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TOWARDS A SMART FACTORY IN THE PHARMACEUTICAL INDUSTRY

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Review Paper

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The Industry 4.0 model is on the way to full maturity in production organisations, after more than a decade of application within them. It can be said that it was a key element for the digitisation of the economy and public services around the world, so today we can discuss the application of this concept in various areas, including the pharmaceutical industry. This paper aims to provide the latest information on the state of development of the Industry 4.0 model in the pharmaceutical industry (Pharma 4.0), which represents the path to a smart factory (SF) in this area. The paper consists of several parts, namely: (i) an analysis of the framework of the Pharma 4.0 model, (ii) its detailed presentation, and (iii) some observations on the future development of this model in application, all to develop a smart pharmaceutical factory (SPF).

Keywords: Industry 4.0, Pharmaceutical Industry, Pharma 4.0, Smart Factory.

INTRODUCTION

This century has brought the Fourth Industrial Revolution, known as "Industry 4.0", which was born half a century after the Third Industrial Revolution, more precisely, it was officially inaugurated at the CEBIT fair (IT equipment and software) in Hanover in November 2011. Today, the concept of smart manufacturing (SM is based on the application of the elements of Industry 4.0, of which there are a total of 48. The essence is to design, build and develop a strong virtual world based on digitisation, which would manage the physical world, first in manufacturing, and later in other economic branches and the public sector. Today, we are witnessing that this concept is realised in practice all over the world.

Industry 4.0 creates a network of all manufacturing entities and enables their mutual interaction in real-time. Cyber-Physical Systems (CPS), Industrial Internet of Things (IIoT), Cloud Computing (CC), Big Data Analytics (BDA), and Artificial Intelligence (AI), supported by learning models (ML/DML), are the key technological foundations of this industrial revolution (Bakator et al., 2019; Kagermann et al., 2013; Karabegović & Majstorović, 2024; Khan et al., 2022; Majstorović et al., 2022; Schuh et al., 2017). This paper aims to explain the application of the Industry 4.0 model in the pharmaceutical industry, as a basis for the development of a smart pharmaceutical factory (SPF).

INDUSTRY 4.0 MODEL IN THE PHARMACEUTICAL INDUSTRY - LITERATURE REVIEW

This systematic analysis was done according to the PRISMA methodology (PRISMA, 2024), and our questions were: Q1. How can a model Industry 4.0 be applied in the pharmaceutical industry, and Q2. How does the Industry 4.0 model improve planning, analysis and process management in pharmaceutical manufacturing, and especially product quality? For these questions, the following are defined: time period of analysis, type of study, Pharma 4.0 model, search methodology and assessment of study quality. The sample included 354 papers and 59 papers met the set criteria. A systemic analysis of the application of the Industry 4.0 model in the pharmaceutical industry was performed here from

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the following angles: (i) defining the framework of the Industry 4.0 model in the pharmaceutical industry, (ii) analysing the Pharma 4.0 project, as today's approach to the application of Industry 4.0 in the pharmaceutical industry, and (iii) expected directions of development of the application of AI and ML/DML in the Pharma 4.0 model.

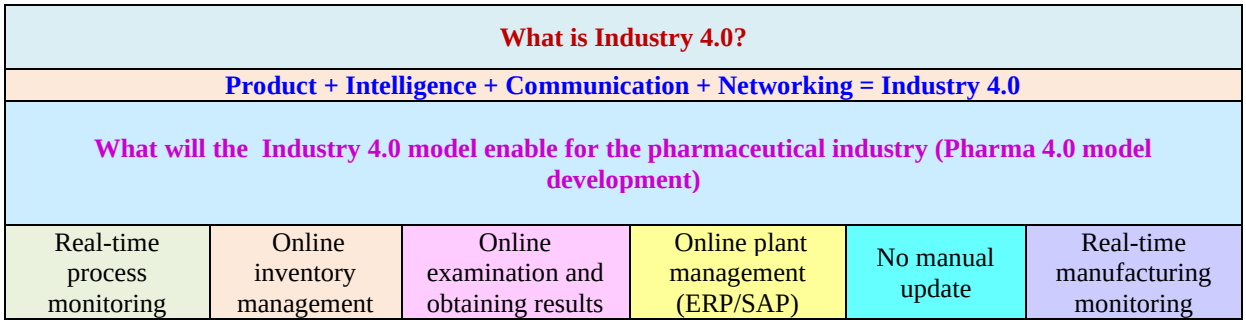

Figure 1: Basic characteristics of Industry 4.0 in pharmaceutical production
Adapted according to: (Barenji, et al., 2019; Binggeli et al., 2018; Coglaiti & UpDyke, 2022; Ephlux, 2024; EPRS, 2022; Herwig et al., 2017; Khan et al., 2022)

