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Quality Assurance in AI-Enabled Manufacturing: Governance, Validation, and GxP Controls for Cell and Gene Therapy

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Abstract: AI technologies are considerably changing biopharmaceutical manufacturing and will continue to influence the operational environment for CGT manufacturing. With the integration of AI-enabled systems in deviation trending, batch record review, environmental monitoring, and automated decision support, QA will have an important role in governing, validating, and monitoring the systems with which they work. The production of cell and gene therapy (CGT) presents unique challenges affecting the deployment of artificial intelligence (AI) methods due to high biological variability, limited shelf life of products, and manual handling in an aseptic environment. Contributing to the growing body of knowledge in this space, this article reviews recent advancements in AI governance in GxP-regulated environments and proposes a framework for Quality Assurance leaders to adopt AI methods in GxP-regulated environments. Benefits such as reduced human error, expedited batch release, and process consistency will be identified, alongside challenges including algorithmic bias, model drift, explainability, and regulatory uncertainties. A realistic phased approach for implementation will be proposed to enable industry stakeholders to scale their digital capabilities. Central to the industry transformation are the imperatives to ensure product quality, patients' safety, and regulatory compliance throughout the transformation process.

Keywords:. Artificial Intelligence In Biomanufacturing, Cell And Gene Therapy Quality Assurance, GXP Validation Frameworks, Machine Learning Governance, Pharmaceutical Data Integrity.

INTRODUCTION

The complexity, variability, and patient-specific nature of the manufacturing processes for CGTs generate large amounts of data. Quality oversight for CGTs using customary methods based on manual review, pre-defined validation protocols, and retrospective analysis proves increasingly hard given the speed and complexity of CGT manufacturing processes. In a discussion paper, the FDA noted that AI and machine learning technologies can be considered unique in the context of drug manufacturing because they may improve production and quality operations and enable real-time decision making in ways that would not be feasible with customary computer technology (U.S. Food and Drug Administration, 2023). The agency also noted that AI may have an important impact on drug manufacturing, including the potential to identify patterns and relationships to manufacturing data that may not be readily clear with customary data analysis systems. However, it is still unclear how AI and machine learning technologies will be validated and what the FDA may require.

The potential use of AI in regulating medicinal products, from development, through manufacturing, and post-market surveillance, is also recognized by the EMA. In its reflection paper, the European Medicines Agency describes AI systems (particularly those that use machine learning algorithms) as systems that differ from customary software in that they are able to learn from data and adapt their behavior accordingly. Due to this flexibility, opportunities for greater process control emerge. However, this is at odds with the customary validation framework, which assumes a deterministic and time-invariant system. As noted, many CGT manufacturers have plans to deploy AI-enabled automation technologies in the near future, creating a need for strong, structured QA frameworks.

AI Adoption in the Context of Cell and Gene Therapy Manufacturing

However, the very variability intrinsic to biological product manufacturing processes and the fact that donor-derived starting material introduces biological variation that is difficult or impossible to assess with customary PC approaches, means the cell and gene therapy landscape presents a unique challenge for the implementation of AI. In the recent FDA report on AI applications in drug manufacturing, AI and machine learning (ML) are particularly applicable to analyze high-dimensional nonlinear relationships of biological manufacturing, when a collection of interdependent variables controls product quality in ways that are too complex for humans to detect simultaneously (U.S. Food and Drug Administration, 2023). Machine learning tools can analyze high-dimensional data from electronic batch records, environmental monitoring

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systems, and in-process tests and identify small signals that may predict a change in product quality before a batch failure or nonconformance occurs.

The application of AI to biopharmaceutical manufacturing can extend beyond customary data analytics to include decision support systems that compile data from multiple sources to support process decision-making. Research has shown mthat achine learning algorithms can classify manufacturing process deviations, which can ease earlier identification of systemic problems and more targeted corrective action (Rathore, A. S., *et al.*, 2023). Classification systems use previously detected deviations to build models of the specific failure mode, equipment malfunction, equipment deviation, or procedure deviation for which they were trained. Artificial Intelligence-enabled electronic batch record systems are able to learn and automatically identify missing records, out-of-sequence steps, and parameter excursions to reduce the amount of quality assurance review needed to maintain or improve finding sensitivity.

With a shift towards closed and automated manufacturing systems for CGT production, AI control algorithms may increasingly be part of the manufacturing machinery and supervisory control systems. Therefore, quality assurance aspects may include some or all of the following items: confirming algorithm logic, inspecting data quality throughout the data pipeline between interconnected systems, and monitoring algorithm performance over time as systems are in use. To attain these capabilities, the EMA's position paper on quality assurance of AI systems indicates a need for quality assurance to gain expertise in data science, algorithm assessment, and digital system lifecycle management.

