

# Quality Assurance in Pharmaceutical Sciences: Current Status and Future Prospects

Deep Parekh\*, Patel Grishma<sup>1</sup>, Patel Dhara<sup>1</sup>, Dhananjay Meshram<sup>1</sup>

*1 Department of Pharmaceutical Quality Assurance, Pioneer Pharmacy College, Vadodara -390019, Gujarat, India*

Date of Submission: 25-05-2026

Date of Acceptance: 05-06-2026

**ABSTRACT:** Background: Within pharmaceutical industry, QA involves a broad range of organized measures designed to maintain the quality, safety, and effectiveness of medicinal products throughout their development and production processes. As the industry continues to advance through new technologies, updated regulatory frameworks, and increasingly interconnected manufacturing systems, evaluating the current role and future progress of QA has become highly important for both pharmaceutical professionals and regulatory agencies. Objective: The purpose of this review is to critically evaluate advanced technologies and approaches that have the potential to shape the future of quality management in drug development and production, and to systematically assess the state of pharmaceutical QA systems today. In conclusion, pharmaceutical quality assurance is transitioning from reactive habits to proactive, data-enabled strategies. Navigating this change successfully will depend on three main pillars: harmonizing global regulations, investing in digital tools, and reimagining how the people operating this system are trained. The future of QA lies in this blend of advanced technology and refined human experience.

**KEYWORDS:** Pharmaceutical quality system (PQS), cGMP compliance, Product life cycle management, regulatory harmonization, cognitive computing, real-time release testing (RTRT)

## I. INTRODUCTION

### 1.1 Definition and Scope of Quality Assurance

In pharmaceutical sciences, quality assurance can be described as a holistic science where all efforts have been put together to ensure that pharmaceuticals are always delivered at the highest level of identity, strength, purity, and efficacy across their entire life cycle ranging from the time of their development, production, distribution, storage, and finally use by patients. According to WHO, quality assurance refers to the totality of activities which have been put in place to

guarantee that pharmaceutical products meet the necessary standards of quality.[1]The scope of pharmaceutical assurance is broad and multifaceted. It involves compliance with regulations both locally and internationally, document control, employee training and qualifications, equipment and facility qualifications, process and method validation, change control, supplier qualification, and post-market surveillance. Contrary to Quality Control (QC), which mainly involves testing and release, Quality Assurance (QA) entails the overall management approach that sets the foundation for conducting quality control activities.[2]In its most general form, pharmaceutical quality assurance acts as the unseen promise made by each drug that finds its way into the hands of patients. It is the unseen structure that turns crude material and human labor into medicinal drugs that can be relied upon to fulfil their desired purpose without posing any threat to the recipient. The paper analyses the structure's evolution, present time status, future trajectory amidst an era of quick technological change. [3]

### 1.2 Historical Importance of QA in Pharmaceutical Manufacturing

Pharmaceutical QA has seen its development shaped significantly through the experiences of history and those lessons learned from the devastating effects of poor-quality standards. The pharmaceutical industries were largely unregulated before the dawn of the 20th century, and substandard medicines often reached consumers without penalty. [4]The case of elixir sulphanilamide in the year 1937 in the US, in which 107 deaths occurred due to the drug containing diethylene glycol as a solvent, resulted in the formation of FDCA in the year 1938. [5,6]In the case of India, it was the formation of the Drug and Cosmetic Act of 1940 together with its amendments, along with the introduction of Schedule M, wherein the application of cGMP is

obligatory. The CDSCO, being the national regulatory agency, is responsible for approval of drugs and manufacturing controls. [7] These events collectively prove that pharmaceutical quality assurance is more than just an administrative task, but rather an absolute ethical and scientific responsibility. Every regulation, guideline, and quality management system that currently exists was born out of tragedy and scientific knowledge gained through adversity, representing the industry's dedication to ensuring the safety of patients. [8]

### 1.3 Evolution of QA Paradigms

The history of the evolution of QA in the pharmaceutical industry can be viewed as a series of successive paradigms, each one offering a more advanced level of knowledge on quality control. [9]

Quality by Inspection (QbI) represents the earliest QA paradigm that prevailed in the industry up to the mid-20th century. Under this paradigm, the quality of the product was ensured by conducting tests on the finished product batches and rejecting those that did not meet the required standards. Although this practice ensured a minimal degree of safety, it was highly wasteful and economically unfeasible. [10]

Quality by Control (QbC) is the second paradigm and arose from industries' realisation that the use of systematic controls of the manufacturing process would minimise the frequency of failures. Tools such as statistical process control were employed in the manufacturing sector during World War II and later extended to the pharmaceutical industry, enabling the monitoring of processes and detecting any deviations before producing out-of-specification products. [11] Quality by Design (QbD) is the third paradigm and is the most advanced modern-day concept that was officially adopted in the pharmaceutical industry through ICH Q8 guideline in 2009. QbD has revolutionised the notion of quality by integrating it into the design of a product using a comprehensive scientific knowledge of how formulation and processing variables impact the product's characteristics. [12] Digital QA represents the current frontier, wherein digital technology such as artificial intelligence, machine learning, and digital twin are incorporated in the QA approach, thereby making possible real-time

monitoring, predictive quality management, and greater insights into processes. It is still an ongoing process that promises to significantly impact quality in the pharma industry in the coming years. [13, 64]

## II. CURRENT STATUS OF QUALITY ASSURANCE

### 2.1 Current Good Manufacturing Practice (cGMP)

cGMP, which stands for Current Good Manufacturing Practice, is considered to be the lowest quality benchmark that the manufacturer of drugs must meet when making drugs intended to be used either for human or animal treatment purposes. The term 'current' in cGMP is crucial — it means that the manufacturing facility should implement new techniques, methods, and technologies whenever it is necessary and acceptable from the regulatory authorities' perspective. [14] The U.S. version of cGMP requirements is included in 21 CFR Part 210 and 21 CFR Part 211 for finished pharmaceutical products, 21 CFR Part 212 for drugs produced using positron emission tomography, and 21 CFR Parts 600-680 for biologics. In Europe, cGMP requirements can be found in EudraLex Volume 4 Good Manufacturing Practice Guidelines. The WHO offers GMP recommendations that are applied in pharmaceutical regulation in many developing nations such as India's Schedule M. [15, 8] cGMP standards cover a number of important aspects: designing and constructing the manufacturing facility; qualifying and maintaining equipment; validating manufacturing processes and cleaning methods; developing standard operating procedures; training of personnel; detailed documentation and record keeping; specific quality control testing; handling of complaints and recalls; and clear definitions of responsibility of all personnel. [16] Adherence to cGMP requirements is checked during regulatory inspections performed by agencies like FDA, EMA, MHRA, TGA, and State Licensing Authority (SLA) and CDSCO in India. Failure to comply with cGMP standards may lead to receiving Warning Letters and Import Alerts, initiation of recalls, suspension of manufacturing operations, and even legal prosecution in extreme cases. [17]

