Available online at www.sciencedirect.com

ScienceDirect

IFAC PapersOnLine 58-8 (2024) 222–227

Application of Digitalisation in Regulated Environments for Predictive Failure Modelling

Frank Doyle*, Samuel Carvalho*, Dr. Zsolt Kovács, Dr John Cosgrove***

**Technical University of the Shannon, Limerick, Ireland (frank.doyle@tus.ie).*

**Technical University of the Shannon, Limerick, Ireland (samuel.carvalho@tus.ie)*

*** Széchenyi István University, Győr, Hungary, (kovacs.zsolt@sze.hu)*

**Technical University of the Shannon, Limerick, Ireland (john.cosgrove@tus.ie}*

Abstract: This paper explores the challenges of applying digitalization in regulated pharmaceutical manufacturing environments. A large range of complex equipment including pumps, valves and vessels may be associated with pharmaceutical batch production processes. Maintenance of such equipment are often based on reactive or preventative strategies which are not always effective and not completely successful in preventing costly downtime or scrap. This research examines how predictive maintenance Key Performance Indicators (KPIs) can be developed through data capture using non-intrusive sensors and their integration with production data derived from Programmable Logic Controllers (PLCs), Enterprise Resource Planning (ERP) systems, and Product Lifecycle Management (PLM) systems. The significance of regulation and the associated challenges in applying digitalization within such a highly regulated environment are also considered. This research aims to shed light on the potential benefits and challenges of implementing digital solutions for predictive maintenance in regulated manufacturing environments to contribute to the enhancement of operational efficiency and product quality while reducing costs due to outages.

Keywords: Digitalization of manufacturing, regulated environments, condition monitoring, acoustic emission, machine learning, dry gas seals

1. INTRODUCTION

In recent years, the widespread application of digitalization under the term Industry 4.0 has revolutionized various industries, including manufacturing processes in regulated pharmaceutical environments. The use of digital technologies including the use of automation, robotics and data-driven approaches has brought significant progress in operational efficiency, quality assurance, and cost reduction across a variety of industries (Arden et al., 2021; Mukhlas et al., 2022; Nazari & Musilek, 2023; Tilley, 2017). The digital transformation of manufacturing has the potential to revolutionize manufacturing across all sectors and, with it, change the world. Through new technologies that have significantly reduced burdens related to data collection, storage, and processing, society has an ever-increasing quantity and quality of data available at its fingertips. These progressions, commonly referred to as digitalization, have allowed companies to increase performance, accuracy, and productivity in ways previously unimaginable. This current manufacturing scenario demands that companies implement robust and comprehensive digitalization strategies in order to remain competitive and satisfy regulatory requirements. Technologies such as Industrial Internet of Things (IIoT), Digital Twins and the widespread application of Data Analytics and Artificial Intelligence are some examples of the trending approaches to tackle the challenges faced by manufacturers nowadays.

The objectives of this research are twofold. Firstly, to illustrate the potential benefits that digitalization and predictive maintenance can bring to pharmaceutical manufacturing processes, by improving operational efficiency and product quality, companies can achieve greater competitiveness in the market. Secondly, to address the complexities and challenges inherent in implementing digital solutions in a regulated environment. It is anticipated that the findings and insights from this ongoing research will support decision-makers in the industry in making informed choices and driving continuous improvement in operational efficiency and product quality.

1.1 Background

While the modern futuristic manufacturing site is seen as an example of Industry 4.0, when we look at the starting point of the modern pharmaceutical industry, Industry 1.0, we find the transition from the manual processing of raw materials to the commercial scale crushing and milling of product increasing quantities of medicines. (Anderson, 2005)

The next advance to Industry 2.0 was facilitated through the development and availability of electrical equipment allowing basic automation and process controls for larger scale production and monitoring of processes and quality. Control was quite basic with passive control strategies including the development of tablet presses producing over a million tablets per hour on a reliable basis. It has been stated that many of the existing manufacturing sites still operate at the Industry 2.0 level. (Berry & Nash, 2003; *Pharma 4.0*^{TM}, 2023)

10.1016/j.ifacol.2024.08.124

The third stage or Industry 3.0 was brought about by the availability of communication technology such as the Internet and wireless communication which facilitated higher levels of automation and control. Human-computer interfaces helped in the development of better control plans and improvements in product and process quality. Increased use of sensors to monitor production and tracking of process steps have reduced the need for personnel and increased throughput. This stage has led to the development of advanced process analytical technology (Bakeev, 2010) with the aim of delivering near real time data-streams monitoring processes and product.