Table 1: AI Applications in Cell and Gene Therapy Manufacturing (Rathore, A. S., *et al.*, 2023; International Society for Pharmaceutical Engineering. 2022)

AI Application Domain	Primary Function	Quality Impact	Implementation Complexity
Deviation Management	Automated classification and trending of quality events	Early identification of systemic issues and failure patterns	Moderate
Electronic Batch Records	Anomaly detection, missing step identification, completeness verification	Reduced manual review burden while maintaining detection sensitivity	Low to Moderate
Environmental Monitoring	Predictive analytics for excursion detection and trending	Proactive intervention before quality impact occurs	Low
Predictive Maintenance	Equipment performance monitoring and failure prediction	Prevention of unplanned downtime and quality events	Moderate to High
Cell Morphology Assessment	Automated image analysis for quality control testing	Reduced subjectivity and operator-dependent variability	High
Process Control	Real-time parameter optimization and adjustment	Enhanced process consistency and reduced variability	High

Benefits and Risks of AI-Enabled Quality Assurance

Cell and gene therapy manufacturers could realize meaningful benefits from using AI in quality assurance to reduce the greatest cause of manufacturing deviation, which is operator-dependent variability. The ISPE GAMP 5 Second Edition guidance suggests computer systems (including systems containing artificial intelligence functionality) have the potential to improve manufacturing quality as they can automate repetitive tasks susceptible to human error, provide consistent decision support through evaluation of multiple data sets, and provide real-time monitoring that flags potential quality issues earlier than a periodic review (International Society for Pharmaceutical Engineering. 2022). AI can achieve process consistency by applying the same rules to all production steps regardless of shift, operator, location, or facility. AI-enabled systems can accelerate batch release by automating review and approval workflows that would otherwise be manual, sequential, and require important human resources within multiple quality assurance and control functions.

Industrial manufacturing applications of Artificial Intelligence processes have been shown to

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considerably increase process efficiency and product quality, through reduced process product variation and optimized manufacturing settings using process predictive and machine learning models (Hort, S., *et al.*, 2023). Many of these applications use predictive models based on real-time sensor data and historical data, as well as contextual information about the process, to predict equipment failures and make recommendations for corrective actions. Another key reason to use AI is to improve data integrity. AI provides full data audit trails and is less prone to transcription errors and omissions than human record-keeping.

With many of the advantages, there are also risks that quality assurance organizations need to reduce. The NIST AI Risk Management Framework describes many of the risks that may be anticipated from the use of AI systems, such as algorithmic bias arising from insufficient coverage in the training data set of the circumstances that the AI system will face in production (National Institute of Standards and Technology. 2023). An additional form of bias is model drift. This occurs when the statistical properties of the production environment change over time, to the extent that the patterns learned by the AI model are no longer representative of the current environment. This prevents the AI model from being general enough to detect and appropriately respond to outlier conditions.

In regulated domains, where quality decisions are made throughout the lifecycle and have to be accounted for in regulatory inspections and audit trials, a major concern for algorithmic transparency and explainability is that in many AI methods, for example deep learning neural networks, a traceable human-understandable reasoning process leading to a particular output cannot be shown (IEEE guidelines on ethically aligned design for autonomous and clever systems, 2019). This lack of transparency can make it difficult for QA staff to understand and explain to regulatory inspectors the reasons behind the decisions made by AI. There can also be resistance to using AI recommendations amongst manufacturing operators and members of quality management, especially if they contradict previous knowledge.

Table 2: Benefits and Risks of AI-Enabled Quality Assurance (Hort, S., *et al.*, 2023; BioPhorum. 2025)

Category	Benefits	Risks
Quality Performance	Reduced operator-dependent deviations; Enhanced detection of subtle process drifts; Consistent decision criteria application	Algorithmic bias leading to missed atypical failures; Model drift causing performance degradation; False negative rates in novel scenarios
Operational Efficiency	Accelerated batch release timelines; Automated review workflows; Reduced manual documentation burden	System downtime impacting operations; Over-reliance on AI recommendations; Integration complexity with legacy systems
Data Integrity	Comprehensive automated audit trails; Elimination of transcription errors; Cross-validation across data sources	Dependence on incomplete or inconsistent datasets; Systematic measurement biases; Data quality propagation issues
Regulatory Compliance	Enhanced traceability and documentation; Proactive quality issue detection; Consistent application of standards	Unclear validation requirements; Explainability challenges during inspections; Change control complexity for adaptive models
Organizational Impact	Improved process understanding; Knowledge capture in models; Standardization across facilities	Cultural resistance and trust issues; Digital literacy gaps; Workforce training requirements

