principles of quality by design

QbD is a systematic, science-based, and risk-informed approach to PD that emphasizes integrating quality into products through focused process understanding. QbD is an experimental design step introduced by ICH Q8(R2) that focuses on sustaining product quality during the product lifecycle using scientific knowledge and QRM tools [2-5].

The QbD framework consists of defining the quality target product profile (QTPP), then identifying CQAs, critical material attributes (CMAs) and CPPs that impact product quality. ICH Q9(R1) describes risk assessment tools used to prioritize critical variables, while DoE elucidates the relationships among material attributes, process parameters, and product performance. Targeted studies help define a design space (DS), where an effective control strategy can provide consistent manufacturing and continued improvement [3,19,22]. This growing access to manufacturing data has also spurred the implementation of AI and ML, enabling QbD-based decisions to improve processes.

Fundamentals of artificial intelligence and machine learning

The term AI refers to computational systems that execute tasks that rely on human intelligence, including learning, pattern recognition, prediction and decision-making [6]. ML is an AI discipline that allows algorithms to learn from data and improve predictions without the programmer dictating every detail of how this will happen. ML is categorized by learning methodology as supervised, unsupervised, and reinforcement learning. Supervised learning (SL) predicts outcomes with labelled datasets, as well as unsupervised learning, which finds hidden patterns in unlabelled data and reinforcement learning that optimizes decisions through interactions with the environment [6-8].

As PD becomes more data-driven, demand for AI/ML has grown in areas such as analysing the rich datasets that emerge from formulation development, manufacturing, and process monitoring [8,15]. Implement predictive modelling, optimizations, anomaly detection and data-driven decision-making by using these techniques, which can enhance development efficiency and quality of products. But their effectiveness relies heavily on high-quality data, suitable model choice and adherence to regulations [6-8,15].

Theory of quality by design and regulatory framework

Through ICH Q8(R2) PD, Q9 QRM and Q10 pharmaceutical quality system guidelines, the QbD paradigm is formalized to provide a systematic approach for incorporating quality into pharmaceutical products based on science-based understanding, as shown in Figure 1 [22]. The ICH Q11 guideline further expands these principles to drug substance development; ICH guidelines Q12, Q13, and the recently adopted Q14 provide guidelines on lifecycle management, continuous manufacturing and analytical procedure development, respectively [23,24]. Collectively, these guidelines produce a unified regulatory infrastructure that promotes innovation while ensuring rigorous QC standards.

QTPP is the core of QbD and may be defined as the quality attributes of a drug product designed to meet appropriate standards for safety and efficacy [25]. The QTPP provides the foundation for determining CQAs, which are physical, chemical, biological, or microbiological properties that should be controlled within an appropriate limit to ensure products meet their intended use [26]. Risk assessment and experimental design to understand the links between CQAs and CPPs help create a DS, a combination of multiple variables that ensures quality while providing flexibility in operation [27].

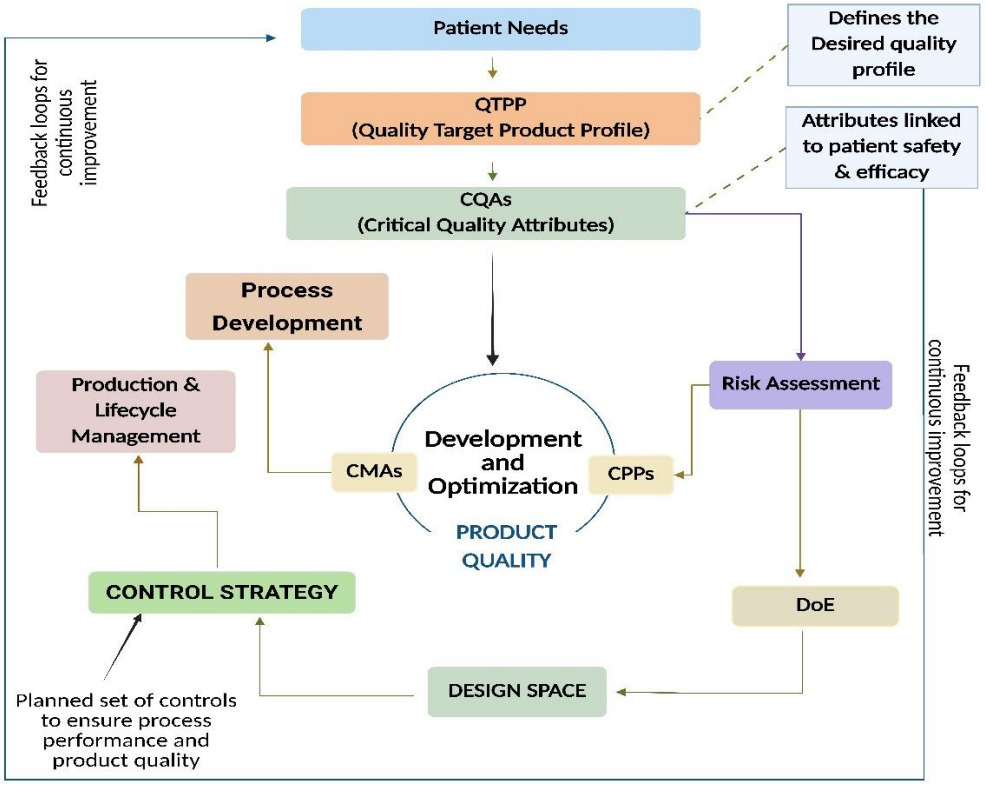


Figure 1. Schematic illustration of the QbD framework and its iterative nature

Critical quality attributes and critical process parameters

CQAs are measurable product factors that directly impact safety and therapeutic efficacy. For solid oral dosage forms, common CQAs include assay, content uniformity, dissolution profile, tablet hardness, friability, and impurity levels [28,29]. For biopharmaceutical products, CQAs may include biological activity indicators such as glycosylation and aggregation biological activity indicators [30]. The effective identification and prioritization of CQAs utilises systematic risk assessment tools like failure mode and effects analysis (FMEA) and Ishikawa diagrams to assess the severity of root cause parameters or features in terms of their potential impacts on product quality [31].