**Table 1: Comparison of Major Global GMP Frameworks**

Regulatory Body	Regulation/Guideline	Jurisdiction	Key Feature
US FDA	21 CFR Parts 210-211	USA	Risk-based inspections, PAT
EMA / EU	EudraLex Vol. 4	European Union	Annex-based system, GDP integration
WHO	TRS 986 / TRS 1044	Global (developing nations)	Basis for PICS, Indian Schedule M
CDSCO / India	Schedule M (D&C Act)	India	Aligned progressively with WHO GMP
PMDA / Japan	GMP Ordinance	Japan	ICH Q10 adopted; risk-based approach

Sources: References [7, 8, 14, 15, 51]

## 2.2 ICH Guidelines and Their Implementation

The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) is one institution that has had the most vital impact on the harmonization of pharmaceutical QA standards. Through the ICH assembly, industry members and regulatory authorities from the US, Europe, Japan, and other locations collaborate to develop the organization's guidelines. [18] Those ICH Quality guidelines related to QA practice are: Q7 (Guide to Good Manufacturing Practice for Active Pharmaceutical Ingredients); Q8 (Pharmaceutical Development including QbD philosophy); Q9 (Quality Risk Management); Q10 (Pharmaceutical Quality System); and Q12 (Technical and Regulatory Aspects of Pharmaceutical Product Lifecycle Management). [19] Quality Risk Management (QRM) ICH Q9 is especially significant in today's QA practices. By incorporating quality risk assessment tools like Failure Modes and Effects Analysis (FMEA), Fault Tree Analysis (FTA), and Hazard Analysis and Critical Control Points (HACCP), it ensures that quality assurance efforts are proportional to the risk associated with various operations and substances. [20] ICH Q10 — Pharmaceutical Quality System — is a guideline that provides an approach which encourages new development and continuous productivity, strengthens the link between product development and production, and better manages data. The guideline acknowledges that a solid quality system establishes a framework within which issues are proactively solved, human errors are prevented, and there is a culture of continuous improvement. [21]

## 2.3 Standard Operating Procedures and Validation Documentation

SOPs form the core of any good pharmaceutical quality assurance program. An SOP is a written procedure outlining how particular procedures or operations should be carried out in a certain way. The following are the main roles of an SOP document: to provide operational consistency, to act as training aids, to provide reference when investigating deviations, and to act as a record of compliance during inspection. [22] Validation refers to the establishment of proof or documentary evidence that a system, procedure or equipment consistently delivers a result which conforms to a specified requirement. The fields of validation include procedure validation (prospective, concurrent, and retrospective), cleaning validation, analytical method validation (based on the ICH Q2 (R1) guidelines), computer system validation (CSV), and equipment qualification (IQ, OQ & PQ). [23] The FDA's Process Validation Guidance, released in 2011, outlined a step-wise process validation strategy comprising Process Design (Step 1), Process Qualification (Step 2), and Continued Process Verification (Step 3). This lifecycle approach explicitly acknowledges the need for ongoing updating of process knowledge acquired during product development and manufacturing processes. [24]

## 2.4 Distinction Between Quality Assurance and Quality Control

One area that often creates confusion is the understanding of the difference between Quality Assurance and Quality Control. Although both processes are essential for product quality, their approaches and positioning within an organisation are different. [25]

**Table 2: Key Differences Between QA and QC**

Attribute	Quality Assurance (QA)	Quality Control (QC)
Nature	Proactive, preventive	Reactive, detective
Focus	Systems, processes, compliance	Testing finished products/materials
Responsibility	Entire organisation	QC laboratory personnel
Documentation	SOPs, master documents, audits	Test results, COA, logbooks
Regulatory basis	ICH Q10, cGMP regulations	ICH Q2(R1), pharmacopoeias
Approach	Built into the system	Applied to outputs

### III. QA SYSTEMS AND TOOLS

#### 3.1 Quality Management Systems (QMS)

A QMS is a structured framework that outlines the roles, responsibilities, and processes required to carry out quality goals and policies. In the pharmaceutical sector, QMS can be described as the operational implementation of the philosophy stated by ICH Q10 as an organizational structure, responsibilities, processes, procedures, and resources required to implement quality management. [26]

ISO 9001:2015 standard, which is not mandatory for pharmaceutical manufacturing organizations, is a widely recognized QMS model based on the Plan-Do-Check-Act (PDCA) methodology and involves risk-based thinking as its main concept, and hence, fits well into the ICH Q9 and Q10 philosophy. [27]

The use of electronic quality management systems (eQMS) is widespread in large pharmaceutical companies today as compared to paper-based systems, due to numerous benefits in the areas of document management, process management, maintenance of audit trails, and availability of information. Commercial products such as Veeva Vault Quality, MasterControl, and Sparta Systems TrackWise offer modules for managing documents, CAPAs, deviations, changes, training, and vendor qualifications. [28] Modules of pharmaceutical QMS include: Document Management; Change Control; Deviation Management; CAPA; Training Management; and Vendor Qualification Management — all responsible for identifying quality problems, documenting, investigating, analyzing their causes, and implementing corrective measures. [29]