Future pharmaceutical production facilities are being designed incorporating advanced digital elements and enablers into the current Pharmaceutical Quality System (ICH Q10) known as Pharma 4.0 (Ding, 2018; Mukhlas et al., 2022; *Pharma 4.0™*, 2023) and the application of these technologies has the potential to significantly improve the agility, efficiency, flexibility, and quality of the industrial production of medicines. The global Food, Chemical and Pharmaceutical industry market is expected to grow at 3-6% cumulative annual growth rate through 2023 to 2027 to about $1.9 trillion (IQVIA, 2023). However existing production sites are restricted to controlled practices due to regulations applied during initial design of facilities which hamper potential improvements in processes and operations (Lee et al., 2015). Analysis in 2008 (Yu, 2008) showed that pharmaceutical development engineers had only then commenced the inclusion of process simulation in the design process to aid product development and optimization of production processes, while process simulation techniques had been successfully applied in the chemical and oil industries since the 1960's. More recently research has documented that the pharma industry is not at the same level as other industries regarding six sigma capabilities (Yu & Kopcha, 2017).
The manufacturing processes in regulated pharmaceutical environments require strict adherence to regulatory standards and guidelines to ensure product safety, efficacy, and compliance. This highly regulated nature poses unique challenges and considerations when implementing digital solutions. Regulatory agencies, such as the Food and Drug Administration (FDA) in the United States, the European Medicines Agency (EMA) in Europe, enforce these regulations. Understanding and navigating these are crucial for successfully integrating digitalization initiatives within such environments.

1.2 Research focus

This research explores the specific application of acoustic emission (AE) analysis and a use case where Dry Gas Seals (DGS) in bioreactor mixing vessels have failed with large resulting financial costs in a pharmaceutical manufacturing site. It focuses on the development of predictive maintenance Key Performance Indicators (KPIs) such as Remaining Useful Lifetime (RUL). Through data capture using non-intrusive sensors, such as acoustic emission, vibration, and current transformers, data can be captured in real-time, providing valuable insights into equipment health and performance. The integration of sensor data with live and historical production data derived from Programmable Logic Controllers (PLCs), Enterprise Resource Planning (ERP) systems, and Product Lifecycle Management (PLM) systems can facilitate the use of machine learning algorithms to learn from past behaviours and conditions to enhance predictive maintenance capabilities further.

This paper is structured as follows: section 1 presents a brief introduction to the topic. Section 2 covers some background knowledge on digitalisation of regulated manufacturing environments. Section 3 discusses the challenges for digitalisation in these environments. Section 4 covers the maintenance strategies in pharmaceutical production, while section 5 presents our proposed methodology and conclusion.

2. DIGITALISATION OF REGULATED MANUFACTURING ENVIRONMENTS

Critical elements of production equipment such as agitator/mixing tanks and electric motors need to be regularly maintained to ensure reliability. A significant amount of equipment failure events do not happen without prior warning indications, these may include for example excessive noise or heat from bearings or seals that are degrading. It is possible that, through regular inspection of critical components it may be possible to detect potential failure of elements before they result in failure of equipment and potential loss of production through unplanned outages. Through the use of hand-held vibrational analysis monitoring tools, the progression of wear of seals and bearings may be monitored and compared with previous readings to determine if sufficient degradation may have occurred to warrant a change. However, the cost of inspections may be significant if the inspection period is very short, but if the inspection period is too great a potential failure may not be detected in time (Guo et al., 2015). This may result in a very large failure cost if it occurs in the middle of a batch process where the product being processed can have a value of several hundred thousand euro, depending on the product being produced.