A Roadmap for QA Integration of AI in CGT Manufacturing

This phased approach also provides QA organizations space to build their digital capabilities in increments, while keeping the GxP compliance aspect of the AI transformation process under consideration. Establishing governance for AI integration and clarifying roles and responsibilities, along with building digital literacy across the organization, should be key areas of focus for the first phase of the AI roadmap. The ISPE GAMP 5 guidance states that a quality risk management approach that is proportionate to the intended use, the computerized system function complexity, the computerized system data and processes criticality, and the corporate capability and maturity regarding computerized system implementation is

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an essential part of a successful implementation of a complex computerized system. The digital maturity of an organization can be evaluated across several dimensions, such as data infrastructure, process understanding, automation, and organizational culture.

Cross-functional governance committees play an important role in AI implementation and include quality assurance, information technology, manufacturing operations, regulatory affairs, and data science. Prioritizing initial AI applications using a risk-based approach analyzes applications that provide high added value and manageable risk levels, considering an organization's experience and maturity levels with AI. Applications such as automated deviation categorization, environmental monitoring trend analysis, and batch record completeness checking represent lower-risk use cases that can help build organizational capabilities for AI validation, integration, and governance.

Due to the particularities of machine learning systems, AI applications cannot be qualified in the customary manner of installation qualification, operational qualification, and performance qualification. Validation of AI systems in regulated pharmaceutical settings requires consideration of several interacting sub-systems as articulated in the BioPhorum position paper on AI systems in regulated settings. These include the quality and representativeness of the data used to train the model, the choice/selection of the algorithm and its tuning parameters, the ability of the model to generalize to different use conditions, and the interaction of the AI system with existing validated systems and business processes (BioPhorum. 2025). The validation of the training data is especially important for these systems, as their performance cannot exceed the quality of their training data.

Evaluation of the performance of AI models should be statistically powered across the full operational design space to show reliable and strong operations in the potential domain of use. Validation protocols should set acceptance criteria for performance metrics such as classification accuracy, true and false positive and false negative rates, and processing times for real-time applications. Monitoring procedures designed to identify model performance drift should be in place and should include criteria defining when to revalidate the model, such as an unacceptable level of performance drift and important changes in the manufacturing process, equipment, or materials.

Purposeful use of AI in GxP should consider appropriate data flow, validating interfaces, and maintaining adequate human oversight of AI activity. Organizations should also have escalation protocols for situations where AI recommendations differ from human actions, and have a process for investigating, documenting, and resolving such situations in place. Human-in-the-loop oversight models should use a human-in-the-loop model proportionate to the risk class of the AI application, with mandatory human oversight for high-risk decisions and the option of self-deployment with statistical monitoring of lower-risk applications.

Table 3: Implementation Best Practices for AI in Regulated Manufacturing (National Institute of Standards and Technology. 2023; Institute of Electrical and Electronics Engineers. 2019)

Phase	Key Activities	Critical Success Factors	Risk Level
Phase 1: Foundational Readiness	Governance structure establishment; Digital maturity assessment; Cross-functional committee formation; SOP development; Training program implementation	Executive sponsorship; Clear accountability definition; Adequate resource allocation	Low
Phase 2: Risk-Based Use Case Selection	Quality risk assessments; Use case prioritization; Pilot project selection; Feasibility evaluation; Business case development	Appropriate risk categorization; Stakeholder alignment; Realistic scope definition	Low to Moderate
Phase 3: Validation and Lifecycle Management	Training data validation; Model performance testing; Validation protocol execution; Continuous monitoring implementation; Version control establishment	Robust validation frameworks; Adequate test coverage; Clear acceptance criteria	Moderate to High
Phase 4: GxP	Interface validation; Human oversight	Seamless system	Moderate

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Workflow Integration	definition; Escalation pathway establishment; Audit trail configuration; System interoperability testing	integration; Effective change management; User acceptance	to High
Phase 5: Maturity and Continuous Improvement	Performance metric tracking; Feedback loop implementation; Expansion to higher-risk applications; Center of excellence development; Benchmarking activities	Sustained improvement culture; Ongoing investment; Regulatory intelligence	Variable

IMPLEMENTATION CONSIDERATIONS AND BEST PRACTICES

Governance of AI in regulated manufacturing should achieve a balance between ensuring that the deployed solutions are adequately controlled and allowing sufficient agility in the system to allow for continual iterative development of the solution, as AI capabilities and organizational capabilities evolve. ISPE's guidelines on data integrity by design advocate a risk-based and proportionate governance strategy, recognizing that quality risks posed by AI applications may vary (International Society for Pharmaceutical Engineering. 2020). Decision rights, roles, and accountabilities should be set for all levels of governance. Operational teams would typically be responsible for low-risk AI applications, with higher levels of governance responsible for applications with high-quality risks, those using novel technology, or those requiring major operational change.

