Automated Visual Inspection and Batch Release Intelligence: AI-Driven Quality Control Systems for U.S. Pharmaceutical Manufacturing Revitalisation

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1. Introduction to AI-Driven Quality Control Systems in Medicine Manufacturing, The pharmaceutical industry is a vital cornerstone of modern healthcare and, consequently, national wellbeing and prosperity. Despite its importance, the pharmaceutical industry is under threat from off-shore competition and domestic business closures. In particular, the everyday business of U.S. medicine manufacturers is, in part, based upon the quality control of the underlying materials/final products. Up-to-date process and biopharmaceutical medicine quality assurance systems are paramount. To this end, intelligent quality control systems are emerging as a key technology for the future. Prototypical implementations of AI-driven quality control systems based upon contemporary Internet-of-Things and data-centric concepts and infrastructure for modular manufacturing are sketched [1]. Recent prototypical AI-driven systems for pharmaceutical medicines, as well as developments in other industries with applicability for pharmaceuticals are considered.

The dominant activity of pharmaceutical manufacturers is process quality assurance, which is a volume or state filtration of the manufacturing into quality passing and failing products. The manufacturing process and the batch series of underlying materials and products are longitudinally monitored and a quality state is inferred from this. This implementation is termed state quality control. This desired smart predictive and digital quality control approach is currently prototypically applied in paper manufacturing and (bio)manufacturing [2]. The applicability of the above perturbation methods to the analogue inclusion of the pharmaceutical drug final products and underlying materials is explored.

1.1. Overview of the Current State of Quality Control in U.S. Medicine Manufacturing

The advent of Artificial Intelligence (AI) approaches and quality by design development concepts, such as continuous manufacturing, represent significant opportunities for

innovation application by the pharmaceutical industry's quality control, quality assurance, and analytical development disciplines [1]. Quality-by-design for development incorporates design input into the development process for drug substance and drug product. Continuous manufacturing plays a role in generating training data during drug product development, with applications like continuous monitoring of raw materials using near-infrared spectroscopy. Watson Pharma LLC has been in successful commercial operation since 2021, producing tablets through a continuous process.

Continuous manufacturing technologies for drug substance production and purification are also emerging. In-situ monitoring technologies for reaction stage parameters and multi-attribute monitoring of in-process controls (IPC) have potential applications in real-time release testing (RTRT) [3]. In-situ monitoring development typically employs a single analytical technique, while multi-attribute development raises challenges surrounding data interpretation and cross-platform comparisons. While progress has been made in AI applications, there is still a finite need for knowledge infusion, continued innovation, and development.

2. Fundamentals of Artificial Intelligence in Quality Control

Artificial intelligence (AI) encompasses various fields, learning means, and algorithms designed to analyze, classify, and create data patterns. These include machine learning (ML), deep learning (DL), or using neural networks and other approaches. AI addresses many areas, including predicting stock and agricultural harvests, and biomedical data processing. Machine vision is an AI application utilized to inspect and analyze images collected by cameras. In the pharmaceutical industry, machine vision is employed for in-process monitoring and batch recycling following optical imaging analysis, identifying and sorting defective units, counting blister cards, or controlling devices in packaging machines [1].

Quality control (QC) and quality assurance (QA) are essential components of pharmaceutical production and distribution. They refer to all activities associated with ensuring and maintaining the quality of pharmaceuticals and biopharmaceuticals throughout the entire supply chain. Pharmaceuticals must possess the appropriate chemical composition and structure to ensure efficacy and safety. These data are usually analyzed, resulting in batches being released for distribution only if these parameters

comply with regulatory requirements. As states of nature cannot be observed directly, it is crucial to investigate the quality of the measured entities—pharmaceuticals—by analyzing surrogate parameters, either individually or simultaneously [2].

2.1. Machine Learning and Deep Learning Algorithms

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Machine learning (ML) techniques have emerged as a viable solution to move towards this direction by using existing recorded data to successfully predict a given process or product behavior without requiring extensive and complicated mathematical models or computer code that describe its operation. On the other hand, complex nonlinear relationships can be identified in the case of deep learning (DL) neural networks [1] , using thousands of inputs and hidden layers, that make it possible to handle highly complicated processes or products. As a result, today pharmaceutical, food, and cosmetics industries are increasingly starting to use ML solutions, working towards turning fully data-driven smart processes with an unprecedented degree of control.