The ability to monitor the status of critical equipment elements over extended periods and associate clear changes in characteristics can be used to perform condition monitoring when a complete understanding of what characteristic behaviours can be used to indicate degradation of components. The potential failure signature of a component may be unknown at the start of monitoring thus rendering typical vibrational analysis of poor value to indicate in sufficient time to prevent a potential failure. In ideal circumstances it would be possible to install appropriate sensors on critical equipment and record monitored data in-sync with production system data to infer condition related information. However, the post-installation of data monitoring equipment for condition monitoring is challenging in existing pharmaceutical manufacturing sites as the required validation costs restrict the installation of additional sensors.(Zürcher et al., 2022)

2.1 Digitalization in Pharmaceutical Manufacturing

Digitalization has emerged as a transformative force in various industries, and pharmaceutical manufacturing is no exception. The integration of digital technologies and data-driven approaches has the potential to revolutionize manufacturing processes, enhance operational efficiency, and improve

product quality in regulated pharmaceutical environments. By leveraging advanced technologies and intelligent data analytics, digitalization enables real-time monitoring, predictive maintenance, process optimization, and regulatory compliance. In the context of pharmaceutical manufacturing, digital transformation encompasses the adoption of technologies such as Internet of Things (IoT), artificial intelligence (AI), big data analytics, cloud computing, and automation. These technologies enable the collection, analysis, and utilization of vast amounts of data to drive decision-making, improve efficiency, and optimize processes.

2.2 The Benefits of Digitalization in Pharmaceutical Manufacturing

Digitalization brings a host of benefits to pharmaceutical manufacturing, including enhanced operational efficiency through optimized processes, reduced downtime through predictive maintenance, improved product quality through real-time monitoring and quality control, streamlined supply chain management, better compliance with regulatory requirements, and increased agility and competitiveness in the market. By leveraging digitalization, pharmaceutical manufacturers can drive continuous improvement, cost savings, and innovation.

2.3 Role of Regulation in Ensuring Safety and Quality

Regulation plays a vital role in pharmaceutical manufacturing by ensuring the safety and quality of medications, minimizing risks associated with drug production, including contamination, adulteration, incorrect dosage, and potential harm to patients. Regulations mandate Good Manufacturing Practices (GMP) and Good Automated Manufacturing Practice (GAMP) to govern every aspect of manufacturing processes, including facility design, equipment qualification, personnel training, quality control, and documentation. These standards promote consistency, traceability, and accountability throughout the production chain, guaranteeing the reliability and effectiveness of pharmaceutical products.

2.4 Implications for Digitalization in Regulated Environments

The application of digitalization in regulated pharmaceutical environments introduces complexities and considerations due to the regulatory requirements. Ensuring compliance with existing regulations while implementing digital solutions is of paramount importance. Challenges arise with cyber and data security, privacy, data integrity, validation, and auditability (Gopal et al., 2019; Nazari & Musilek, 2023). Implementing digitalization requires the development and implementation of robust systems and processes to address these concerns. Also, the adoption of digital technologies should include validation procedures and comprehensive risk assessments to ensure that the safety, efficacy, and quality of pharmaceutical products are not compromised. Collaboration between regulatory agencies, industry stakeholders, and technology providers is essential to develop guidelines, standards, and best practices that facilitate the adoption of digital solutions without compromising safety and quality.

3. CHALLENGES IN APPLYING DIGITALIZATION IN REGULATED PHARMACEUTICAL ENVIRONMENTS

3.1 Compliance with Regulatory Requirements

A primary challenge in applying digitalization in regulated pharmaceutical environments is ensuring compliance with stringent regulatory requirements. Regulations governing pharmaceutical manufacturing encompass various aspects, including data integrity, validation, documentation, and traceability. Implementing digital solutions requires careful consideration of these regulations to ensure data generated and utilized by digital systems are compliant and can be audited. The alignment of digital processes and technologies with regulatory frameworks requires clear guidelines and industry standards to ensure compliance without impeding innovation.

3.2 Data Integrity and Security

Data integrity and security are critical concerns when implementing digitalization in regulated pharmaceutical environments. The collection, storage, and transmission of data throughout the manufacturing processes must adhere to strict security protocols to safeguard sensitive information and prevent unauthorized access or tampering. Ensuring the integrity and authenticity of digital records and data trails is crucial for regulatory compliance and maintaining trust in the system. The compliance document 21 CFR part 11, for example, is a regulation from the FDA that guides industry regarding the scope and application of electronic records and electronic signatures (McDowall, 2011). Robust data management systems, encryption techniques, access controls, and audit trails are necessary to address these challenges and minimize the risk of data breaches or manipulation.