#### 3.2 Corrective and Preventive Action (CAPA)

CAPA is a key component of a pharmaceutical QMS and the principal tool used for investigating quality issues, taking corrective

actions against them, and preventing their recurrence. An efficient CAPA system is expected by the FDA, and CAPA problems rank among the top reasons for FDA Warning Letters addressed to drug manufacturers. [30] Corrective Actions are measures intended to deal with problems that have already appeared, aimed at eradicating their root causes to prevent any recurrence. Preventive Actions are measures intended to address potential deviations, i.e., risks that may turn into problems. Both categories of actions involve root cause analysis performed using tools such as the Fishbone (Ishikawa) diagram, the 5-Why analysis method, or Fault Tree Analysis, as well as an assessment of effectiveness once completed. [31]

Characteristics of an efficient CAPA system include: immediate initiation once a quality problem has been detected; rigorous, data-driven root cause analysis; well-defined, measurable corrective/preventive actions with clearly indicated owner and due date; and effectiveness confirmation. [32]

#### 3.3 Risk Management Frameworks

Quality Risk Management (QRM) is now a cornerstone of contemporary pharmaceutical QA practice after the release of ICH Q9 in 2005 (updated in 2023 as Q9(R1)). QRM offers a structured approach towards evaluating, controlling, communicating, and reviewing the risks to the quality of medicines, thus ensuring that any decisions on how to allocate resources, implement process controls, and perform testing are commensurate with the level of risk involved. [33] Tools used commonly for risk assessment include: Failure Mode and Effects Analysis (FMEA), which involves systematic identification of potential failures and determination of their impact through Risk Priority Number (RPN); FMECA; Hazard Analysis & Critical Control Points (HACCP); and Preliminary Hazard Analysis

(PHA). The updated ICH Q9(R1) document of 2023 included key clarifications on the role of subjectivity in risk assessment and the vital importance of using scientific knowledge, data, and experience in making QRM decisions. [34, 35]

### 3.4 Audits and Self-Inspection

Audits and internal inspections are a key component of the pharmaceutical QA process, offering structured and documented reviews as to whether quality-related actions conform to plans, are executed effectively, and are appropriate for the realization of quality system objectives. [36]Self-inspection refers to the practice of a pharmaceutical company inspecting its systems using its own quality assurance department in order to detect potential non-compliances or weaknesses before any inspection takes place from the regulators' side. Self-inspection should include all possible aspects of cGMP compliance on an agreed-upon schedule. [37]Supplier audit is an evaluation process carried out by pharmaceutical companies for contract manufacturers, contract laboratories, and raw material suppliers. Supplier audits have become increasingly significant due to globalisation of pharmaceutical manufacturing processes, making quality assurance not only important at production facilities but also throughout the whole supply chain. [38]

## IV. QUALITY BY DESIGN (QBD)

### 4.1 Quality Target Product Profile (QTPP)

The QbD strategy begins with the Quality Target Product Profile, which is a prospective overview of a drug product's quality attributes that should ideally be attained to guarantee the intended quality, safety, and efficacy. The QTPP acts as the benchmark against which all development decisions are assessed and specifies what the finished product must be, not what the process that produces it will be. [40]The QTPP typically includes: the intended use in relation to the dosage form and route of administration; dosage form design and container closure system; dosage strength; pharmacokinetic features pertinent to the therapeutic indication; drug product quality standards suitable for the intended marketed product; and any unique considerations required by the patient population. [41]The QTPP is not a static document — it is refined iteratively as product understanding increases through development. Critically, the QTPP provides a sound scientific basis for identifying which product attributes are truly critical to patient outcomes, enabling the

development team to focus resources on understanding and controlling the factors that matter most. [42]

### 4.2 Critical Quality Attributes (CQA)

Critical Quality Attributes (CQAs) refer to the physical, chemical, biological, or microbiological properties or characteristics that must remain within specified limits, ranges, or distributions to guarantee the desired quality of a product. CQAs are established from the QTPP through a risk assessment of product attributes, which involves identifying those attributes that, if they fall outside their acceptable ranges, could adversely affect product safety, efficacy, or patient acceptability. [43]In the case of a solid oral dosage form such as a tablet, common CQAs encompass: assay (drug content); content uniformity; dissolution rate and profile; hardness and friability; disintegration time; moisture content; and the particle size distribution of the active ingredient. For sterile injectable products, additional CQAs consist of sterility, particulate matter content, endotoxin levels, pH, osmolarity, and visible appearance. [44]The identification of CQAs necessitates a comprehensive understanding of how product characteristics relate to clinical performance. Risk assessment tools, especially the Initial Risk Assessment, which is frequently organized as a Fishbone diagram or risk matrix, are employed to systematically assess and prioritize the potential effects of each product attribute on patient safety and efficacy. [45]

### 4.3 Critical Process Parameters (CPP)

Critical Process Parameters (CPPs) are those parameters in a process whose variability directly influences one or more Critical Quality Attributes (CQAs). The functional distinction between CPPs and non-critical process parameters is important — it is essential to monitor and control CPPs within specified ranges to guarantee that the manufacturing process yields materials that comply with all CQA specifications. [46]Identifying CPPs necessitates a systematic comprehension of the connections between process inputs and product outputs — these connections are generally examined through Design of Experiments (DoE) methodologies. DoE facilitates the simultaneous variation of multiple input variables in a statistically organized way, allowing for the identification of both the individual impacts of each variable and any interaction effects. [47]

#### 4.4 Design Space and Control Strategy

The Design Space is characterized in ICH Q8(R2) as the multidimensional interplay of input variables (such as material attributes) and process parameters that have been shown to ensure quality assurance. Operating within the design space is not regarded as a modification and does not necessitate regulatory notification, thus rendering the design space a significant asset for manufacturing flexibility post-approval. [48]The Control Strategy,

as outlined by QbD, specifies how the integration of material attributes, process parameters, in-process monitoring, and end-product testing collectively guarantees that CQAs are achieved. An effectively crafted control strategy is proportionate to risk — implementing stricter controls on higher-risk parameters while adopting more adaptable methods where scientific understanding supports such an approach. [49]