CPPs are also process variables that significantly influence CQAs and are controlled to ensure product quality. During tablet manufacturing, blending time, granulation endpoint, compression force, coating parameters and drying conditions are incorporated into CPPs [32]. In bioprocessing applications, CPPs also include pH, temperature, dissolved oxygen, agitation speed, and nutrient feed rates [33]. This approach involves systematically identifying CPP-CQA relationships using DoE, which supports predictive model development that serves as a basis for control strategy design [34].

Design space and control strategy

According to the QbD framework, design space (DS) is the most significant innovation. DS refers to the multi-dimensional space of input variables within which the process can operate while still ensuring quality [35]. It provides regulatory flexibility for manufacturing and allows movement within the defined area without any prior regulatory filing. Establishing the DS requires comprehensive, versatile experimentation, which is usually conducted using DoE methods such as full factorial designs, central composite designs, and D-optimal designs [36].

The control strategy combines process controls, material controls, and monitoring systems to ensure that CQAs are consistently within specification. Modern control strategies increasingly rely on PAT tools that facilitate online measurement and feedback control [37]. Feedforward control, feedback control and model

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predictive control are examples of advanced control strategies, such as controlling the process based on the predicted properties of incoming materials [38]. To develop effective control strategies, a sound understanding of process dynamics, measurement system performance, and statistical characteristics of process variability is imperative [38,39].

Comparison of traditional approaches and quality by design approaches

The evolution from traditional approaches to QbD represents a fundamental philosophical shift in PM. Table 1 represents a detailed comparison of traditional and QbD approaches across various aspects.

Table 1. Comparison of traditional QbT and QbD approaches [40-43]

Features	Traditional approach	QbD approach
Quality paradigm	Relative QC through end-product testing	Proactive quality built into process design
Process understanding	Limited understanding of parameters relationship	Comprehensive multivariate process understanding
Experimentation	One-factor-at-a-time approach	DoE for multivariate optimization
Regulatory flexibility	Fixed process parameters; changes require filing	DS allows movement without filing
Control strategy	Offline testing with manual intervention	Real-time monitoring with automated control
Risk management	Ad hoc approach to quality issues	Systematic risk assessment throughout lifecycle
Continuous improvement	Limited post-approval optimization	Built-in lifecycle management and optimization
Data management	Siloed data systems; paper records	Integrated digital systems with analytics

Artificial intelligence and machine learning technologies in quality by design

AI and ML are increasingly incorporated into pharmaceutical QbD modelling, as they readily convert formulation, process, and monitoring data into predictive and decision-support modelling [44]. The primary benefit of these methods in regulated manufacturing is not only improved predictions but also faster identification of CQAs, CPPs, and hidden process patterns that affect product quality [45]. Regulatory and scientific guidance increasingly emphasizes traceability, risk-based validation, lifecycle monitoring, and transparent communication of model behaviour, which makes AI/ML most beneficial when implemented as part of a controlled QbD framework rather than in isolation as a black box [44-47].

Supervised learning algorithms

SL algorithms have been used in the field of pharmaceutical QbD systems to learn predictive relationships among critical CMAs, CPPs and CQAs [44,48]. Regression models are often applied to estimate quantitative quality metrics such as dissolution, assay or particle size [44,49]. Classification models assist in batch quality evaluation and defect detection [44]. Of these approaches, support vector machines (SVMs) and ensemble learning methods have been shown to be among the best-performing algorithms in predictive tasks on more complex pharmaceutical datasets [49]. SL supports process DS development, process optimization, and risk-based decision-making across the pharmaceutical product lifecycle by enabling robust quality prediction while minimizing experimental burden [48-50].

Deep learning architectures

The field of pharmaceutical QbD has recently garnered considerable interest in the use of DL techniques to reveal meaningful patterns in large, complex datasets [44]. CNNs are utilized predominantly in image quality-control applications such as tablets, including defect detection, coating quality evaluation and morphology analysis [51]. Whereas recurrent neural networks (RNNs) enable monitoring the manufacturing

process over time by analysing sequential data from the corresponding process [52]. Autoencoders help make processes more reliable by recognizing abnormal operating conditions and potential quality deviations early on [53]. Such capabilities make DL a powerful guarantee for advanced process monitoring, predictive QC and intelligent pharma factories [51-53].

Reinforcement learning for process control

Reinforcement Learning is a new method for process control in the QbD context. In contrast to classical prediction models, RL learns in real time from process feedback and optimizes control strategies in response to changing manufacturing conditions [54]. This capability enables CPPs to implement adaptive process control in real time, leading to consistent product quality [48,54]. In combination with PAT, RL can enable automatic closed-loop manufacturing systems that respond to in-process variations [54,55]. While RL is still in early phases of its industrial implementation, the potential to improve process robustness, operational efficiency and manufacturing flexibility in future PM environments is significant [54].