3.3 Change Management and Cultural Shift

Digitalization initiatives require a cultural shift within organizations and often disrupt existing processes and workflows. Resistance to change, lack of digital literacy, and organizational inertia can pose challenges when introducing digital solutions in regulated pharmaceutical environments. Change management strategies, training programs, and effective communication are essential to overcome resistance and foster a culture that embraces digital transformation. Additionally, collaboration and engagement across different departments and stakeholders within the organization are crucial for successful implementation and adoption of digital technologies.

3.4 Integration of Non-Intrusive Sensors and Data Systems

The integration of non-intrusive sensors, such as vibration and current transformers, with existing production data systems poses technical challenges. Data standardization, data mapping, and establishing robust communication protocols are necessary to enable the efficient exchange and utilization of data from multiple sources. Technical expertise and collaboration between IT, operations, and engineering teams are crucial to address these integration challenges. Production area sensor installation is typically considered intrusive, so non-intrusive alternatives sourced for installation in these environments aid research. In this research case environment, installing wired sensors in clean rooms with data logging units

in external control rooms, requires drilling of walls and layout changes. Thus, the actual process of installing data logging equipment on specific production equipment may take several months due to approval checks and may be limited in capability and flexibility to gather, store and transmit data. Portable self-contained data loggers are preferred and will be used where possible.

4. MAINTENANCE STRATEGIES IN PHARMACEUTICAL PRODUCTION

Continual and successful manufacturing operations requires effective maintenance of equipment and systems with specific maintenance schedules being proscribed for critical production equipment (Ali & Abdelhadi, 2022). Operations management aims to manage maintenance schedules of equipment to optimise maintenance costs, maximise uptime and minimise costly service disruption. Effective operation of equipment and systems require explicit and tacit knowledge of system behavioural characteristics at various stages of operations or production, this requires relevant data capture and analysis to generate associations between production activities and potential failure events (Shaheen & Németh, 2022).

Condition-based maintenance uses sensors to collect real-time measurements from equipment about various conditions, such as temperature, pressure, or vibration. While predictive maintenance is a type of condition-based maintenance, it uses the constant stream of sensor data on a larger scale and is a proactive approach that uses data and advanced analytics to predict equipment failures and perform maintenance activities before breakdowns occur. It aims to maximize equipment uptime, optimize maintenance schedules, and minimize unplanned downtime (ISPE, 2023). In the context of pharmaceutical production, predictive maintenance plays a crucial role in ensuring the reliability and availability of critical manufacturing equipment, reducing the risk of production disruptions and maintaining product quality.

5. PROPOSED METHODOLOGY

The intrinsic challenges and scenarios described so far can be considered applicable to the pharmaceutical and other highly regulated manufacturing sectors in general. This research examines the maintenance of Dry Gas Seals (DGS) used on the shafts of agitators in bio-reactive mixing vessels for Active Pharmaceutical Ingredients. These seals require a high-quality supply of nitrogen gas, which is responsible for the thin separation layer between the rotating component on the shaft and the fixed part of the seal on the vessel opening, which enables a nearly frictionless operation. While these seals are deemed to be a reliable component, this research examines an industrial site where several seals have failed unexpectedly. A seal failure can lead to potential leakage or contamination of the biological product which will need to be discarded and the production system decontaminated. The loss of product and production time can have a cost of over €500k per incident. The pre-emptive replacement of seals before the manufacturer's recommended replacement interval did not result in improved performance which conformed to the 'Waddington effect' mentioned earlier.

A critical phase in DGS operation is the lift-off period when the seals' faces begin to separate. This is a period of friction and wear between the faces, resulting in higher AE levels in comparison to the normal operation level of the shaft. The red line on Figure 1 below represents the shaft rotation speed. As this increased from 0 RPM we can see an increase in the AE RMS up to a peak value. As the shaft speed increases the AE value reduces as lift-off occurs. Within the full-speed stage, the AE RMS values fall to a minimum level.