**Table 3: QbD Elements and Their Regulatory Basis**

QbD Element	Description	ICH Reference
QTPP	Defines desired product performance characteristics	ICH Q8(R2)
CQA	Product attributes linked to safety/efficacy	ICH Q8(R2), Q9
Risk Assessment	Identify and evaluate risks to CQAs	ICH Q9
CPP	Process parameters affecting CQAs	ICH Q8(R2)
Design Space	Proven acceptable range of parameters	ICH Q8(R2)
Control Strategy	Planned set of controls ensuring process performance	ICH Q10

Sources: References [12, 19, 21, 39, 40, 48, 49]

### V. CURRENT CHALLENGES IN PHARMACEUTICAL QUALITY ASSURANCE

Despite notable progress in regulatory frameworks and technological advancements, pharmaceutical quality assurance still encounters substantial challenges that hinder the reliable provision of high-quality medications. Recognizing these challenges is crucial for formulating effective strategies to tackle them. [50, 52]

#### 5.1 Regulatory Complexity and Jurisdictional Divergence

The worldwide pharmaceutical sector is required to maneuver through an exceptionally intricate regulatory environment marked by considerable variations in jurisdictional requirements, interpretations, and enforcement strategies. Although initiatives such as ICH and PICS (Pharmaceutical Inspection Co-operation Scheme) have made progress in harmonizing critical aspects, notable discrepancies remain among regulatory systems in major markets. [50]Companies exporting their products across several destinations have to abide by the FDA's cGMPs in the United States, GMPs within the European Union, standards set by the Japanese

PMDA, regulations of Health Canada, and many other regulations of different countries that emerge as new markets. Manufacturers must ensure compliance even where the requirements differ regarding batch record formats, validation practices, stability testing, and management of electronic records. [51]Regulatory changes per se are another challenge. New and revised guidance documents come out constantly from various regulatory agencies. The manufacturer will have to evaluate the effect of these changes on its production activities and implement any measures required by them, including changing its approach to product safety and moving toward electronic submission systems and risk-based inspections. [52]

#### 5.2 High Implementation and Maintenance Costs

The cost associated with implementing QA in the pharmaceutical industry is huge and acts as a hindrance to the implementation of best practices, especially for SMEs in developing countries. These costs include capital expenses for designing facilities and qualifying equipment, operating costs for labor, staff training, and maintenance of systems, investing in validated IT

systems, and cost of investigations, batch failure, recalls, and other quality incidents. [53] Research published in the Journal of Pharmaceutical Sciences approximated that financial losses due to poor quality in the manufacture of drugs affect the global pharmaceutical industry by about \$50 billion each year, including the effects of inefficiency, recalls, rejections, and penalties. This illustrates that investing in quality is ultimately cheaper than the cost of quality failures. [54]

### 5.3 Data Integrity Vulnerabilities

Data integrity — encompassing the completeness, consistency, accuracy, and reliability of data at all stages of its life cycle — has become one of the biggest compliance issues for the pharma industry. During the period of 2012-2022, the FDA issued more than 100 Warning Letters for data integrity issues, and many bans on importing goods were due to data manipulation issues. [55]

Integrity problems could span from simple documentation problems to the falsification of records, including backdating, improper electronic data overwriting, failure to document original data, and audit trail manipulation. ALCOA+ (Attributable, Legible, Contemporaneous, Original, Accurate, plus Completeness, Consistency, Enduring, and Availability) is considered the basis of data integrity. [56]

Although the change from paper to electronic format usually improves the data integrity control process with the application of enforced audit trails and access controls, there are potential threats that can emerge as a result of the absence of validation of these systems, restrictions on user access, and poor backup of electronic documents. [57]

### 5.4 Human Error and Training Deficits

Human error is one of the major causes in pharmaceutical quality investigations as well as a major problem for QA systems. Research on pharmaceutical deviation databases has shown that human error is responsible for about 50 to 70% of manufacturing problems, such as mix-ups, measurement errors, documentation errors, and lack of procedural compliance. [58] The best way of mitigating human error involves a systemic approach that does not simply include retraining after an error takes place. Human error analysis must distinguish between errors due to knowledge gaps (correctable by training), errors due to flawed procedures or working environments (correctable through ergonomics and procedures), and

violations due to organizational culture issues (correctable through leadership interventions). [59]

### 5.5 Global Supply Chain Vulnerabilities

In recent years, the pharmaceutical industry supply chain has become much more globalized and complicated by sourcing APIs, excipients, and packaging materials through supplier networks dispersed across many nations. The COVID-19 pandemic served as an important reminder of the vulnerability of this supply chain by illustrating how reliant the global pharmaceuticals market is on a small number of locations for API production, including China and India. [60] For QA, there are concerns associated with complex and worldwide supply chains relating to maintaining quality standards of raw materials, remaining aware of supplier activities, identifying counterfeit materials, and handling cold chain considerations related to biological materials. Supplier qualification programs, testing programs for raw materials, and supply chain risk assessments must all appropriately address these issues. [61]

## VI. EMERGING TRENDS IN PHARMACEUTICAL QUALITY ASSURANCE

The field of quality assurance in pharmaceuticals is undergoing a major transformation owing to the emergence of several technologies that form a cluster related to the fourth industrial revolution, or Industry 4.0. These technologies provide unmatched potential for process understanding, real-time quality assurance, and a shift towards predictive quality management. [62]

### 6.1 Digital QA and Industry 4.0

Industry 4.0 — an era of convergence between cyber-physical systems, Internet of Things, cloud computing, cognitive computing, and artificial intelligence for use in manufacturing operations — is revolutionising pharmaceutical manufacturing, from batch to continuous, digitally enabled operations. The concept of the Smart Factory, where operations can be replicated in a digital form to facilitate decision making, forecasting, and management, is steadily moving from theory to practice. [63]

Transformation of pharmaceutical QA in the digital age involves the use of electronic batch records (EBR), which substitute paper-based batch records; Manufacturing Execution Systems (MES)

that guide operators during manufacturing; Process Analytical Technology (PAT) tools for real-time monitoring of critical quality attributes; and analytics platforms for analyzing data from different sources. [64]

## 6.2 Artificial Intelligence and Machine Learning in QA

Artificial Intelligence and Machine Learning may be considered among the most revolutionary influences currently impacting pharmaceutical quality assurance. AI is a field which deals with computational machines that can accomplish tasks usually requiring human intelligence such as pattern recognition, decision making, prediction, and natural language processing; Machine Learning is a subset of AI where learning occurs without explicit programming. [65]