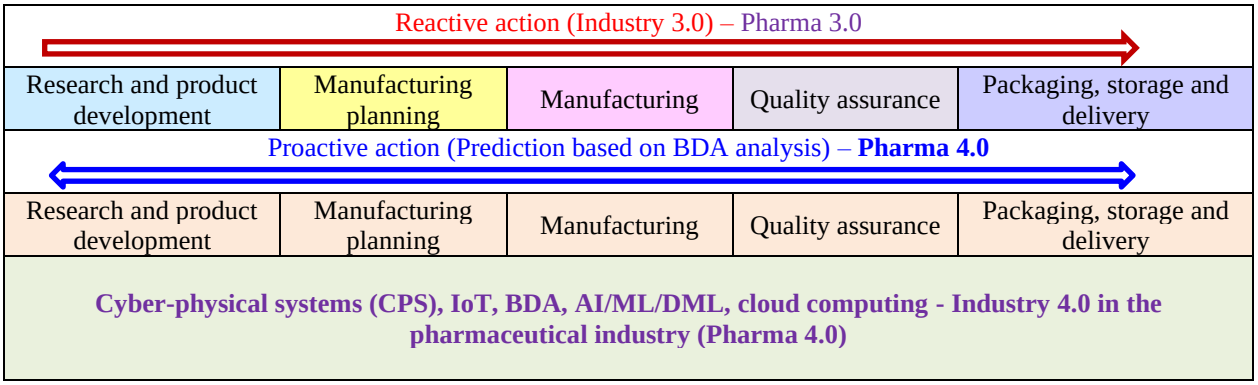

Figure 2: From today (reactive action) to cyber (proactive action) pharmaceutical manufacturing (Pharma 4.0)
Adapted according to: (Basset, et al., 2013; Hzrat et al., 2023; Herve et al., 2013; Reinhardt et al., 2020; Schneider Electric, 2024)

Under the influence of the Industry 4.0 model, in recent years, terms suitable for the application of the Industry 4.0 model have been increasingly used in pharmaceutical manufacturing: "Digital pharmaceutical manufacturing", "Pharma 4.0", "Smart pharmaceutical factory", "Intelligent pharmaceutical manufacturing", or "Factory of the future" in pharmaceutical manufacturing. All the mentioned terms represent a narrower or broader model of Industry 4.0 application in the pharmaceutical industry. This practically means that in pharmaceutical manufacturing, individually automated machines and the separate processes that take place on them will experience the full integration of all their entities into a single digital system of pharmaceutical manufacturing, which will be managed intelligently, using AI and machine learning techniques (ML/ DML), Figure 1 (Barenji, et al., 2019; Binggeli et al., 2018; Coglaiti & UpDyke, 2022; Ephlux, 2024; EPRS, 2022; Herwig et al., 2017; Khan et al., 2022).

Therefore, it can be said that the term Pharma 4.0 is essentially the same term for a pharmaceutical factory, as Industry 4.0 is for a manufacturing organisation from the metal processing industry, which means (Hariry et al., 2021; Mukhlas et al., 2022): (a) planning and monitoring of orders in real-time and based on this management of stocks of materials and raw materials of pharmaceutical products, also in real-time, (b) online monitoring of quality, incoming materials and raw materials, as well as of finished products, (c) online management of the pharmaceutical workshop (manufacturing) (ERP/SAP model), with monitoring of key business parameters, including manufacturing (KPI). What is the basic difference between today's pharmaceutical manufacturing model and the model representing the concept of Pharma 4.0 is shown in Figure 2 (Basset, et al., 2013; Hazrat et al., 2023; Herve et

al., 2013; Reinhardt et al., 2020; Schneider Electric, 2024). The application of the Industry 4.0 model in the pharmaceutical industry means the transition from automated process control and reporting of reactive events to predictive and event analytics (BDA) in the entire supply chain, manufacturing, packaging and delivery of drugs and medical devices.

The Pharma 4.0 model creates a key difference in process management in pharmaceutical manufacturing. Today's automation model in this area monitors and shows us how the process is currently taking place regarding the defined parameters (boundaries) and when a scrap may appear, so that the system under human supervision could react, which represents reactive action. The new approach in Pharma 4.0 is based on predictive analysis, which means that sensor systems collect large amounts of process data, which are systematically analysed (BDA) and based on which events are predicted, including, for example, future process quality parameters, enabling proactive control. This means that the potential occurrence of scrap is prevented in advance.