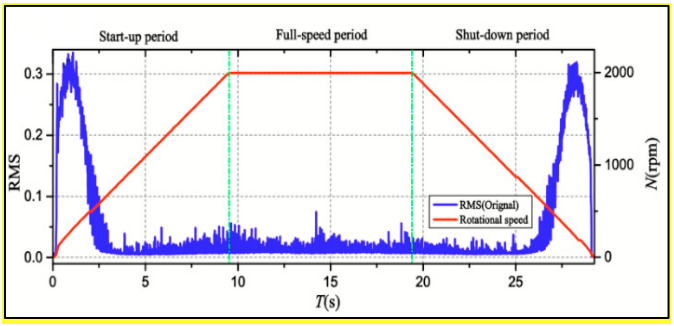

Figure 1 Dry Gas Seal AE profile during startup phase: (Fan et al., 2020)

This AE profile shown was from a lab-based experiment on DGS units common to pumps and compressors with defined operational vibration profiles and typical shaft speeds of 500-3000 RPM.

This research aims to use non-intrusive AE sensor-based condition monitoring and data analytics techniques to generate an AE profile of the DGS on the actual vessel.

Challenging aspects of this work include the fact that this analysis is not lab-based (and consequently, subject to all the regulatory challenges previously cited), and the fact that it focuses on an application where typical RPM values are significantly lower when compared to the ones reported in the current literature on this topic, typically in the range of 50-120 RPM. Most of the current body of knowledge currently found on DGS analysis discusses lab-based tests on seals in use on compressors and pumps, where the RPM range is typically 600 to 2000 RPM (as presented Figure 1 above). However, the equipment covered in this research work rotates at less than 120 RPM, this implies a different DGS design and possible AE profile during the lift-off phase.

The expected AE profile of bioreactor mixing vessels is also different from the typical ones analysed in previous works, there, the AE level is low and constant for the full-speed period. This well-defined operational behaviour can last for long periods of time in the case where pumps are pumping the liquid all the time, for example. The result being that the main wear on these DGS units is at startup and shutdown.

The profile for a lower RPM DGS in a mixing vessel can have large variations in vibration due to its operational stages (which can have cycle times of up to 4 weeks). Stress factors include tank filling, product lumping variations, temperature and pressure changes and agitator design. AE profiles of DGS for this type of mixing vessel and in a working environment is

absent in the current literature, thus present an unknown element in the research.

The acquisition of context data from the production process to map with the AE and other raw time-series data extracted from the factory floor is a challenge as installation of logging equipment on-site is a slow process and process data is protected. Agreement has been given to extract time-delayed contextual process by querying the site OSI PI software using matching timestamps for the monitoring periods. This way, process data such as vibration or AE can be labelled with higher level process variables such as temperature, pressure, tank content level, motor speed, motor torque, etc. from production PLCs which have been stored in the ERP. This will provide contextual information about the different manufacturing stages throughout the cycle time. This data will then be fed to an ensemble of Machine Learning algorithms for analysis. Figure 2 below illustrates how the low-code Orange Data Mining Machine Learning software can be used to identify the most appropriate ML algorithms for the application. As multiple algorithims can be evaluated in parallel it is expected data sets can be processed in a productive manner using this tool.

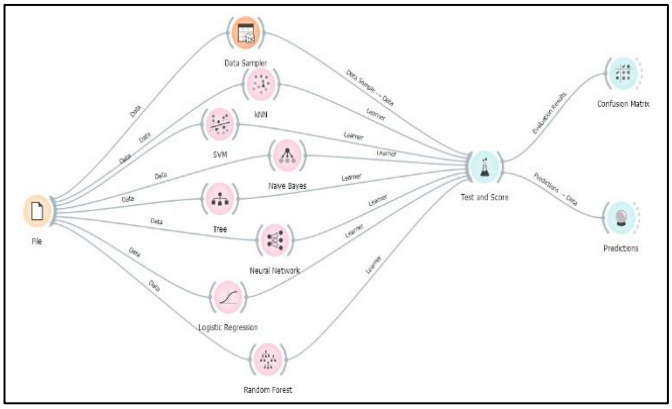

Figure 2: Supervised Machine Learning model comparison.