Explainable artificial intelligence and model interpretability

Model transparency and interpretability have gained significant attention and adoption of AI in PD over time [54,55]. Explainable AI (XAI) methods such as Shapley additive explanations (SHAP) and local interpretable model-agnostic explanations (LIME) help explain how much input variables influence a model's output, improving understanding of processes and supporting scientific decision-making [56]. These techniques can identify the relative importance of CMAs and CPPs that affect CQAs, thereby strengthening confidence in AI-generated outcomes [57]. In addition to being important from a scientific standpoint, model interpretability also meets increasing regulatory demands for transparency, validation and lifecycle management of AI-based systems in regulated pharmaceutical settings [58].

Comparative performance analysis

In addition to predictive accuracy, the choice of AI techniques for QbD applications should pay attention to aspects such as robustness, interpretability, computational burden, and suitability for regulatory compliance [1]. Traditional ML models are usually easier to implement and validate but tend to outperform on larger, more complex datasets, while DL approaches provide better performance [44,48]. Reinforcement learning offers greater potential for process-control adaptation but requires a higher level of implementation and validation [51,52]. As a result, the best AI strategy will adapt by use case, data access and regulatory landscape [54]. Effective AI adoption in QbD within the pharmaceutical industry requires a balance among performance, transparency, and operational feasibility [50-56].

Conceptual framework for artificial intelligence enhanced quality by design

AI-aided QbD extends the classical QbD paradigm by adding data-guided prediction, optimization, and feedback to product and process understanding, risk-based decision-making, and lifecycle management [59]. The concept of QbD was introduced in ICH Q8(R2) based on a scientific understanding of the product and its manufacturing process, including DS, specifications and control strategy [3,60]. While structured QRM throughout the lifecycle is addressed in ICH Q9(R1), a pharmaceutical quality system that supports continual improvement and knowledge management has been provided in Q10 [61]. The PAT framework by the FDA continues to support real-time or near-real-time monitoring and control, and AI has been recognized by the FDA as a tool in process design, process control, smart monitoring, and maintenance/replacement decisions for continuous improvement toward PM [19].

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Integrated architecture layer

A strong data acquisition and preprocessing infrastructure forms the base of an AI-enhanced QbD framework, which can absorb, integrate, and harmonize data from PAT tools, manufacturing equipment, laboratory information systems, and quality management platforms [62]. Data preprocessing using cleaning, normalization, feature extraction and context making provides high-quality datasets for downstream analytics/models [63]. This integration of real-time process data with historical manufacturing knowledge enhances understanding of the process by bolstering CQA, CMA and CPP identification of the QbD framework [64].

The development of AI models and validation components converts process and quality data into predictive knowledge using ML, multivariate analysis and advanced statistical modelling [65]. These models enable the prediction of product quality outcomes, identification of sources of process variability, establishment of optimal DS, and early warning of deviations [66]. To ensure regulatory compliance, reliability, and reproducibility in GMP environments, model validation, explainability and lifecycle management are crucial for pharmaceutical purposes [65-67].

Validated AI models are used in real time for decision support and control, providing process monitoring, predictive quality assessments, anomaly detection and adaptive process control [66]. By integrating AI with PAT and advanced control strategies, manufacturers can shift from reactive quality testing to proactive quality assurance, leading to continuous verification and a more robust process. This methodology also enables real-time release testing and operational efficiency without sacrificing product quality within predetermined specifications [66,68].

Implementation roadmap

A systematic roadmap is necessary to support the integration of AI in PD and manufacturing, which could be achieved through a QbD-based AI-enhanced system. The proposed framework (Figure 2) includes four critical phases in sequence to establish a data infrastructure for continuous learning and optimization. This gradual approach facilitates regulatory compliance, process strength and continuous quality enhancement along the product life cycle [66-70].

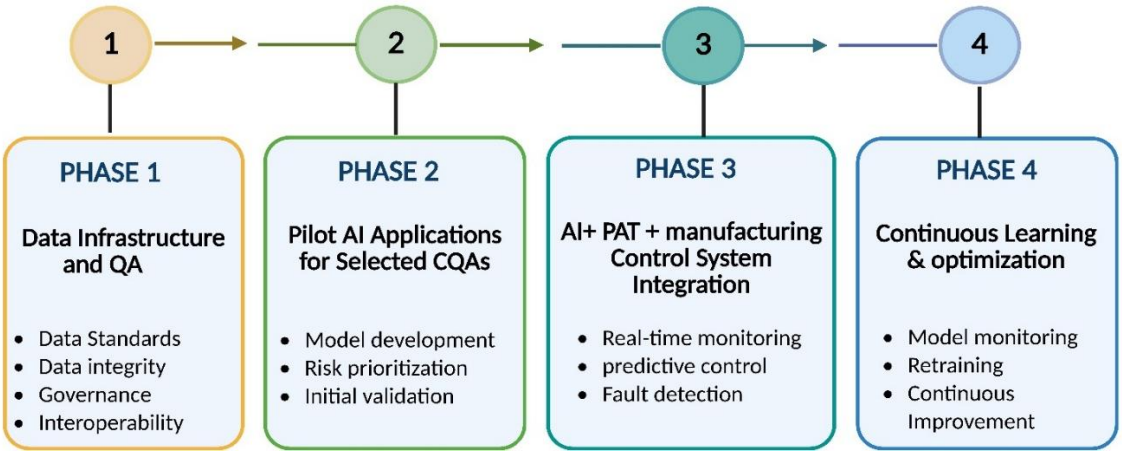


Figure 2. AI-enhanced QbD implementation roadmap [66-70]

Maturity assessment model

A staged maturity model can be used to assess AI adaptation within QbD frameworks as development categories evolve from traditional automation to fully autonomous systems. This model offers an organized framework for technology capability assessment, such as data utilization, decision support and process adaptability in PM environments [3,19,61-66]. Figure 3 shows how the four maturity levels are characterized and what their expected influence is on quality and process performance.