In addition to general risk-based quality management principles for software validation, validation principles for AI systems also need to address a wider range of topics. Studies have indicated that a complete set of validation principles for AI applications in industrial and regulated settings needs to cover data quality assessment, algorithm selection justification, model performance characterization, system integration validation, and post-market operational validation. More specifically, cover the representativeness and lack of systemic bias of training datasets, the rationale for selecting certain algorithms over others, the accuracy and robustness of the model in relevant operational situations, etc (Hort, S., *et al.*, 2023).

Data integrity is important to AI systems as they need quality data to be used for training and decision-making during operation. According to the ISPE data integrity by design guidance, data governance for AI systems should address the full data life cycle from data generation, processing, storage, analysis, risk assessment, through to data archival or destruction (International Society for Pharmaceutical Engineering. 2020). These controls include that data must be attributable, legible, permanently recorded, contemporaneously recorded, original or a true copy, accurate, and accessible for as long as the data must be retained.

Change management, including training, should be considered a critical success factor that is too often overlooked in the planning of AI implementation. A review of manufacturing digitalization projects likewise found technology implementation and organizational change (culture, competencies, and ways of working) as necessary success factors (Gribbin, M., *et al.*,). Training should be role-based: Quality managers need planned knowledge of AI validation and governance, quality specialists need practical knowledge of validating AI output processes and how to escalate when problems occur, and manufacturing operators need practical experience of using AI tooling in their operations.

Table 4: Implementation Best Practices for AI in Regulated Manufacturing (International Society for Pharmaceutical Engineering. 2020; Gribbin, M., *et al.*,)

Domain	Key Considerations	Best Practices	Common Pitfalls to Avoid
Governance	Tiered decision-making; Change control procedures; Risk-based oversight; Incident management protocols	Establish clear authority levels; Define AI-specific SOPs; Implement risk registers; Conduct quarterly governance reviews	Overly bureaucratic processes; Unclear accountability; Inadequate cross-functional representation
Validation	Risk-based testing; Performance criteria;	Employ statistically powered test scenarios; Include boundary and	Insufficient test coverage; Inappropriate acceptance

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	Revalidation triggers; Documentation requirements	stress conditions; Monitor performance continuously; Maintain comprehensive validation records	criteria; Neglecting edge cases
Data Integrity	Training data quality; Data lifecycle controls; Audit trail completeness; Lineage documentation	Implement data quality assessments; Ensure ALCOA+ compliance; Maintain data provenance records; Conduct regular integrity audits	Poor training data curation; Inadequate data governance; Missing lineage documentation
Explainability	Model transparency; Decision justification; Regulatory defensibility; Visualization tools	Select interpretable algorithms when possible; Implement SHAP or LIME techniques; Provide confidence scores; Develop decision reconstruction capabilities	Using black-box models unnecessarily; Insufficient documentation; Lack of user-friendly explanations
Change Management	Training programs; Stakeholder engagement; Cultural transformation; Communication strategies	Deploy role-based curricula; Engage early adopters; Address resistance proactively; Celebrate successes visibly	Inadequate training investment; Poor communication; Ignoring cultural concerns

CONCLUSION

Against this background, AI-enabled manufacturing would be a meaningful opportunity for the cell and gene therapy sector to improve product quality and time-to-patient, cost, and consistency in compliance with the Good Practice standards. Achieving this will depend on the establishment of a realistic quality assurance framework, based on risk-based principles, which also provides the right framework for the effective governance, validation, and lifecycle monitoring of AI systems. This roadmap gives quality assurance leaders strategies to progressively develop governance models, validate machine learning models, adopt AI in regulated processes, and mature digital quality practices to balance pioneering digital applications with regulatory and patient safety considerations. To enable the adoption of AI in CGT manufacturing, quality assurance organizations should shift from customary quality assurance practices, including retrospective review and fixed validation, to a digital quality stewardship model that incorporates proactive risk management with real-time system monitoring and adaptive quality strategies that evolve in line with technology development. The rapid pace of development of artificial intelligence technologies is matched by a rapidly expanding demand for guidance from international regulatory bodies in the use of AI systems in pharmaceutical manufacturing. Progressive guidance is being developed by the FDA, EMA, and other regulatory agencies to set standards for the validation, monitoring, and management of the lifecycle of AI in the pharmaceutical domain. Quality assurance leaders who begin their journey toward digital maturity today by implementing foundational governance, pilot project(s), and evolving capabilities in a purposeful fashion will be best prepared for the future regulatory landscape as the industry gains experience with best practices across different manufacturing environments and therapeutic areas.

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