Captured AE data must include data from new seals, known to be in perfect condition, and ideally, from very worn seals that are about to fail. This classification of AE data for DGS good and bad states will be difficult at the start of the research as it will not be clear what threshold level of AE data will correspond to good and bad states. AE data logging will also be conducted before and after DGS units are due to be replaced on vessels as part of normal preventative maintenance tasks. It is expected this will capture the difference in AE values of new seals and those with a longer operational lifetime. As DGS units fail on site, a portable data logger will also be used to capture emission levels on units which have clearly failed.

Multiple short batches or cycles can also be performed in order to obtain data, this will later be split into training, validation and test datasets. The confusion matrices and confidence scores of each algorithm will then be evaluated, so the most reliable and accurate model can be chosen among the available ones. It is intended that this analysis will help identify the production parameters with the greatest impact on AE. Therefore, predictions of the RUL of the seals under analysis can be done and failures can be prevented in a better-informed way.

It is planned to verify the reliability and accuracy of the model generated by continuous logging of DGS units and comparing RUL indicators with actual AE data from failed and new units.

Given the restrictions imposed by the highly regulated environment of the pharmaceutical industry, as well as the current body of knowledge, we propose the following structure for parameter digitalisation, data acquisition, KPI generation and notification:

- Extensive use of non-intrusive, process-independent, sensors and logging equipment, to avoid significant interventions on machines, network infrastructure and production plants, and avoid the need for additional validation efforts and disruption to production. Network isolated portable data acquisition equipment with wireless data connection and direct access to cloud-based databases are a viable option in this case, especially for temporary or pilot experiments.
- Massive collection of context data, such as PLC, ERP and SCADA data, and AE data from failed units when available, in order to provide context/labels to time-series AE data acquired directly from the DGS by the data logging equipment.
- On the feature extraction and feature engineering stages of data analysis, exploring both time and frequency domains of the acquired AE raw data, since a vast range of equipment are known to present early signals of failure in specific frequency bands of vibration and acoustic emissions. Following this, feature selection strategies will be applied such as stepwise backward and forward elimination and PCA.
- Analyse and study the specific regulations around data analysis and machine learning methods, as well as using context data to allow the use of supervised methods (classification and regression methods, for example).
- Through continuous monitoring and logging of DGS, build a reliable and accurate model for the operation of these equipment, where classification of normal operation or failure events can be performed using machine learning algorithms typically cited in similar research works, such as Support Vector Machines (SVM) or Artificial Neural Networks (ANN).
- Implementing a suitable interface or dashboard for operators where they can monitor and clearly see KPIs indicating potential failures of the DGS, so that preventative maintenance can be carried out in time to prevent critical outages.

This research aims to capture DGS AE data using a portable AE sensor and data logger, which together with process data will be fed to supervised ML algorithms. The end goal is to generate a RUL KPI indicating the change of status of the health of the DGS. This will help the decision-making on maintenance scheduling and should save significant time, resources and costs currently estimated at several hundred euro per incident on site.

REFERENCES

Ali, A., & Abdelhadi, A. (2022). Condition-Based Monitoring and Maintenance: State of the Art Review. Applied Sciences, 12(2), Article 2. https://doi.org/10.3390/app12020688

Anderson, S. (2005). Making Medicines: A Brief History of Pharmacy and Pharmaceuticals. Pharmaceutical Press.

Arden, N. S., Fisher, A. C., Tyner, K., Yu, L. X., Lee, S. L., & Kopcha, M. (2021). Industry 4.0 for pharmaceutical manufacturing: Preparing for the smart factories of the future. International Journal of Pharmaceutics, 602, 120554. https://doi.org/10.1016/j.ijpharm.2021.120554

Bakeev, K. A. (2010). Process Analytical Technology: Spectroscopic Tools and Implementation Strategies for the Chemical and Pharmaceutical Industries. John Wiley & Sons.

Berry, I. R., & Nash, R. A. (Eds.). (2003). Pharmaceutical process validation (International 3rd ed., rev.expanded). Marcel Dekker.