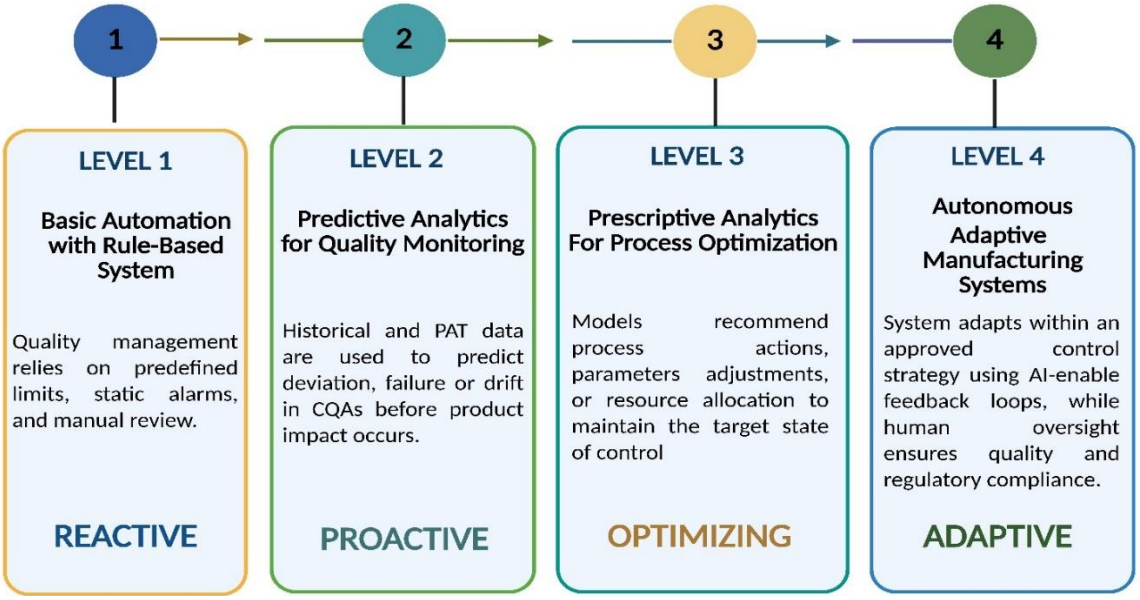


Figure 3. Maturity Assessment model for AI-enhanced QbD implementation in PM [3,19,61-66]

Integration of quality by design with artificial intelligence and machine learning

The integration of QbD with AI and ML is the next phase in data-led PD. Conventional QbD approaches rely on a series of experimental investigations, statistical analysis and proficiency assessments to identify relationships among formulation components, production processes and product quality. Such approaches still retain scientific validity, but the ongoing rise of manufacturing complexity, together with the accelerating growth of pharmaceutical datasets, is unavoidably revealing shortfalls in traditional statistical methodologies when faced with non-linear key interactions in higher-dimensional spaces [1,7-9,15].

QbD benefits from AI and ML's continuous capabilities to analyse data sets generated across product milestones, including formulation experiments, DoE, PAT measurements, sensor outputs, manufacturing records, and stability data. These computational methods complement established statistical approaches by uncovering complex relationships that might otherwise go undetected in conventional regression-based analyses [1,69]. Within the QbD framework, AI and ML contribute at multiple stages of PD as shown in Table 2.

Table 2. Integration of AI and ML across the QbD lifecycle

QbD stage	Traditional QbD approach	Role of AI and ML	Demonstrating AI and ML techniques	Benefits	Ref.
QTPP	Define desired product characteristics based on clinical and regulatory requirements	AI analysed historical formulation, clinical and manufacturing datasets	ML, knowledge graphs	Faster product design, knowledge-driven decision-making	[3,71,72]
CQAs	Identify product attributes influencing safety and efficacy through experimental studies	Features selection and predictive modelling	Random forest, XGBoost, SHAP, artificial neural networks	Improved identification of critical attributes and reduced experimental improbability	[3,73]
CMAs	Material characterization using laboratory experiments	Material property prediction	Support vector machine, random forest, ANN	Faster excipient screening and formulation optimization	[74,75]
CPPs	Process optimization using DoE and statistical analysis	Process optimization models	ANN, gradient boosting, Gaussian process regression	Improved process robustness and reduced variability	[3,15]
QRM	Expert-based FMEA, HACCP, Ishikawa diagrams	Risk prediction	Bayesian networks, decision trees, random forest	Objective and data-driven risk prioritization	[61,48]

