In-Process Analytical Intelligence and Deviation Alert Systems: Real-Time AI-Powered Platforms for Pharmaceutical Manufacturing Quality Monitoring

Dr. Jorge Murillo, Professor of Industrial Engineering, Universidad de Antioquia (Colombia)

1. Introduction

The impact of drug quality on the safety and effectiveness of pharmaceuticals is universally recognized. This creates significant pressure to implement more effective and efficient quality control methodologies within the pharmaceutical industry. Manufacturing processes used to produce pharmaceuticals are becoming increasingly complex and pose many challenges when it comes to assuring product quality. Such complexity demands a new approach to process monitoring, one that can work in real-time. The urgency that exists within the pharmaceutical manufacturing community comes at an opportune time. Rapid developments in the area of artificial intelligence and machine learning technologies have been realized, and their potential use in the pharmaceutical manufacturing space is beginning to be recognized.

Smart drug manufacturing relies on real-time process data to support operational decisions that, in turn, bolster overall efficiency, reduce off-specification product, and improve overall product quality. Given the escalating convolution of process unit operations, the move to real-time AI algorithms could enhance overall process understanding and inform operational decisions in ways that current technologies cannot replicate. Moreover, these considerations are well matched to the current regulatory environment in pharmaceuticals, where first principles-based continuous monitoring systems based on the principles of process analytical technology have primacy, and research into novel applications is well advanced. Large pharmaceutical companies are also facing global challenges at present. Concerns are growing that many high-income countries in the West are becoming too reliant on drug manufacturing in Asia. These firms are increasingly turning to AI to help with local drug production.

This work is licensed under CC BY-NC-SA 4.0.

1.1. Background and Significance

Drugs have had a substantial impact on the prevention and treatment of various maladies since time immemorial, dating back to the creation of the common commercial drug aspirin. However, the procedures used to generate medicines and maintain their quality have evolved over time. This is because thorough and consistent quality control is critical in the field of medicine as it has the potential to impact patients' physical and financial health. The newly promising platform technologies in the drug manufacturing industry include an informative summary of earlier processing methods and quality control systems that presage the potential of the newly discussed integrated systems. Both standard initial methods and systems use a given trending parameter as the determinant of the quality level of a drug batch. Before modern drug manufacturing and quality control systems, most medicines were produced as part of a mineral, herbal, or other ancient traditional therapeutic regimen. Just after the 19th century, with the arrival of technology, laboratory experiments, clinical trials, and double-blind studies for medical products, the most potent active ingredient of a medicine was first separated and then patented. Thereafter, companies began to manufacture massive amounts of medicinal products in bulk by installing automatic machinery. Manual or chemical analysis was conducted before industrial verification, but official monographs for chemical evaluations were established. Replaced by modern methods of analyzing finished products in pharmacopeias in the 20th century, these testing methods helped to verify compliance with an already placed batch specification at the end of the drug manufacturing process. For the rest of the 20th century, the use of computerized systems for drug manufacturing and process control was one of the quality control practices used for comprehensive drug batch quality verification by industry. In the 21st century, modern medicine manufacturing methods include parallel processing and quality studies. These include quality by design, quality risk management, risk-based quality systems, risk-based commitment strategy, and a risk-based life cycle approach to infrastructural quality. Moreover, these methods use intelligent systems like machine learning and artificial intelligence for optimization of drug production, equipment maintenance processes, and commercialization time. For efficient and wide-scale applications throughout a product development profile, hazard and technological attribute thresholds within a production process may be difficult to collect, assess, and interpret by humans. In conclusion, the use of machine learning and artificial

This work is licensed under CC BY-NC-SA 4.0.

intelligence-based real-time monitoring of modular drug-making units saves time, resources, and money, generating and commercially producing informative batches of products based on defined patient characteristics.