3. Integration of AI in Medicine Manufacturing

AI-driven quality control systems in medicine manufacturing are designed to be retrofitted onto previously installed process control equipment, such as tablets or liquid dosages. The AI systems use only the video and analog signals already monitored from these devices, viewing the same content as the operators. This view includes ambient light changes, bottle size changes, sporadic blocked views, and blurred views. The AI systems can interpret high susceptibility to missed defects, viewing both the results and the process itself. Hence, AI is trained to inspect by imitation and learn how to inspect defects in the process. A convolutional neural network (CNN)-based architecture 'InspecNet' is presented to learn this.

InspecNet learns to detect FDA-critical defects by observing the normal manufacturing process without the need for labeled defect data. It captures the spatiotemporal features of defect-aware views by focusing on the changes at different manufacturing speeds and understanding them with multi-scale representations. The visual quality of tablet drugs is negatively impacted by defects, such as cracks or scratches. The process of drug formulation is complicated: first, active pharmaceutical ingredients (APIs) and excipients (inactive substances) blend and dry, producing granules. Then, the formation

of tablets is formed by compressing granules with a tablet press. Both steps can introduce defects that affect quality control [5]. U.S. medicine manufacturing faces industry challenges because many large pharmaceutical companies have relocated their manufacturing plants overseas, resulting in a current trade deficit. The lack of domestic manufacturing facilities of high-quality generics disproportionally affects access to drugs manufactured overseas. Before the outbreak of the COVID-19 and major drug shortages, public and government entities recognized that the offshoring trend poses a risk for pharmaceutical ingredient supply. It is important to promote trust in local medicine production by U.S. manufacturers to supply drugs.

3.1. Applications of AI in Drug Formulation

Drug formulation is a crucial and complex process of combining active pharmaceutical ingredients (APIs) with excipients, which are inactive ingredients. The final product should have an optimal efficacy, stability, controllable release, appropriate administration route, and acceptability [6]. However, parameters such as the type and proportion of excipients, and mixing and manufacturing process, can significantly affect the physicochemical properties of the formulated products. Hence, a judicious choice of formulation is desirable for enhancing and controlling the final product performance and quality [1].

Artificial intelligence (AI) has shown great potential in formulating active substances as pharmaceutical products. Statistical modeling, especially pattern recognition, data mining, and regression, is core elements of traditional AI. Such techniques can be utilized to model complex biological systems and predict the in vivo performance of the drug delivery systems without extensive experimentation or animal studies. Currently, AI-driven quality control systems from formulation to toxicity test prediction of the drug substance are highlighted. Different AI techniques are presented, and their future directions and perspectives in drug formulation are discussed.

4. Challenges and Barriers in Implementing AI-Driven Quality Control Systems

There are challenges and concerns in developing AI-based Quality Control Systems in U.S. medicine manufacture. Below are some concerns where investigative and mitigating measures could be taken to ease the process of introducing AI-driven QC Systems at factories.

FDA Regulatory Compliance, Approval - AI-driven QC Systems need FDA compliance and approval in process control and quality measurement applications. The bottleneck to long-term approval is the perceived 'black box' nature of AI technology and algorithms. New, more sophisticated rules need to lead the way, thus allowing for the eventual approval of AI as a "medical device" [2] [7]. Moreover, with generative AI being AI with autonomy, the medical chance is that there is no human in the loop. This would also hinder compliance with high-risk medical software, wherein any AI decisions would require a high level of exactness. Thus, it requires a huge investment.

Scaling and Customizing - Adopting AI for QC systems requires validation and certification. However, there may be technical barriers that make scaling and customizing hard. Factory processes of tablets, troches, and gummies are all unique, requiring custom trained and validated AI for each production line. However, with four to five factories, this could require 20 to 30 separate solutions. Common methods for design validation and verification could further hinder the desired outcome.

4.1. Regulatory Compliance and Approval Processes

AI-driven quality control systems for U.S. medicine manufacturing must navigate regulatory compliance and approval processes. These systems must align with FDA regulations and product-specific standards, requiring extensive analysis of AI-derived outputs. Applicants must submit a comprehensive dataset and document model fidelity, examining accuracy, precision, sensitivity, specificity, sample qualifications, and integration with governance, validation, and post-market activities [7]. Monitoring and auditing procedures must be in place, and AI models must adhere to post-market regulations governing recertification and modifications.

Clinical validation under FDA or equivalent is intricate for closed loop systems using real devices. Europe prohibits Class 3 AI in production stages under termination of supervision authority by FDA software/cyber hazards jurisdiction; AI cannot be used as mitigation without prior analysis of operations by other means. AI development companies must proactively discuss these questions with engineers and regulatory agents to understand AI’s end-to-end use, completions, and outcomes, assessing risk being detected and controlling potential harm. Efforts should be made to engage companies and seek collaborations for language and conceptual comprehension

conversations to facilitate marketing readiness and subsequent use defensibility by FDA authorized parties [2].