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QbD stage	Traditional QbD approach	Role of AI and ML	Demonstrating AI and ML techniques	Benefits	Ref.
DoE	Response surface methodology, factorial & Box-Behnken designs	Experimental optimization	Bayesian optimization, active learning, ANN	Reduced experimental workload and faster optimization	[76,73]
DS development	Mathematical modelling using regression equations	Nonlinear predictive modelling	ANN, Gaussian Process Regression, DL	More accurate and flexible design space establishment	[3,51]
PAT	Real-time monitoring using spectroscopic sensors	Real-time sensor data analysis	CNN, PCA, partial least squares, LSTM	Early fault detection and improved process control	[19,77]
RTRT	Product testing after manufacturing	Quality prediction using process data	Random forest, ANN, DL	Reduced batch release time and enhanced manufacturing efficiency	[19,78]
CM	Conventional feedback control systems	Adaptive process control	Reinforcement learning, DT	Adaptive manufacturing and reduced production failures	[77,15]
Lifecycle management and continuous improvement	Periodic review of manufacturing data	Predictive analysis	Predictive analytics, DL	Continuous process optimization and knowledge management	[78,23]

PAT in AI-enhanced QbD implementation

Principle and regulatory background

PAT is a scientific and risk-based framework (as shown in Figure 4) that was developed to design, analysed, and regulate PM processes, where critical quality and PA are measured in real-time [19]. The primary goal is to ensure product quality through understanding and controlling the manufacturing process rather than relying solely on end-product testing [79].

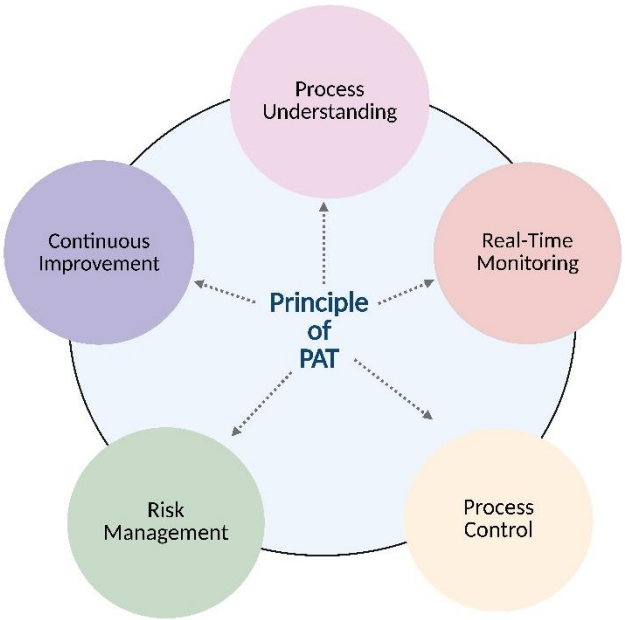


Figure 4. Fundamental principle of PAT

The definition of PAT is given by the U.S. Food and Drug Administration (FDA) as: "A system for designing, analysing, and controlling manufacturing through timely measurements of critical quality and PA of raw materials, in-process materials, and processes to ensure the final product quality" [80].

Implementing PAT within the QbD framework shifts process development from experimental to a more procedural, knowledge-based approach. By continuously providing data on process conditions and product

attributes, PAT tools establish causal relationships between CPPs and CQAs, providing a scientific basis for defining the DS [81]. PAT enables process support RTRT, where the product is released based on in-process data rather than end-point testing [82].

Spectroscopic process analytical technology tools

Spectroscopic PAT tools are generally analytical techniques used in the QbD for continuous monitoring and control of the PM process in real-time, as shown in Table 3**.** They typically enable rapid, non-destructive, and high-accuracy measurements for raw materials, intermediates and finished products to increase process knowledge and product quality [82,83]. Common spectroscopic techniques include Near-Infrared (NIR) spectroscopy, Raman spectroscopy, Fourier Transform Infrared spectroscopy, and Ultraviolet-visible spectroscopy. NIR spectroscopy is among the most commonly applied PAT tools and enables continuous monitoring of blend homogeneity, moisture content, and content uniformity during production [82-85].

Raman spectroscopy can authenticate chemical composition, such as polymorphism, and monitor the spatial distribution and number of analyte species present during a process [86]. Spectroscopic PAT tools create quantitative relationships between spectroscopic features of the raw material feed and monitored CQAs using chemometric methods, thereby reducing dependence on end-product testing and enabling RTRT. Implementing them aids process optimization, minimizes variability and waste, and ensures consistent product quality throughout the product lifecycle [86,87].

Table 3. PAT Tools and their application in Pharmaceutical QbD implementation.

PAT tool	Measurement principle	Application	Advantages	Ref.
NIR spectroscopy	Measure absorption of near-infrared light by molecular bonds (C-H, O-H, N-H)	Blend uniformity, moisture content determination, content uniformity, granulation endpoint monitoring	Rapid, non-destructive, real-time analysis, support RTRT	[19,88]
Raman spectroscopy	Measure inelastic scattering of monochromatic laser light caused by molecular vibrations	Raw material identification, polymorph detection, blend monitoring, content uniformity assessment	High chemical specificity, non-destructive, real-time monitoring	[19,89]
UV-Vis spectroscopy	Measure absorption of ultraviolet and visible light by analyte molecules	Drug concentration analysis, dissolution testing, assay determination	Fast analysis, simple operation, cost-effective	[19,90]
Inline particle sizing	Uses laser diffraction or dynamic image analysis to measure particle size distribution	Milling, granulation, crystallization, drying process monitoring	Continuous monitoring, improved process control, enhanced product consistency	[37]
Terahertz imaging	Uses terahertz radiation to generate an image based on material absorption and reflection characteristics	Tablet coating thickness measurement, coating uniformity evaluation, and defect detection	Non-destructive testing, deep penetration capability, and high resolution internal imaging	[91,92]
Acoustic sensors	Analyse sound waves and vibration signals generated during processing operations	Monitoring granulation, drying, mixing efficiency, powder flow behaviour, end point detection	Real-time monitoring, non-invasive measurement, suitable for a continuous process	[19,93]