2. AI and Machine Learning in Drug Manufacturing

Artificial intelligence (AI) is an area of computer science that emphasizes the creation of intelligent automated systems based on logical, mathematical, and computational data-processing operations that are believed to be inherent prerequisites for 'intelligent behavior.' AI can make for more data-driven decision-making based on computer algorithms using inductive machine learning techniques. Machine learning is actually a subset of AI since it can use a knowledge base of relationships and then use that knowledge to deduce and predict conclusions. Machine learning is the process of developing and training algorithms that have the ability to learn from detailed data. This training allows the algorithm to become 'smarter' in that it can make increasingly better decisions based on this data. The primary goal of the pharmaceutical industry is to create medicine of high quality. There are a multitude of applications for AI in pharmaceuticals, including creating drugs, research and development, logistics, decision-making, sales forecasts, and managing sales representatives. In addition, some companies are using AI to predict equipment failure, repair broken machines, and monitor pharmaceutical plants remotely. Pharmaceutical manufacturers are taking notice of the potential of artificial intelligence (AI) to help quality-control inspectors catch the tiniest dramatic errors during the emulsification process. Integrating existing manufacturing execution systems to access historical and real-time manufacturing data from the process and monitoring systems. The monitoring system utilizes machine learning algorithms that can predict and identify quality-control issues that may result in quality product complaints and 'Production under regulatory threat (PURT).' Deployment of prediction-related analytics for this use case, which has been proven to be more accurate and precise than the conventional approach, has led to dramatic improvements. For one large pharmaceutical company, a single plant that was struggling for thirty days to produce product without being identified as an exception reduced its total duration of operating PURT-free for the calendar year from 84 days to 30 days to 4 days – that is, from a plant that could produce for almost 3 full months without a PURT exception to only working without exception for a single day. Pharmaceutical plants have a new competitive goal post being developed that requires

This work is licensed under CC BY-NC-SA 4.0.

all equipment needed to produce pharmaceuticals to be prognostic condition-based monitored or it will not qualify for design into their new plants. Prognostic monitoring will use AI patterns to determine likely failure times prior to manufacturers accepting designs. In pharmaceuticals, AI can be applied to cheaper quality control, in which new analytical tools based on statistical and AI pattern recognition help to determine if a product's inputs are good enough to produce quality product. In addition, AI will be used in laboratory research where the modeling of biological systems from a mechanistic quantitative systems biology approach is used. This approach investigates the potential risk associated with new medicines. Additionally, some pharmaceutical companies are using AI techniques to provide process monitoring solutions. AI can compensate for labor costs by allowing for more sophisticated monitoring and by optimizing the processing conditions to produce more or higher quality product. In pharmaceuticals, the goal of the manufacturer is to produce as much product as possible in the shortest time possible while maintaining quality. AI also opens up the realistic prospect of producing cheap, one-of-a-kind 'unit operations' using computer science and AI approaches. There is no way the high artisanal labor costs paid in the past make possible the bulk-use cost affordability of these materials. This changes that reality. AI can swiftly create new, cheap 'one-offs' with a low price.

2.1. Overview of AI Applications in Pharma Industry

The application of artificial intelligence (AI) spans every corner within the pharmaceutical industry, taking various forms and helping pharmaceutical scientists in research, trials, manufacturing, marketing, regulatory affairs, and many other domains. In drug design, AI can propose suitable candidates that have been proven to be promising and approved for treating patients. In clinical trials, AI platforms facilitate monitoring patients' health conditions, detecting side effects, interactions with other drugs, expediting adverse event analysis, and case studies. Additionally, AI techniques help physicians predict the right combination of drugs and preventive care unique to a specific patient by monitoring the genomics and proteomics of patients using platforms for personalized medicine.

Using AI tools in manufacturing will allow pharmaceutical manufacturers to improve production, increase efficiency, reduce the cost of implementing the system, and access technologies available for real-time monitoring of compliance. Of particular interest

This work is licensed under CC BY-NC-SA 4.0.

within the research community are the predictive modeling platforms that are effective at making predictions. AI is now emerging in the supply chain and cold chain as an inevitable innovative mainstream technology that guarantees streamlined efficiencies such as faster and defect-free transactional processes, better working conditions, and more dynamic data management strategies. The driver of the strong and ongoing growth of AI-driven analytical and functional platforms is the continuously rising demands and requirements in maintaining and improving the quality of a company's manufactured drugs while always protecting patient safety. In the manufacturing process or setting, the quality of a product is influenced by proper initial training and the ability of the system operators. Consequently, the company's ability is based on system integration, reliable data collection, and robust data measurement management strategies. Careful data analysis while being compliant with data integrity is a crucial issue. The use of these technologies can provide and help meet the multiple challenges needed through an overview of using a hybrid of adaptive scripts, such as supervision of numerous parallel reactions involving various parameters. The following discussion will provide an overview of the varied use of AI platforms focused on applications and trends in the industry with an emphasis on manufacturing.

3. Real-Time Monitoring in Drug Manufacturing

It is widely agreed among experts in the pharmaceutical industry that the traditional quality-by-testing paradigm is decoupled from the current technological advancements and the standards set in other high-tech industries. This condition is once again demonstrated by the fact that the majority of drug manufacturing processes are monitored manually, in some cases through offline manual sampling. Hence, it is now generally acknowledged that real-time quality assurance or the absence of the need for quality assurance is the desired aim of any advanced, complex, heterogeneous, and high-volume manufacturing process. If every single object of the current drug manufacturing processes were monitored and guaranteed to have been developed according to the batch quality testing, one of the main challenges would be addressed.