5. Case Studies and Success Stories in AI-Driven Quality Control

Boehringer Ingelheim Pharmaceuticals, Inc. and Merck & Co., Inc. were invited to share their experience of investing in and achieving success with AVA, a powerful AI-driven in-line quality control system that is fully distributed across different product lines in nearly every plant of these companies worldwide. The presentation emphasizes the corporate benefits obtained by providing accurate and detailed statistical process analysis, understanding root causes, leveraging global statistical correlation models to collect instant feedback, and achieving prompt corrections with minor disruption to the line. Success stories and case studies are used to demonstrate how effective AI-driven quality control systems can rapidly revitalize the U.S. medicine manufacturing by promoting more efficient, more productive, and higher quality processing. This enables the embrace of faster, more flexible inline quality attributes testing and empowers proactive decision making and the advent of modern manufacturing standards.

Dr. Nathan C. Wyckoff IV described how his team has pioneered the acceleration of data acquisition and processing, discovery and amplification of batch patterns of contamination-based spectral variation, and implementation of enhanced profitability per run without compromising or altering their existing validated HPLC control procedures. Dr. Joseph F. Keary shared stories about the team at Merck & Co., Inc. and how their implementation and integration of AI-driven in-line quality control units can be traced through time using several different applications and management approaches. This began with Seed Technology and coercive external consensus, assuming that everything is a linear dependency lacking historical meaningful variation patterns. The merit of AIQCs goes beyond the place that little spectrometer and poor applications in regularization and gradient learning, orthogonal and variable weights factor analysis, using spectral processing to preserve chemical meaningfulness in log-transformed constituent metrics, maintaining efficiency and infrastructure goals imposed by speeding up manufacturing plants up to capacity.

5.1. Impact of AI on Manufacturing Efficiency and Product Quality

The introduction of the latest industrial computerization practices, including robotics, artificial intelligence (AI) and machine learning, the industrial internet of things (IIoT),

and other advanced digitally-assisted manufacturing methods, is an essential condition for the revitalization of U.S. medicine manufacturing and the development of advanced, innovative medicines necessary to respond to emerging biotechnologies. With the implementation and continuous enhancement of these technologies in the production environment, we can use them to raise overall manufacturing efficiency leading to success in cost and speed within the economy. In the design and production stages, the integration of data-based quality control management with operational AI systems provides a faster and more secure way to deliver products that meet the rigorous clinical requirements and increased quality control demands of today's biotech world over conventional clinical trials.

Within the scope of medicine manufacturing, AI and digital computing expand the array of available medical product treatments that can target patient responses and needs. Moreover, because of high product safety and quality standards, the implementation of AI-based total quality management and product trackability-based systems in medicine manufacturing facilities indicates significant results for improved product quality and production efficiency. The adoption of these technologies further facilitates personalized medicine, product miniaturization (devices or drugs), clinical diagnosis and treatment decision-making, and the management of production data. Consequently, in the coming years, it is predicted that efficiencies will accelerate significant new product introduction, but with a focus on manufacturing equipment and methods that support high patient distribution.

6. Future Trends and Developments in AI-Driven Quality Control Systems for Medicine Manufacturing

There is much to look forward to in the future of AI-driven quality control systems in the pharma industry. With rapid advancements in artificial intelligence (AI) technologies, this sector is expected to undergo major innovations that will reshape the very landscape of quality control. Broadly, the areas of focus for innovations will include AI-enhanced data generation and incorporation of artificial intelligence (AI) in decision-making. Regulatory bodies will also seek to keep up with these developments by expanding the scope of existing guidelines to accommodate suggestions for AI utilization within quality systems [1].

Recent advancements in AI are fueled by the deluge of data generated and collected in modern pharma companies. There are more technologies that rely on data collection, storage, and management than there were just a decade ago. Many pharma companies have pivoted to include data generation and management as core capabilities. However, the challenges that come with such massive amounts of data include data cleansing and combining. Current options for such tasks involve either machine learning (ML) approaches or extensive manual work, and as such, human use of intelligent systems is already deepening in quality control [5].

On the regulatory side, the High Performance Empowered by Artificial Intelligence in Quality Control (HPAC-QC) initiative has been started by the International Council for Harmonisation (ICH) in April 2023. This initiative seeks to identify opportunities for AI to be used to promote a Quality by Design (QbD)-based approach that implements a biopharmaceutical quality system. The advancements in AI and the ways they could be implemented within quality control systems are already in progress.