Advanced PAT and multivariate data analysis

Advanced PAT is the comprehensive utilization of sophisticated analytical instruments, automation systems and models, and advanced control strategies to provide greater understanding and control of a process. These exist in real-time PAT identification solutions as well as in advanced tools that integrate PAT with chemometrics, ML, AI-based predictive modelling, and automated feedback control systems [94]. This allows for real-time monitoring of CPPs and CQAs during the manufacturing process. A highly sophisticated

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PAT can identify process drift early and autonomously regulate process parameters to ensure a high-quality product meets specified quality specifications [19,95]. Advanced use of PAT enables continuous manufacturing to be efficient, cost-effective, and regulatory compliant. In addition, the implementation of advanced PAT aligns with the objectives of QbD by enabling understanding of each step and its effect on quality, rather than relying solely on end-product testing [94-96].

Multivariate data analysis *(*MVDA) is a statistical approach for interpreting complex datasets resulting from many automatically correlated variables during PM processes. Large volumes of data from spectroscopic instruments, sensors and process monitoring systems are collected in PAT applications [97]. MVDA approaches capture hidden information in these datasets and identify relationships between CPPs and CQAs. Popular MVDA methods include Principal Component Analysis, Partial Least Squares, Orthogonal Partial Least Squares, and Multiple Linear Regression [98]. These are commonly used for monitoring, trend analysis, fault detection, process optimization and predictive modelling. MVDA improves process comprehension by identifying sources of variability and supporting the establishment of DS within a QbD framework. Additionally, the chemometric modelling of spectroscopic PAT tools is important and supports data-driven decision-making across the product lifecycle [19,96-98].

Advanced application in pharmaceutical manufacturing

The transition of the pharmaceutical industry towards QbD principles through Pharma 4.0 strategies, which combine digitalisation, predictive analytics and continuous control to implement quality at the process level [99]. Advanced AI/ML tools, including PAT, predictive models, DT, and natural language processing, are transforming batch QC into proactive data-driven systems [100]. These innovations facilitate continuous monitoring and real-time release testing that comply with ICH Q8-Q13 guidelines and regulatory requirements, such as FDA and EMA for electronic records [101]. Figure 5 shows the interlinked AI/ML-enabled automation, simulation, and regulatory intelligence that enables effective, compliant manufacturing.

Predictive quality control system

The predictive quality control (PQC) system uses AI and ML learning algorithms to provide consistent methods for real-time QA, departing from traditional end-product testing and moving toward a sustained methodology of continual process verification. These systems integrate PAT tools, including NIR, Raman, and ultraviolet-visible spectroscopy, with multivariate data analysis methods for monitoring CQAs during manufacturing [102].

Various ML algorithms, such as SVMs, random forests and CNNs, demonstrate superior accuracy (>95 %) in classifying spectral data and predicting CPPs in solid dosage from manufacturing [103]. Prediction of tablet dissolution profiles with root mean square error below 2.5 % is achieved using long-term memory networks, while Bayesian neural networks enable uncertainty quantification, which is crucial for risk-based decision-making [104].

PQC systems fall under the regulatory framework of ICH Q12 and Q13 guidelines and are propelled toward commercialization through implementation supported by the FDA Emerging Technology Program [105].

Digital twins and virtual experimentation

DT technology enables the creation of near real-time high-fidelity virtual replicas of pharmaceutical processes through an integration of first principles modelling and data-driven surrogate models, which allow for rapid simulations and optimization while not disrupting production [106]. Predictive accuracy within 5% of experimental observations has been achieved using very sophisticated mechanistic models based on

population-balanced equations and computational fluid dynamics, integrated with reduced-order models trained *via* ML [107].

The DS can be explored systematically by running virtual experiments with Bayesian optimization algorithms, resulting in 60 % fewer experimental trials than traditional design-of-experiments approaches [108]. Integrating the digital twin with continuous manufacturing platforms enables dynamic process control and real-time release testing, achieving process capability indices >1.67 and batch failure rates <0.5 % [109].

Automation and continuous manufacturing integration

Continuous manufacturing (CM) coupled with advanced automation aligns with the principles of QbD and Industry 4.0 and provides better understanding while minimizing scale-up risks compared with batch processing [9,99]. Model predictive control systems use real-time PAT data to regulate CQAs within deterministic acceptance criteria, rejecting disturbances during residence times [110].

Automated material handling and collaborative robots greatly reduce human contact, eliminating the risk of transfer contamination in sterile manufacturing. Several recent initiatives, including the FDA Quality Management Maturity Program and the ICH Q13 guideline, have facilitated the implementation of CM in automated processes, resulting in over 20 commercial facilities being approved by 2023 [111]. Automated CM facilities reduce manufacturing costs by 30 to 50 % and waste by up to 90 % compared to traditional batch facilities [112].