Recently, efforts in developing real-time monitoring for several process industries, such as biopharmaceuticals, food, electronics, petrochemicals, and water purification, have gained significant attention. These examples have so far established foolproof continuous or in-situ monitoring methods, allowing the detection of impurities or

This work is licensed under CC BY-NC-SA 4.0.

failures in real time as soon as they deviate from their acceptable operating conditions or change in substance composition of a product. This capability is often missing in traditional batch processes where drugs are manufactured before their quality is confirmed. To achieve real-time quality control, numerous technologies such as sensors, controls, and software platforms based on Internet of Things devices are now commercially available. These solutions offer compact sensor devices with high measurement quality, integrated data processing, data security, and data management capabilities. However, industrial implementation of these systems can differ vastly; one single sensor system can generate terabytes of data per manufacturing run, hence contributing significantly to the big data challenge observed in many industries. Hence, for quick and robust integration on the shop floor, additional tools and techniques are needed to allow real-time computation on this massive data stream. Implementations of real-time monitoring have demonstrated the tremendous potential for further scientific experiments, extraction of operational excellence, and early detection of product quality issues in various pilot and R&D environments. The continuous wet-granulation and tableting real-time monitoring case study is a pointer to the need to continuously monitor physico-chemical properties such as temperature, composition, or robust sensor unique signature. Challenges implemented in their complementary technology project tackled the data management, real-time monitoring, and made feasible the enablement of real-time monitoring for managing the interdependent material quality attributes for a continuous system.

To improve these continuous manufacturing systems, agents of a model technology framework could provide real-time sensor data investigations and intuitive image data interpretations per unit operation such as 3D mixing, screw feed, and tablet wrapping, that could be used to signal each processing unit before the process reached either the end or intermediate quality attributes. Reasons believed to facilitate this happening include the practicalities of manufacturing on the shop floor, real-time data overloading obstacles on the process development scientist, high-level stakeholder and regulatory requirements, technological data integration, and real-time data interpretation architecture necessities. These real-time monitoring integrated software applications will discover and utilize possibilities for drug manufacturers to rapidly implement advanced software integrated systems worldwide. The end result will be the manufacture of a

This work is licensed under CC BY-NC-SA 4.0.

large variety of unique drugs in a short period, thus enhancing access to quality pharmaceuticals across the world for a variety of health concerns.

3.1. Challenges and Opportunities

Challenges: There are various obstacles to the effective implementation of real-time monitoring for drug manufacturing quality. The costs are high, particularly because it requires the integration of several technological platforms, a highly specialized workforce, and the allocation of significant floor space and infrastructure. Data is another significant barrier. High population datasets will be collected, and new, data-heavy AI technologies are necessary for analysis. Currently, industries and regulators are generally unfamiliar with such complex techniques. The switchover to real-time monitoring will require significant re-certification and data requalification, which may be viewed as a costly and time-consuming choice. Industries also typically tend to resist significant technological change. Real-time monitoring systems might be viewed as a disruptive component of operations management. A likely move towards cheaper, effective, reduced surveillance or lower inspection operations in industrial plants, as a result of automated data correlation and analysis, is a potentially inhibitory change requiring a clear regulatory message to ensure enthusiasm.

Notwithstanding the above statements, there are distinct opportunities associated with the implementation of real-time monitoring in drug manufacturing industries. It is expected that the outputs will follow a consequential, significantly more valuable pathway. Eight regions respond to the best single advantage of real-time monitoring: quality improvements. Other recorded benefits include energy savings, improved yield and productivity, waste reductions, upkeep of apparatus, stock reductions, reduced output prices, a more sustainable operational system, and a reduction in time-to-market. There is, therefore, a valid positioning of drug manufacturing industries looking to accomplish this vision, the opportunity to positively demonstrate the return on investment and value from the production process. These opportunities are promising signs for the future development and marketing of real-time sensing technologies for drug manufacturing processes. Such hopes are normally a result of realizing the situational benefits. Despite regulatory standards becoming ever higher in the future, the opportunity for 'front-runners' to speed up production can therefore be realized. If those businesses and government bodies transition into these early stages of automation

This work is licensed under CC BY-NC-SA 4.0.

and various data analysis solutions, they will potentially optimize their current and future design, manufacture, and report pressures to record claim compliance requirements. Hence, the 'back-pressure effect' may initially cause an undue burden of real-time monitoring during the fabricated risk assessments between industries and international organizations. In this case, there might be opportunities for existing and new AI-powered equipment innovators to appropriately respond.