The key elements of Pharma 4.0 are: pharmaceutical cyber-physical systems (CPS), pharmaceutical Internet of Things (IoT), and pharmaceutical cloud computing, all supported by AI and machine learning (ML/DML) methods and techniques, which is a complete analogy with technological systems (Khan, et al., 2024; Kolluri et al., 2022). The goal of Pharma 4.0 is a smart pharmaceutical factory (Smart Pharmaceutical Factory), which has an intelligent manufacturing environment, in which manufacturing and logistics entities are organised to work mostly without human intervention. Networking of manufacturing entities and dynamic business, pharmaceutical and engineering processes enable profitable manufacturing according to personalised customer requirements (Adhikari et al., 2022; Ding, 2018). The complex digital model of Pharma 4.0 includes (Sharma et al., 2023; Tetteh et al., 2023): PLM of the pharmaceutical product that forms the basis for all other digital entities: supply chains, sales, manufacturing, quality control, outsourcing processes, transport and logistics.

The aim of Pharma 4.0 is to create a networked factory (using the Internet of Things) for a PLM model of pharmaceutical products (supported by ML/DML and BDA analyses), characterised by: (a) online monitoring of process and machine parameters according to regulatory requirements, thus enabling increased market and revenue (no scrap manufacturing), (b) minimising downtime due to sudden failures and smart maintenance (increasing revenue and reducing costs), (c) monitoring and forecasting complex KPI parameters (increasing productivity and revenue), and (d) eliminating all manual operations and performing automatic operations based on big data analysis (cost reduction), as illustrated in Figure 3 (Pansare et al, 2023; Soni, 2024).

Regulatory compliance and traceability (tracking via bar codes) *Increase in revenue/market growth*	Reducing unplanned downtime *Predictive maintenance* *Capital asset management* *Increase in revenue/market growth*
Monitoring and forecasting of complex business KPIs *Metrics for KPIs* *Predictive analytics of big data* *Increase in income*	Eliminate manual operations *Automated activities initiated based on predictive analytics and reactive information* *Cost reduction*

Figure 3: Key elements in the application of the Pharma 4.0 model
Adapted according to: (Pansare et al, 2023, Soni, 2024)

PHARMA 4.0 – PROJECT EXAMPLE

In 2017, the International Society for Pharmaceutical Engineering (ISPE) started the project: "Development of a Roadmap for the Application of the Industry 4.0 Model in the Pharmaceutical Industry". The global goal was the development of a smart pharmaceutical factory called Pharma 4.0 (ISPE, 2024; Sethu et al., 2021). The initial goal is to enable pharmaceutical organisations to use the full potential of digitalisation, in order to implement pharmaceutical innovations faster for the benefit of patients.

Although the name Pharma 4.0 symbolises the Fourth Industrial Revolution, its application is closer to evolution, towards a new model of automation in pharmaceutical manufacturing, in which digitalisation and automation manage very complex processes of the life cycle of pharmaceutical products. In addition, it is extremely important to understand the requirements for

additional digital elements in ICH Q10 - Pharmaceutical Quality System (Soni, 2024). Digitisation is a basic component of the Pharma 4.0 model, which defines and connects all levels of management in the pharmaceutical plant, as the basis for the manufacturing of medicines. Therefore, Pharma 4.0 is a holistic model for pharmaceutical factories and supply chains of the future, based on Industry 4.0 characteristics, digital maturity and data integrity for design, Figure 4 (Guilfoyle, 2018).

<table>
<tr><td colspan="2">Digital maturity</td></tr>
<tr><td>Automation, resources, digitisation, workforce 4.0</td><td>Vertical/horizontal integration of the entire manufacturing chain</td></tr>
<tr><td colspan="2">Pharmaceutical industry 4.0 (Pharma 4.0)</td></tr>
<tr><td>Predictive quality management, holistic management</td><td>Management of knowledge and skills, communication, decision-making</td></tr>
<tr><td colspan="2">Integrated project data (Products, Processes)</td></tr>
</table>

Figure 4: Holistic model of the drug factory 4.0, according to the Pharma 4.0 model
Adapted according to: (Guilfoyle, 2018)

This model was developed by the ISPE Special Interest Group (SIG), starting with the Industry 4.0 model, which is based on big data analytics and its connection (BDA), collaborative robotics, AI tools and cloud-based distributed network architecture, with the help of which they develop the basis for new drugs, which will be used for advanced therapies for new generations of patients. In this way, a chain is created between patient and clinical laboratories (personal advanced therapy) or patient and patient (clinical trials) (Ding, 2018).