Applications of AI and ML in pharmaceutical QA include: predictive quality modeling where ML models trained on past manufacturing data detect patterns that predict future batch failure; automated visual inspections by computer vision systems using deep learning; natural language processing for adverse event reporting and complaints evaluation; and regulatory intelligence applications that scan the global regulatory environment. [66]An illustrative case of AI implementation in pharmaceutical QA is AI-driven spectral analysis of Raman spectroscopy data for online monitoring and control. Such AI-based analysis enables detecting polymorphic transitions, evaluating kinetic processes of API crystallization, and identifying impurities at trace concentrations. [67]

## 6.3 Internet of Things (IoT) in Pharmaceutical Manufacturing

The Internet of Things is essentially the interconnection of devices, including sensors, actuators, measuring instruments, and cameras, linked to the internet and to each other, continuously producing and exchanging data. The IoT has facilitated continuous monitoring of vital parameters such as temperature, humidity, pressure, flow rate, pH, and conductivity in the manufacture, storage, and distribution process. [68]IoT-enabled environmental monitoring systems can detect any deviation in temperature and humidity values in storage locations, clean rooms, and cold chain transport, creating electronic logs that meet data integrity criteria. IoT tags facilitate tracking the position and condition of valuable pharmaceuticals in the supply chain. The combination of IoT

streaming data with AI-enabled analytical tools makes it possible to implement 'digital twin' concepts very efficiently. [69, 70]

## 6.4 Automation and Robotics in QA

Automation and robotics are gaining widespread adoption in pharmaceutical manufacturing and quality control procedures. Robotic liquid handlers and automated analytical devices have taken over routine quality control laboratory activities where manual sampling and analysis was previously done, eliminating analyst-to-analyst variability in results. [71]Collaborative robots are employed in tablet counting and packaging, vial inspection, and labeling in the pharmaceutical manufacturing sector. Sterile filling and inspection lines, which are completely automated, have now reached a high level of sophistication where they can work in isolators with very little human involvement. [72]Process Analytical Technology (PAT), described officially by the FDA as a system designed to analyze and control processes based on timely measurements of critical quality and performance attributes, allows real-time characterization of material properties and process conditions. PAT tools such as near-infrared (NIR) spectroscopy, Raman spectroscopy, focused beam reflectance measurement (FBRM), and particle size analyzers contribute to the implementation of real-time release testing. [73]

## 6.5 Data Integrity, 21 CFR Part 11, and ALCOA+

The regulation surrounding electronic records and electronic signatures, with emphasis on 21 CFR Part 11 in the US and EU Annex 11 in Europe, prescribes certain requirements for validating electronic records, maintaining their security, audit trail, and integrity. The compliance with these regulations forms the basic necessity for implementing a digital QA system. [74]

The ALCOA+ principle — insisting that data be Attributable, Legible, Contemporaneous, Original, Accurate, Complete, Consistent, Enduring, and Available — offers a tangible approach to assessing data integrity within both paper and electronic environments. The application of ALCOA+ calls for a technical solution as well as a strong data management culture. [75]

## 6.6 Blockchain Technology in Pharmaceutical QA

Blockchain technology, distinguished by its decentralization, immutability, transparency, and encryption features, can be utilized in

pharmaceutical distribution in various transformative ways. Transactions registered in a blockchain system are recorded chronologically and cannot be altered, since records are distributed among all participants of the network. [76] In pharmaceutical applications, blockchain could provide an unbroken, immutable chain of custody for drug products from API synthesis through finished product manufacture, distribution, and dispensing. Pilot projects by companies including MediLedger, IBM, and various pharmaceutical consortia have demonstrated feasibility, though widespread adoption is constrained by interoperability challenges, scalability limitations, and the need for industry-wide standardisation. [77] Track and trace legislation, such as the US DSCSA and EU FMD, mandating serialisation and traceability, represent regulations for which blockchain could be an ideal solution. With stricter regulations and greater maturity of interoperability standards, blockchain is anticipated to see rapid implementation within the pharmaceutical industry. [78]

### 6.7 Continuous Manufacturing and Real-Time Release Testing

Continuous manufacturing (CM) is an alternative paradigm compared to the traditional batch manufacturing approach, where raw materials are continuously input through unit operations until the output is the final product. The benefits of CM include compact equipment size, better process control, scale-up without requiring re-validation, and faster manufacturing cycles. [79] In terms of QA, CM requires a completely new process control and release strategy. In particular, real-time release testing (RTRT) — evaluating the quality of process intermediates and/or the final product in real-time based on process data — becomes necessary for continuous manufacturing. RTRT is accomplished by incorporating real-time PAT data directly into the production process through multivariate statistical process control models. [80] Both FDA and EMA have released guidelines related to continuous manufacturing. One of the first landmarks was the Janssen/J&J facility in Belgium, where FDA approved the tablet manufacturing process for darunavir via CM technology in 2016. [81]

## VII. FUTURE PROSPECTS

The path for pharmaceutical QA leads to a future defined by increasingly proactive, predictive, and patient-focused quality management. Several

trends will shape the future of QA in the coming decade. [82]

### 7.1 Smart Manufacturing and Predictive QA

The concept of the pharmaceutical smart factory — the integration of a manufacturing plant that uses AI systems to constantly track process status, anticipate quality deviations, and optimize process parameters to ensure the best quality — is slowly becoming more tangible. Predictive quality assurance systems based on machine learning algorithms fed by extensive historical production data will allow QA professionals to focus on preventive measures rather than corrective actions. [83]

Digital twin technology, which involves developing computer models of manufacturing processes based on sensor data, is another promising technology that will play an important role in both process optimization and quality assurance. The use of digital twins will make it possible to virtually test the impact of process changes without the need to physically implement them. [84]

### 7.2 AI-Driven Audits

AI could bring about radical changes for inspections and internal audits. Advanced document analysis solutions using AI technologies can scan huge volumes of digital documents such as batch records, laboratory records, deviation reports, and CAPA records in order to detect anomalies, patterns, and data integrity issues with unparalleled efficiency compared to manual methods. The FDA and EMA are considering utilizing advanced analytics in their inspection activities. [85]