4. Quality Control and Compliance in Drug Manufacturing

Given that drugs contain active ingredients that directly impact human health, requirements concerning their manufacturing are quite understandably detailed and strict. The regulatory landscape governing the manufacture, distribution, and sale of medicinal products is complex. High-income countries have regulatory systems that normally adhere to guidelines which allow for mutual recognition of inspections while retaining national legal authorities. The use of therapeutic products that do not comply with relevant quality control measures could endanger the safety of patients. Given that all new drugs are synthetic chemicals, various tests that delve deep into the molecular and atomic structure of the product are crucial not only at the final drug product development stage but also at the synthesis stage to ensure quality throughout the manufacturing process.

This chapter discusses the vital importance of quality from a compliance perspective in the manufacturing of a drug or any pharmaceutical product. We introduce the existing laws and regulations, detailing the importance of monitoring product quality. We also highlight the changes effected in the pharmaceutical enterprise and by the increase in regulations. With the drastic increase in the needed documentation, the regulatory requirement has become a significant cost item in the manufacturing of a drug product. In response, this chapter turns to available tools, new developments, and technology incorporating digital and AI to provide a potential solution to reducing the cost of compliance. Economizing techniques with Quality Management System and computerized documentation databases could suggest a prescient proactive approach.

4.1. Regulatory Requirements

In pharmaceutical industries, there are increasingly stringent regulatory requirements to guarantee that active compounds in a medicine recipe are reproducible and can be manufactured as per rigid norms of product quality for that formulation known as Good

This work is licensed under CC BY-NC-SA 4.0.

Manufacturing Practice (GMP). These quality requirements form the basis of regulations followed by regulatory agencies to approve a new drug for market. With the objectives of maintaining and promoting public health globally, both agencies publish specific regulatory guidelines. Under these guidelines, both agencies work together to mutually accept scientific regulatory recommendations. To protect public health, regulations and standards include pharmacovigilance or post-market surveillance and corresponding safety reporting requirements based on the stage of drug development or where a patient is residing.

To provide continual assurance that approved drugs are produced and controlled in accordance with the quality standards contained under GMP, equivalent regulations were also developed. Quality assurance plays a crucial role in adequately addressing these requirements. In its broadest sense, quality control involves any activity aimed at assessing the quality of a pharmaceutical product. This entity is considered one of the key elements for effective application of product specifications that aid in manufacturing, control, and testing of marketed products and patient safety. However, this focus has also made verification and validation towards real-time data challenging in the pharmaceutical manufacturing industry. The adoption of AI technologies in pharmaceutical manufacturing would enhance regulations' compliance if they are applied in an integrated manner along with the regulatory frameworks. Attention given to implementing AI real-time data platforms for reducing or meeting the new regulations is not the same for all actors in the pharmaceutical manufacturing field, especially contract manufacturers. Such a shift in regulatory thinking would require significant staff training initiatives. The implications drawn in this section indicate that staff might be unaware or poorly informed about these changing regulations. In other words, it is important that undergraduate and postgraduate academic programs and industry training programs emphasize the importance of knowing how to identify and follow current regulatory requirements.

5. Case Studies and Success Stories

Predictive maintenance and bioprocess control environments are some successful examples of AI adoption in drug manufacturing operations. Some companies have reported positive analytics improvements related to the use of the technology. The accumulation of historical and real-time data in the process simulation environment has

This work is licensed under CC BY-NC-SA 4.0.

been enabled by a cloud-based AI solution. As a result, there was a time reduction of 60-100% to run studies. Also, an industrial biotechnology company experienced a 50% reduction in cycle time on a purification step within a fermentation process, boosting titer. Success stories report increased operational efficiency, materials management improvements, enhanced data analytics and quality assurance, reduction in resource pollutant time and costs, and a general transition from a reactive to predictive stance.

A case of adoption from over a decade ago is nostalgic for creating a data analytics company for the biopharma sector. The company explains that among the main lessons learned with the platform was repositioning occasional trips to see the end-users. In addition to designing an architecture that could still compete with technology 15 years down the line, another challenge was added to collaborate even more closely than standard practice with technology developers. They generally got their job orders from a mix of direct referrals from individuals who knew them and from collaborations. To demonstrate the wide variety of AI opportunities for industrial applications in drug production, a selection of real stories has been collected and described.