Ding, B. (2018). Pharma Industry 4.0: Literature review and research opportunities in sustainable pharmaceutical supply chains. Process Safety and Environmental Protection, 119, 115–130. https://doi.org/10.1016/j.psep.2018.06.031

Fan, W., Huang, W., Liu, Y., Yin, Y., Liu, X., & Wang, Y. (2020). State Evolution of Dry Gas Seal during Repeated Start–Stop Operation Using Acoustic Emission Method. Tribology Transactions, 63(1), 173–181. https://doi.org/10.1080/10402004.2019.1674984

Gopal, G., Suter-Crazzolara, C., Toldo, L., & Eberhardt, W. (2019). Digital transformation in healthcare – architectures of present and future information technologies. Clinical Chemistry & Laboratory Medicine, 57(3), 328–335. https://doi.org/10.1515/cclm-2018-0658

Guo, H., Szidarovszky, F., Gerokostopoulos, A., & Niu, P. (2015). On determining optimal inspection interval for minimizing maintenance cost. 2015-May. Scopus. https://doi.org/10.1109/RAMS.2015.7105163

Igba, J., Alemzadeh, K., Henningsen, K., & Durugbo, C. (2015). Effect of preventive maintenance intervals on reliability and maintenance costs of wind turbine gearboxes. Wind Energy, 18(11), 2013–2024. https://doi.org/10.1002/we.1801

Ignizio, J. P. (2010). The Waddington Effect, C4U-Compliance, and Subsequent Impact on Force Readiness. Phalanx, 43(3), 17–21.

IQVIA, I. (2023). Global Market for Medicines to Rise to $1.9 Trillion by 2027, says Report from IQVIA Institute. https://www.iqvia.com/newsroom/2023/01/global-market-for-medicines-to-rise-to-19-trillion-by-2027-says-report-from-iqvia-institute

ISPE. (2023, June 23). An Introduction to Predictive Maintenance. ISPE | International Society for Pharmaceutical Engineering. https://ispe.org/pharmaceutical-engineering/may-june-2017/introduction-predictive-maintenance

Lee, S. L., O'Connor, T. F., Yang, X., Cruz, C. N., Chatterjee, S., Madurawe, R. D., Moore, C. M. V., Yu, L. X., & Woodcock, J. (2015). Modernizing Pharmaceutical Manufacturing: From Batch to Continuous Production. Journal of Pharmaceutical Innovation, 10(3), 191–199. Scopus. https://doi.org/10.1007/s12247-015-9215-8

McDowall, R. D. (2011). Is GMP Annex 11 Europe's Answer to 21 CFR 11? Spectroscopy, 26(4), 24–33.

Mukhlas, A., Talip, B. A., Che Mustapha, J., & Ismail, S. (2022). Industry 4.0 (IR 4.0) for Pharmaceutical Industry: An Exploratory Review. 2022 International Visualization, Informatics and Technology Conference (IVIT), 103–109. https://doi.org/10.1109/IVIT55443.2022.10033386

Nazari, Z., & Musilek, P. (2023). Impact of Digital Transformation on the Energy Sector: A Review. Algorithms, 16(4), 211. https://doi.org/10.3390/a16040211

Pharma 4.0TM: Hype or Reality? (2023, June 23). ISPE | International Society for Pharmaceutical Engineering. https://ispe.org/pharmaceutical-engineering/july-august-2018/pharma-40tm-hype-or-reality

Shaheen, B. W., & Németh, I. (2022). Integration of Maintenance Management System Functions with Industry 4.0 Technologies and Features—A Review. Processes, 10(11), Article 11. https://doi.org/10.3390/pr10112173

Tilley, J. (2017). Automation, robotics, and the factory of the future. McKinsey.

Yu, L. X. (2008). Pharmaceutical quality by design: Product and process development, understanding, and control. Pharmaceutical Research, 25(4), 781–791. https://doi.org/10.1007/s11095-007-9511-1

Yu, L. X., & Kopcha, M. (2017). The future of pharmaceutical quality and the path to get there. International Journal of Pharmaceutics, 528(1), 354–359. https://doi.org/10.1016/j.ijpharm.2017.06.039

Zürcher, P., Badr, S., Knüppel, S., & Sugiyama, H. (2022). Data-driven equipment condition monitoring and reliability assessment for sterile drug product manufacturing: Method and application for an operating facility. Chemical Engineering Research and Design, 188, 301–314. Scopus. https://doi.org/10.1016/j.cherd.2022.09.005