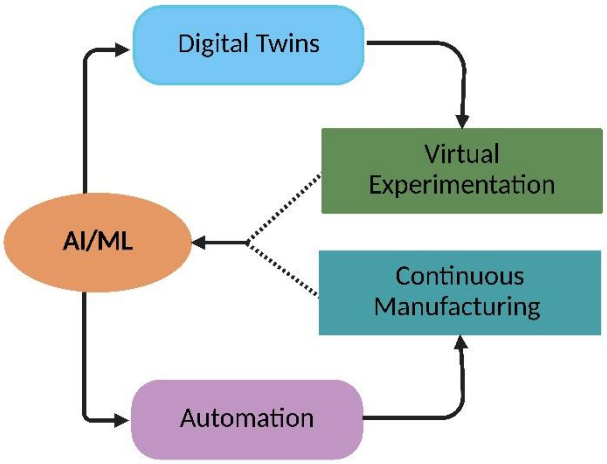


Figure 5. Implementation roadmaps for AI-Driven QbD in PM [106-112]

Comparative performance of Artificial intelligence techniques for Critical quality attributes prediction

A comparative analysis of AI technologies used for CQA prediction in PM is presented, including their predictive performance metrics and key features, as shown in Table 4.

Table 4. Comparative performance of AI techniques for CQA prediction.

AI Technique	CQA prediction	R^2 / %	Key process	Data requirements	Ref.
Random forest	Tablet hardness, dissolution	0.90	Compression	Medium	[113]
Support vector machine	Content uniformity	0.99	Blending	Small-medium	[114]
Artificial NN	Dissolution profile	0.90 to 0.96	Formulation	Medium	[115]
Deep NN	Multiple CQAs	0.95	Continuous Mfg	Large	[116]
Convolutional NN	Defect classification	0.97 to 0.997	Coating	Very large	[117]

Evolution of regulatory framework for artificial intelligence/machine learning pharmaceuticals

The evolution of regulatory frameworks related to AI/ML was implemented from 2019 to 2025 in PM, as shown in Table 5.

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Table 5. Evolution of regulatory framework of AI in PM (2019-2025)

Year	Regulatory authority	Regulatory framework	Relevance to PM	Impact on AI/ML-QbD Integration	Ref.
2019	U.S. Food and Drug Administration	Proposed regulatory framework for modifications to AI/ML-based software as a medical device (AI/ML SaMD)	Introduced the total product lifecycle approach and continuous learning concept for AI systems	Established the foundation for AI model lifecycle management, supporting QbD principles, continual improvement, risk management and process understanding	[45]
2020	World Health Organization	WHO AI governance Initiatives	Promoted ethical AI governance, transparency, and accountability	Reinforced QbD through reliable data governance, explainable AI and risk-based decision-making for AI-assisted pharma manufacturing.	[118]
2021	U.S. Food and Drug Administration	FRAME	Promote adoption of advanced manufac-turing technology including AI, digital twin and continuous manufacturing	Supported integration of AI with PAT, RTRT, predictive process control, and increased QbD application through continuous process verification	[119]
2021	European Commission	Drafted AI act	Proposed a compre-hensive risk-based legal framework for AI systems	Pharmaceutical manufacturing to incorporate AI risk management, documentation, QbD development and manufacturing strategies	[120]
2022	World Health Organization	Ethics and Governance of AI for health	Published six ethical principles governing trustworthy AI	AI enables QbD by promoting transparency, reproducibility, explainability, human oversight, and data integrity throughout the pharmaceutical product life-cycle management	[121]
2023	U.S. Food and Drug Administration	AI in drug manufacturing	FDA document speci-fically addressing AI application in PM.	Clarified expectation for AI model validation, lifecycle management, data integrity, GMP compliance and documentation	[122]
2023	European Medicines Agency	EMA AI Workplan	Developed a coordi-nated regulatory strategy developed for AI across the medicinal product lifecycle.	AI integration into pharmaceutical quality systems, predictive quality assurance, and manufacturing optimization	[123]
2024	European Union	Regulation (EU) 2024/1689 (AI act)	AI legislation estab-lishing a mandatory requirement for high-risk AI systems	Required quality management systems, technical documentation, cybersecurity and post-market monitoring	[124]
2024	European Medicines Agency	Use of AI in the medicinal product lifecycle	AI implementation in drug development, manufacturing, inspections and quality assurance	Provides detailed recommendations for AI validation, governance, lifecycle documentation and risk management that complement ICH Q8, Q9, and Q10 QbD principles	[125]
2025	U.S. Food and Drug Administration	Use of AI in regu-latory decision making for drug and biological products	AI credibility assessment and regulatory submission	Established standard validation for AI models supporting QbD	[126]
2025	European Commission	Draft EudraLex volume 4-GMP annex 22 (AI)	First GMP annex dedicated exclusively to AI systems used in PM	Represent the first specific GMP framework integrating AI into pharmaceutical quality systems. AI lifecycle validation, continuous monitoring, audit trails and human oversights. Creating a comprehensive regulatory basis for AI-driven QbD implementation in smart PM	[127]

Challenges and future perspectives

Technical and scientific challenges

While significant advances have already been made in integrating AI and ML with QbD, several technical challenges still limit widespread industrial use. The main limitation is the lack of high-quality pharmaceutical datasets. Additionally, the experimental data generated are not only expensive but also limited in size and proprietary, thus hampering the development of robust and generalizable AI models [1]. Furthermore, PM creates heterogeneous data through PAT, manufacturing execution systems, laboratory information management systems, batch manufacturing records and regulatory documents. The difficulties of using these different sources are evident in the need to integrate them into a common analytical framework, a task that requires sophisticated data engineering and standard data architectures [128].