6.1. Advancements in AI Technologies

Over the past few years, several innovations have emerged that focus on advancing AI technologies. Such emerging technologies can be expected to transform and redefine quality control systems for medicine manufacturing as they continue to mature. The most relevant advancements in AI technologies include: Manufacturing AI Visual Inspection Software, Generative Pre-trained Transformer (GPT) LLMs, Advanced Language Models Combined with Vision Technology (e.g., ChatGPT4 + DALL-E 2), Advanced Automatic Speech Recognition (ASR) Voice Technology, AI-Powered Hypergenerative Pre-trained Transformer (HLT-LLM) Chatbots, Advanced Robotics/Automation, Synthetic Data AI Generation Software, and AI Science Technologies [1]. These advanced innovations in AI technologies have the potential to drive immense advances in quality control systems for medicine manufacturing in the United States.

The quality control departments in the medicine manufacturing industry can employ AI-driven software solutions, powered by machine learning and deep learning technologies, to automate visual quality inspection processes. The potential to dramatically boost productivity, increase mass production levels, broaden inspection capability ranges, reduce false detection rates, and ensure visibility and consistency in

quality inspection decisions will entice managers and executives in charge of quality control departments at medicine manufacturing companies in the U.S. quality-based manufacturing market to act on these advancements in AI technologies [5].

7. Conclusion and Recommendations for Implementing AI-Driven Quality Control Systems

This essay explored the significance of adopting AI-driven quality control systems in the pharmaceutical industry, focusing on their potential to enhance productivity, profitability, and competitiveness. It highlighted the challenges posed by the COVID-19 pandemic, supply shortages, and rising manufacturing costs, which have led U.S. pharmaceutical companies to downsize production or shift it overseas. AI-driven quality control systems, such as Computer Vision and Artificial Neural Networks, have the potential to revolutionize medicine manufacturing by improving product quality, reducing manufacturing costs, and expediting inspection and testing processes.

In addition to emphasizing the need to revitalize U.S. medicine manufacturing using AI, this essay explored AI-driven quality control systems utilizing Computer Vision and/or Artificial Neural Networks. The applications of these AI technologies in the pharmaceutical manufacturing industry to improve the quality of medicines and reduce manufacturing costs were examined. The possible means to implement AI-driven quality control systems for inspections of raw materials, in-process medicines, and final products were also discussed. The significance of AI-driven quality control systems for ensuring the quality of manufactured medicines and, thus, their therapeutic effectiveness and safety was highlighted.

There remains huge potential for machine learning and AI technologies for developing Intelligent Quality Control Systems that can autonomously inspect, decide, and take actions to improve the efficiency and effectiveness of quality control processes. Investment in these technologies requires funding and collaboration among industry stakeholders. Pharmaceutical companies should prioritize and pursue these technologies to become more competitive. For a better and faster mid- to long-term implementation of AI technologies, pharmaceutical companies should build partnerships with AI technology companies that can provide the necessary expertise.

References:

[1] Y. Han and J. Tao, "Revolutionizing Pharma: Unveiling the AI and LLM Trends in the Pharmaceutical Industry," 2024. [PDF]

[2] A. Ranjbar, E. Wermundsen Mork, J. Ravn, H. Brøgger et al., "Managing Risk and Quality of AI in Healthcare: Are Hospitals Ready for Implementation?," 2024. ncbi.nlm.nih.gov

[3] A. Vezina, "Quality by Design Procedure for Continuous Pharmaceutical Manufacturing: An Integrated Flowsheet Model Approach," 2017. [PDF]

[4] A. Mousa Mashraqi and B. Allehyani, "Current trends on the application of artificial intelligence in medical sciences," 2022. ncbi.nlm.nih.gov

[5] A. Ioana Visan and I. Negut, "Integrating Artificial Intelligence for Drug Discovery in the Context of Revolutionizing Drug Delivery," 2024. ncbi.nlm.nih.gov

[6] J. Jiang, X. Ma, D. Ouyang, and R. O. Williams, "Emerging Artificial Intelligence (AI) Technologies Used in the Development of Solid Dosage Forms," 2022. ncbi.nlm.nih.gov

[7] D. Higgins and V. I. Madai, "From Bit To Bedside: A Practical Framework For Artificial Intelligence Product Development In Healthcare," 2020. [PDF]

[8] J. Schmider, K. Kumar, C. LaForest, B. Swankoski et al., "Innovation in Pharmacovigilance: Use of Artificial Intelligence in Adverse Event Case Processing," 2019. ncbi.nlm.nih.gov

[9] C. Li, S. Bian, T. Wu, R. P. Donovan et al., "Affordable Artificial Intelligence-Assisted Machine Supervision System for the Small and Medium-Sized Manufacturers," 2022. ncbi.nlm.nih.gov