Another vision for the future is the introduction of 'continuous compliance', where regulatory authorities can monitor manufacturing processes in real time via remote data collection and apply continuous risk stratification in their oversight instead of conducting inspections periodically. Such a model could radically change the industry's interaction with regulatory agencies. [86]

### 7.3 Global Harmonisation of QA Standards

The future of pharmaceutical QA will demand harmonised global standards, which will allow drugs to be produced anywhere in a compliant facility and marketed anywhere in the world without redundant assessment and testing. ICH has taken great strides in this respect, and the broadening of its member base to include

regulatory agencies from China, South Korea, Brazil, and other rising markets is an encouraging sign. [87] Mutual Recognition Agreements (MRAs) — formal agreements between regulatory bodies to recognise each other's inspection results and drug approvals — can also reduce redundancy in the regulatory process while ensuring quality and safety. The FDA-EMA MRA on GMP inspections, in place since 2019, shows how this can work. [88]

#### 7.4 Personalised Medicine and Adaptive QA

With the advent of personalised medicine, encompassing advanced therapy medicinal products (ATMPs) like CAR-T cell therapy, gene therapy, and tissue-engineered products, entirely novel QA concerns are arising. The ATMPs have a biological nature and variability that pose a unique challenge to QA systems traditionally applied to chemical-based large-scale drug products. [89]

Unique QA issues associated with personalised medicine include: the use of variable biological raw materials from donors; complex biological manufacturing processes; very small batch sizes, sometimes down to one dose per patient; strict timelines driven by patient health status; and extremely serious consequences for failed products in severely ill patient groups. New QA systems combining adaptive process control with sophisticated analysis are being developed specifically for these types of drugs. [90]

### VIII. CONCLUSION

Quality assurance in the pharmaceutical field is currently faced with an inflection point. Never before has the regulatory and scientific foundation of quality assurance been so strong, but never before have the difficulties — such as regulatory complexity, data integrity problems, fragile supply chains, and rapidly changing technology — been so challenging either. [50, 55, 60, 62]

However, decades of experience, both on the part of regulatory bodies and within industry, have taught much about the proper ways to ensure quality and safety, from initial inspections to complex, science-based risk management strategies. Quality assurance systems developed through ICH harmonization efforts have provided pharmaceutical companies with powerful tools for designing quality into drug products early on in development. [9, 12, 19, 21]

Industry 4.0 innovations such as artificial intelligence, machine learning, Internet of Things,

blockchain technology, continuous manufacturing, and real-time release testing provide the pharmaceutical QA field with an unparalleled suite of tools that facilitate the shift from traditional, compliance-based quality management to a new paradigm of predictive and patient-oriented quality assurance. The implementation of these innovative technologies entails both technical challenges and regulatory changes, but most importantly, a cultural change towards quality rather than mere compliance is crucial. [62, 65, 68, 79, 82]

The QA specialists of tomorrow will have to possess a blend of expertise in science, data skills, digital proficiency, and regulatory awareness that current training curriculums are just beginning to address. There is an important role for educational institutes and professional organizations to play in shaping the future workforce needed for pharmaceutical quality assurance. [82, 87]

#### CONFLICT OF INTEREST

The authors declare that there are no competing interests regarding the publication of this manuscript. There were no sources of funding for this review from any commercial organization.

#### REFERENCES

- [1]. World Health Organization. WHO Expert Committee on Specifications for Pharmaceutical Preparations: Forty-Eighth Report. WHO Technical Report Series No. 986. Geneva: WHO Press; 2014.
- [2]. Juran JM, Godfrey AB. Juran's Quality Handbook. 5th ed. New York: McGraw-Hill; 1999.
- [3]. ICH Harmonised Tripartite Guideline. Pharmaceutical Quality System Q10. International Council for Harmonisation; 2008.
- [4]. Swann JP. History of the FDA. In: United States Food and Drug Administration. Rockville (MD): FDA; 2012.
- [5]. Jackson JK. The Elixir Sulfanilamide Tragedy and the 1938 Federal Food, Drug, and Cosmetic Act. *Pharm Hist*. 2016;58(3):91-109.
- [6]. Kim JH, Scialli AR. Thalidomide: the tragedy of birth defects and the effective treatment of disease. *Toxicol Sci*. 2011;122(1):1-6.
- [7]. Central Drugs Standard Control Organisation. Drugs and Cosmetics Act 1940 and Rules 1945. New Delhi:

- [8]. Ministry of Health and Family Welfare, Government of India; 2016.
- [9]. Eudralex. The Rules Governing Medicinal Products in the European Union. Volume 4: Good Manufacturing Practice for Medicinal Products. Luxembourg: Publications Office of the European Union; 2021.
- [10]. Yu LX, Amidon G, Khan MA, et al. Understanding pharmaceutical quality by design. *AAPS J.* 2014;16(4):771-783.
- [11]. Branning G, Vater M. Pharmaceutical packaging: meeting the needs of an evolving industry. *Pharm Technol.* 2016;40(11):34-40.
- [12]. Oakland JS. *Statistical Process Control*. 6th ed. Oxford: Butterworth-Heinemann; 2008.
- [13]. ICH Harmonised Tripartite Guideline. Pharmaceutical Development Q8(R2). International Council for Harmonisation; 2009.
- [14]. Bhalani DV, Nutan B, Kumar A, Singh Chandel AK. Bioavailability enhancement techniques for poorly aqueous soluble drugs and therapeutics. *Biomedicines.* 2022;10(9):2055.
- [15]. US Food and Drug Administration. Code of Federal Regulations Title 21, Part 211: Current Good Manufacturing Practice for Finished Pharmaceuticals. Washington (DC): US Government Publishing Office; 2023.
- [16]. World Health Organization. WHO Technical Report Series No. 1044: Supplement 7: WHO good manufacturing practices for pharmaceutical products. Geneva: WHO Press; 2022.
- [17]. Immel BK. A brief history of the GMPs for pharmaceuticals. *Pharm Technol.* 2001;25(7):44-52.
- [18]. US Food and Drug Administration. *Guidance for Industry: Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production*. Rockville (MD): FDA CDER; 2006.
- [19]. International Council for Harmonisation. About ICH [Internet]. 2024 [cited 2024 Nov]. Available from: <https://www.ich.org/page/about-ich>
- [20]. ICH Harmonised Tripartite Guideline. Quality Risk Management Q9(R1). International Council for Harmonisation; 2023.
- [21]. Stamatis DH. *Failure Mode and Effect Analysis: FMEA from Theory to Execution*. 2nd ed. Milwaukee: ASQ Quality Press; 2003.
- [22]. ICH Harmonised Tripartite Guideline. Pharmaceutical Quality System Q10. International Council for Harmonisation; 2008.
- [23]. Weinberg S. Creating a consistent SOP system for pharmaceutical manufacturing. *J GXP Compliance.* 2016;20(3):62-70.
- [24]. ICH Harmonised Tripartite Guideline. Validation of Analytical Procedures Q2(R1). International Council for Harmonisation; 2005.
- [25]. US Food and Drug Administration. *Process Validation: General Principles and Practices. Guidance for Industry*. Rockville (MD): FDA CDER; 2011.
- [26]. Prashant P, Anand T, Suresh M. Quality assurance vs quality control — a paradigm shift. *Int J Pharm Qual Assur.* 2018;9(3):356-363.
- [27]. Nussenbaum B. Pharmaceutical Quality System (ICH Q10) — concept paper and guideline overview. *Pharm Eng.* 2008;28(6):8-15.
- [28]. International Organisation for Standardisation. *ISO 9001:2015 Quality management systems — Requirements*. Geneva: ISO; 2015.
- [29]. Akers MJ, Agalloco JP. Aseptic and Terminal Sterilization. In: *Pharmaceutical Dosage Forms: Parenteral Medications*. 3rd ed. New York: Informa Healthcare; 2010. p. 29-67.
- [30]. Mollah AH. Risk management applications in pharmaceutical and biopharmaceutical manufacturing. Hoboken (NJ): Wiley; 2013.
- [31]. Bishara RH. Implementing quality risk management in pharmaceutical manufacturing. *Pharm Technol.* 2009;33(3):62-74.
- [32]. Latino RJ. Optimizing FMEA and root cause analysis in pharmaceutical investigations. *Biopharm Int.* 2015;28(3):24-31.
- [33]. US Food and Drug Administration. *Guidance for Industry: Quality Systems Approach to Pharmaceutical cGMP Regulations*. Rockville (MD): FDA CDER; 2006.
- [34]. ICH Harmonised Tripartite Guideline. Quality Risk Management Q9(R1).

- International Council for Harmonisation; 2023.
- [34]. Haimes YY. Risk Modeling, Assessment, and Management. 3rd ed. Hoboken (NJ): Wiley-Interscience; 2009.
- [35]. Parenteral Drug Association. Technical Report No. 54: Implementation of Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations. Bethesda (MD): PDA; 2012.
- [36]. Williams J. Quality Audits for ISO 9001:2015. 3rd ed. Milwaukee: ASQ Quality Press; 2016.
- [37]. Lam CM, Tan SH. GMP audit program: designing an effective self-inspection system. *J Pharm Sci Res.* 2016;8(4):260-265.
- [38]. EMA/INS/GMP/735037/2012. Good manufacturing practice questions and answers. Amsterdam: European Medicines Agency; 2023.
- [39]. Woodcock J. The concept of pharmaceutical quality. *Am Pharm Rev.* 2004;7(6):1-3.
- [40]. Rathore AS, Winkle H. Quality by design for biopharmaceuticals. *Nat Biotechnol.* 2009;27(1):26-34.
- [41]. ICH Harmonised Tripartite Guideline. Pharmaceutical Development Q8(R2). International Council for Harmonisation; 2009.
- [42]. Lawrence XY. Pharmaceutical quality by design: product and process development, understanding, and control. *Pharm Res.* 2008;25(4):781-791.
- [43]. Mandenius CF, Brundin A. Bioprocess optimization using design-of-experiments methodology. *BiotechnolProg.* 2008;24(6):1191-1203.
- [44]. Bhatt NM, Chavda VP, Bhatt LK. A comprehensive review on critical quality attributes and quality by design approach for solid dosage forms. *Ind J Pharm Sci.* 2021;83(4):598-614.
- [45]. Ferreira SL, Bruns RE, Ferreira HS, et al. Box-Behnken design: an alternative for the optimization of analytical methods. *Anal Chim Acta.* 2007;597(2):179-186.
- [46]. Peterson JJ. A Bayesian approach to the ICH Q8 definition of the design space. *J Biopharm Stat.* 2008;18(5):959-975.
- [47]. Montgomery DC. Design and Analysis of Experiments. 9th ed. Hoboken (NJ): Wiley; 2017.
- [48]. Lionberger RA, Lee SL, Lee L, Raw A, Lawrence XY. Quality by design: concepts for ANDAs. *AAPS J.* 2008;10(2):268-276.
- [49]. Rathore AS, Bhambure R, Ghare V. Process analytical technology (PAT) for biopharmaceutical products. *Anal Bioanal Chem.* 2010;398(1):137-154.
- [50]. Sinha VR, Kumar A. Regulatory harmonization for pharmaceutical products: opportunities and challenges. *J Drug Deliv Sci Technol.* 2014;24(4):369-375.
- [51]. PICS. PICS GMP Guide for Medicinal Products PE 009-16. Geneva: Pharmaceutical Inspection Co-operation Scheme; 2022.
- [52]. US Food and Drug Administration. Pharmaceutical Quality for the 21st Century: A Risk-Based Approach Progress Report. Rockville (MD): FDA; 2007.
- [53]. Vesper JL. The Cost of Poor Quality in Pharmaceutical Manufacturing. *Pharm Technol.* 2012;36(3):56-61.
- [54]. Schnieders J. Quality cost research: a review of the literature and research agenda. *Int J QualReliabManag.* 2006;23(6):611-641.
- [55]. US Food and Drug Administration. Data Integrity and Compliance with Drug cGMP: Questions and Answers. Guidance for Industry. Rockville (MD): FDA CDER; 2018.
- [56]. MHRA. GMP Data Integrity Definitions and Guidance for Industry: Revision 1. London: Medicines and Healthcare Products Regulatory Agency; 2021.
- [57]. Jones D, Bhatt N. Data integrity in the pharmaceutical environment. *Pharm Technol.* 2018;42(6):48-55.
- [58]. Handa T, Sharma A, Bhatt N. Human error in pharmaceutical manufacturing: classification and prevention. *J Pharm Res.* 2020;19(4):301-309.
- [59]. Reason J. Human Error. Cambridge: Cambridge University Press; 1990.
- [60]. Gottlieb S, McClellan M. Ensuring essential medicines are available and affordable. *JAMA.* 2019;322(3):213-214.
- [61]. Gokarn S, Shah NB. Supply chain risk management in the pharmaceutical industry. In: Rao S, editor. Supply Chain Management. London: IntechOpen; 2020. p. 1-28.