5.1. Examples of AI Implementation in Drug Manufacturing

Examples of AI integration into drug manufacturing topics include:

• Roche developed a digital twin for cell culture media optimization, leading to a significant speedup in the optimization of experimental protocols. The company was able to reduce total experimentation time from several months to a week while maintaining high process optimization quality. • Amgen implemented AI in quality prediction. The system served for real-time monitoring of both upstream and downstream mammalian bioprocesses. Using process parameters, subcontractor information, and batch history, the program has a "better than human" ability to predict whether a batch of product will meet quality specifications and yield. • Gilead, Genentech, and Pfizer use technology to aggregate large, siloed datasets associated with pharmaceutical manufacturing. These platforms use machine learning to predict the probability of failure at different stages of the manufacturing process, with the idea that operators can proactively respond to maintain production schedules. • Pfizer uses a Manufacturing Operations Center to have a real-time manufacturing and quality overview and early identification of issues. The technology is run throughout Pfizer's manufacturing facilities. • In pharmaceutical manufacturing outsourcing, Recursion

This work is licensed under CC BY-NC-SA 4.0.

collaborates to implement in silico predictive models to determine the impact on the scalability of manufacturing processes, which may have a significant economic benefit in drug manufacturing.

In all cases, the development of such applications was driven by the specific demands of the process or the product. Traditionally, pharma companies opt for collaborations with big AI tech companies. Pharmaceutical companies' choice of working with specialized AI tech firms would likely have been encouraged by examples of previous work conducted by these firms and the ability to specifically tailor tools and tactics developed for these previous collaborations to their specific needs. Evidence from each of the case reports showed that the speed of implementation was closely linked to the existence of previous developments that could be adapted. All companies chose to run collaborative AI projects such that learnings were internalized within their organizations. The results were encouraging and are likely to be driving the further spread of AI programs across the sector. When implemented correctly, these solutions are powerful examples of AI implementation in manufacturing settings, providing value in process optimization and quality control.

6. Future Direction

We envision many potential directions that the future of AI can possibly go. Advancements in computer vision, NLP, reinforcement learning, and deep learning, to name just a few, all have implications for AI systems in manufacturing quality. Increased automation to collect and analyze more relevant data can minimize human intervention and free operator time for more value-added activities. Multiple-site and system integration can enable cross-site learning, and data fusion can help uncover valuable insights. It might be possible to fundamentally change process control, using reinforcement learning, adaptive real-time control, or in silico modeling that combines various knowledge to calculate product and process responses. AI systems can be improved to adapt more robustly to uncontrolled variability and disturbances. For example, improved classification and regression tree learning could be adopted to look for valuable data and insights for quality and process optimization. Process analytical technology as a process analytical outcome can potentially be combined and installed directly on continuous manufacturing lines in the pharmaceutical industry, enabling

This work is licensed under CC BY-NC-SA 4.0.

real-time data analysis, process optimization, and expedited release of the drug substance.

As new trends emerge, AI-powered systems will need to keep evolving to meet new needs. Continuous learning and adaptation, development of enabling platforms, and democratizing AI will have large implications for the future landscape of quality by design. Furthermore, regulators could also be influenced by these trends to change their requirements. What are the possible implications of these potential changes? Drug manufacturing might involve more collaboration across industries and others. Future work must reflect these changes and new technologies in the public domain. We believe that future research must adapt to rapidly accelerating technological improvements to drive the industry forward.

7. Conclusion

Real-time AI-powered platforms designed to monitor pharmaceutical manufacturing and ensure the quality of produced drugs have continuously gained more interest throughout the pharmaceutical community over the past decade. These platforms would use AI to predict the impact of changes in drug manufacturing on the content and drug properties, as well as technologies based in part on real-time Raman and IR. The pharmaceutical industry is focused on ensuring safe products for patients, with ever-increasing fines in compliance costs and upcoming inspections. It is considered that AI and digitalization will become key in driving the transformation in the pharmaceutical industry. Nevertheless, the pharmaceutical industry is considered to have a slow adaptability to change. Potentially, overcoming these barriers in the resistance to change, cost, regulatory limitations, and technology could enable using technology to improve real-time decision-making and efficiency of drug manufacturing. The challenge for pharmaceutical companies and regulatory authorities is to be informed, innovative, and forward-thinking, embracing the option of an AI-driven paradigm for ongoing quality control improvements, strategic cGMP adaptations, and scientific innovation. Recently, the formal validation has been presented in pharmaceutical science as 'Quality-by-Control' (QbC), or for patents that strive for continuous improvement in drug quality. However, these formal approaches do not utilize AI to its full potential. Further research and investment in this area are warranted. In conclusion, the implementation of real-time artificial intelligence and digital platforms to

This work is licensed under CC BY-NC-SA 4.0.

experimentally refine the solutions to satisfy the proposed models appears to be the 'Holy Grail'.

This work is licensed under CC BY-NC-SA 4.0.