The complexity of pharmaceutical processes is one more major challenge. Conversely, multiscale process interactions, polymorphism, nonlinear solid-state transformations and other biological variation phenomena are also unlikely to be modeled well by purely data-driven techniques [129]. As a result, hybrid modeling is also receiving more attention, combining process-based know-how with AI/ML algorithms to accomplish greater predictive power while maintaining scientific interpretability [130].

Model transparency is another central issue for regulatory acceptance in RTA products. Most advanced AI systems are “black box” models, and one must explain the algorithms operating in a high-dimensional information space through explainable AI, especially DNNs that prescribe features from the data. Explainable AI methods originally developed to explain black-box models, including SHAP and LIME, have improved model interpretability. However, further research is required to establish sufficient scientific confidence for regulatory decision-making and GMP application [131].

Regulatory and organizational challenges

Regulatory frameworks for AI/ML applications in the PHMM are still under development. While regulatory agencies such as the U.S. FDA and the EMA have released discussion papers and strategic guidance on AI, harmonized international standards for AI model validation, lifecycle management, cybersecurity, and change control remain unestablished [45,132]. Finally, the fundamental characteristic of continuously learning AI systems from new data makes their validation a unique challenge, given the different assumptions traditionally used in AI validation compared with traditional methods [45].

In addition to compliance, successful AI implementation requires transformative organizational change. This can be achieved by pharmaceutical manufacturers developing digital infrastructure, data governance strategies and workforce training, as well as interprofessional collaboration among quality assurance, manufacturing, regulatory affairs, information technology, and data science teams [133-135]. Establishing organizational capability around AI governance, model lifecycle management, and regulatory compliance will be necessary to unlock the full capabilities of AI-powered QbD [135].

Future perspective and emerging trends

In line with this discussion, future pharmaceutical manufacturing is expected to innovate and increasingly adopt AI-enabled advanced digital technologies integrated into intelligent, automated, and data-driven production systems. Among the most exciting developments is when AI is integrated with Digital Twin technology to allow not only for virtual simulation of various processes during a product lifecycle, but also for predictive maintenance, real-time optimization and proactive quality control [136].

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Federated learning is another emerging approach that provides a framework for collaborative AI model development across institutions while safeguarding data privacy, helping overcome limitations in available datasets in the pharma industry [137]. Similarly, large language models are expected to support regulatory intelligence input, scientific knowledge extraction, and automated document preparation for deviation investigation and compliance management in sponsors and CROs, improving operational efficiency while reducing manual effort [138].

By combining AI-driven QbD with personalized medicine and pharmaceutical additive manufacturing (3D printing), intelligent control of printing parameters and quality prediction could enable real-time optimization of patient-specific dosage forms [139]. Moreover, pairing AI with continuous manufacturing and advanced PAT is expected to trigger autonomous process control, RTRT, reduced manufacturing variability and more robust pharmaceutical supply chains [140].

In summary, as global regulatory frameworks evolve, data-driven methods for AI validation develop, and pharmaceutical companies bolster their digital capabilities, it is expected that AI/ML will play a prominent role in designing modern QbD strategies. This integration will enable process understanding, faster regulatory decision-making, sustainable manufacturing practices, and improved patient safety and regulatory compliance.

Conclusion

This comprehensive review highlighted current trends in automation, with an emphasis on QbD, the modern approach to this concept, and its revolutionary implementation in AI and ML in pharmaceutical manufacturing. The convergence of QbD principles with emerging computational technologies also represents a paradigm shift that is truly redefining our approach to both pharmaceutical products and their development, manufacture and control. It shows that AI/ML technologies provide unique capabilities to understand processes, the ability to predict quality and autonomous optimization that fit well within the original intentions of QbD.

The regulatory environment of the industry has also embraced these advances, with a solid quality framework provided by ICH Q8-Q14 guidelines for the influence of science on product and manufacturing quality, along with FDA initiatives including ETP, FRAME, and AI-assisted review pilot programs demonstrating regulatory readiness to embrace novel pharmaceutical capabilities in the industry. These selected industrial use cases highlight the potential of applying advanced AI technologies to accelerate QbD practices, leading to substantial gains in process robustness, consistency, and operational efficiency.

But unlocking intelligent PM is not without its challenges related to data management, interpretability, regulatory harmonization and organizational transformation. The way forward to addressing these limitations is through the development of Explainable AI techniques, hybrid mechanistic-data-driven models, and robust validation frameworks. While the way forward to Pharma 4.0 is still in progress in our industry, no doubt the integrated use of AI/ML together with the principles of QbD will be a key aspect in enabling the delivery of consistent medicines globally that meet and exceed safety and efficacy standards.

Abbreviations

QbD	Quality by design
PD	Pharmaceutical development
QbT	Quality by testing
AI	Artificial intelligence
ML	Machine learning
CQAs	Critical quality attributes

PM	Pharmaceutical manufacturing
DNNs	Deep neural networks
QC	Quality control
ICH	International Council of Harmonization
QRM	Quality risk management
CPPs	Critical process parameters
ETP	Emerging technology program
FDA	Food and Drug Administration
QA	Quality assurance
CNNs	Convolutional neural networks
PAT	Process analytical technology
DT	Digital twins
PA	Performance attributes
RTRT	Real-time release testing
QTPP	Quality target product profile
FMEA	Failure mode and effects analysis
DoE	Design of experiments
DL	Deep learning
CMAs	Critical material attributes
SL	Supervised learning
DS	Design space
RNNs	Recurrent neural networks
RL	Reinforcement learning
SHAP	Shapley additive explanation
LIME	Local interpretable model-agnostic explanations
NIR	Near-infrared

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