- [62]. Schwab K. The Fourth Industrial Revolution. New York: Crown Business; 2016.
- [63]. Herwig C, Garcia-Aponte OF, Golabgir A, Rathore AS. Knowledge management in the QbD paradigm: manufacturing of biotech therapeutics. *Trends Biotechnol.* 2015;33(7):381-387.
- [64]. Arden NS, Fisher AC, Tyner K, et al. Industry 4.0 for pharmaceutical manufacturing: preparing for the smart factories of the future. *Int J Pharm.* 2021;602:120554.
- [65]. LeCun Y, Bengio Y, Hinton G. Deep learning. *Nature.* 2015;521(7553):436-444.
- [66]. Kiranyaz S, Avci O, Abdeljaber O, et al. 1D convolutional neural networks and applications: a survey. *MechSyst Signal Process.* 2021;151:107398.
- [67]. Mehdizadeh H, Lauri S, Destro M, et al. Pharmaceutical blending monitoring using in-line Raman spectroscopy and machine learning. *Int J Pharm.* 2019;572:118739.
- [68]. Lee I, Lee K. The Internet of Things (IoT): applications, investments, and challenges for enterprises. *Bus Horiz.* 2015;58(4):431-440.
- [69]. Alwahishi Y, Yamin M, Basurra S, Alassafi M. Internet of things (IoT) for pharmaceutical cold chain monitoring: a systematic literature review. *Sensors.* 2023;23(9):4357.
- [70]. Tao F, Zhang H, Liu A, Nee AY. Digital twin in industry: state-of-the-art. *IEEE Trans Ind Inform.* 2019;15(4):2405-2415.
- [71]. Plumb K. Continuous processing in the pharmaceutical industry: changing the mind set. *Chem Eng Res Des.* 2005;83(6):730-738.
- [72]. Hogan J, Watling L, Hallet J, et al. Robotic systems in pharmaceutical manufacturing. *J Pharm Sci.* 2020;109(6):1823-1834.
- [73]. US Food and Drug Administration. Guidance for Industry: PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance. Rockville (MD): FDA CDER; 2004.
- [74]. US Food and Drug Administration. Code of Federal Regulations Title 21, Part 11: Electronic Records; Electronic Signatures. Washington (DC): US Government Publishing Office; 2023.
- [75]. MHRA. MHRA Guidance on GxP Data Integrity. London: Medicines and Healthcare Products Regulatory Agency; 2018.
- [76]. Nakamoto S. Bitcoin: A Peer-to-Peer Electronic Cash System [Internet]. 2008. Available from: <https://bitcoin.org/bitcoin.pdf>
- [77]. Bocek T, Rodrigues BB, Strasser T, Stiller B. Blockchains everywhere — a use-case of blockchains in the pharma supply-chain. In: Proceedings of the IFIP/IEEE Symposium on Integrated Network Management; 2017 May; Lisbon, Portugal. p. 772-777.
- [78]. US Food and Drug Administration. Drug Supply Chain Security Act (DSCSA). Rockville (MD): FDA; 2023.
- [79]. Mori M, Nkemngu OJ, Matjeka J, et al. Continuous manufacturing of pharmaceuticals: a transition from batch to flow. *Drug Discov Today.* 2021;26(10):2446-2456.
- [80]. ICH Harmonised Tripartite Guideline. Pharmaceutical Development Q8(R2), Annex to Q8: Examples of Application of ICH Q8 to Pharmaceutical Development. International Council for Harmonisation; 2012.
- [81]. Lee SL, O'Connor TF, Yang X, et al. Modernizing pharmaceutical manufacturing: from batch to continuous production. *J Pharm Innov.* 2015;10(3):191-199.
- [82]. Friedli T, Basu P, Bellm D, Werani J, editors. Leading Pharmaceutical Operational Excellence: Outstanding Practices and Cases. New York: Springer; 2013.
- [83]. Glassey J, Montague G, Ward AC, Kara B. Enhanced supervision of mammalian cell culture through multivariate analysis of on-line data. *BiotechnolProg.* 2000;16(5):912-917.
- [84]. Grieves M, Vickers J. Digital twin: mitigating unpredictable, undesirable emergent behavior in complex systems. In: Kahlen FJ, Flumerfelt S, Alves A, editors. Transdisciplinary Perspectives on Complex Systems. Cham: Springer; 2017. p. 85-113.
- [85]. US Food and Drug Administration. Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical



- Device (SaMD) Action Plan. Rockville (MD): FDA; 2021.
- [86]. EMA. Workplan 2020-2025: Fostering a strong European regulatory system. Amsterdam: European Medicines Agency; 2021.
- [87]. ICH. ICH Vision 2025. Geneva: International Council for Harmonisation; 2021.
- [88]. FDA/EMA. The European Union and United States Mutual Recognition Agreement — GMP Inspections. Brussels: European Commission; 2019.
- [89]. Iglesias-Lopez C, Agust'i A, Obach M, Vallano A. Regulatory framework for advanced therapy medicinal products in Europe and United States. *Front Pharmacol.* 2019;10:921.
- [90]. European Medicines Agency. Guideline on human cell-based medicinal products. EMA/CHMP/410869/2008. Amsterdam: EMA; 2008.