Pharma 4.0 is a digital business model of a pharmaceutical organisation, based on a new automation model, which inaugurates the Industry 4.0 model. What are the origins of the evolution of the Pharma 4.0 model? What is its philosophy and how will it affect the future of pharmaceutical manufacturing? So, for example, in 2005, Dr Janet Woodcock (U.S. Food and Drug Administration, 2011; U.S. Food and Drug Administration, 2018) presented the vision of the US Food and Drug Administration (FDA) on pharmaceutical manufacturing good practice (GMP) for the 21st century as: "A maximally efficient and flexible pharmaceutical manufacturing sector, reliably producing high-quality medicines without extensive regulatory oversight." In addition, the International Council for Harmonization of Technical Requirements for the Registration of Pharmaceutical Products for Human Use (ICH), which supported this approach, defined a life cycle model for pharmaceutical products, document ICH Q12 (Pansare et al., 2023; Soni, 2024). The current quality management strategy in pharmaceuticals is based on individual process management (SPC), which ensures critical quality characteristics (CQA), and achieves the projected quality of pharmaceutical products. However, this approach does not allow for the management of changes that occur in manufacturing and are related to GMP, manufacturing entities, and outsourced processes, which would reduce the variability of the process, and thus the scrap. So we have, that the impact of unknown disturbances of process parameters, changes in material properties with the appearance of impurities in it, is not taken into account in SPC. As a result, it is difficult to predict these variations, which occur throughout the product's life cycle, such as those that occur during each phase of drug development (and there are twelve of them in total).

In case of changes to the product or process, using GMP documentation, the regulatory body is notified. When it is necessary to change the quality management model, and the changes come from product development, it should be done in such a way that it can be effectively applied in manufacturing (Juthuri, 2023). Data integrity is often a problem in the pharmaceutical value chain, primarily because of its robustness, making it difficult to implement. The quality management model in Pharma 4.0 is supplemented with four elements: resources, information system, holistic process model and culture (Soni, 2024). This model combines manufacturing quality management strategies and quality control strategies throughout the product life cycle. This approach enables the integration of digital maturity data and design data integrity, resulting in a holistic quality control strategy across the product life cycle. This implies the exchange of information in the decision-making hierarchy, in the value chain and network for the pharmaceutical product.

ICH Q10 defines critical quality characteristics (CQA), critical process characteristics (CPP) and critical material characteristics (CMA) in the product design phase (Vora et al., 2023; Zhavoronkov et al., 2020). On the other hand, ICH Q12 also defined key process characteristics (KPP); these are parameters of the manufacturing

process that may not be directly related to CQA but should be monitored in the process of moving to the Six Sigma model (manufacturing without scrap). That is why the parameters: KPP, CPP, CQA and CMA are defined in ICH Q12 as required conditions (EC). For these reasons, they are monitored through KPI process performance, and for parameters that are in trend or out of control limits. ICH Q12 provides guidelines for communication between regulatory bodies and regulatory organisations when changes to EC parameters occur, Figure 5 (Arabi, 2021).

Pharmaceutical manufacturing process parameters (ICH Q12) *Risk-based management (product quality, process performance)*	
KPP (Key Process Characteristics)	*CPP (Critical Process Characteristics)*
Product quality characteristics	
Critical Quality Characteristics (CQA)	*Critical Material Characteristics (CMA)*

Figure 5: Model of established conditions (EC) in ICH Q 12
Adapted according to: (Arabi, 2021)

Holistically defined processes on the pharmaceutical manufacturing platform ensure the fulfilment of a number of functional requirements, which are used for interdisciplinary knowledge management. All organisational units (internal and external) of pharmaceutical manufacturing are included here. In this way, all GxP (good practices) are integrated, using information technology (IT) (Singh, & Upkar, 2019). Thus, a model of the integrity of the relevant data was generated, from which big data for BDA analysis are created and used for decision-making. Also, a process analytics model (PAT) was developed (Michele et al., 2019), for highly automated manufacturing, which additionally enables the use of advanced technologies in pharmaceutical manufacturing. The four quadrants of the Pharma 4.0 operating model, Figure 4, are common in all phases of the pharmaceutical industry, but how they are implemented varies from plant to plant. It is important to point out that the digital maturity of pharmaceutical manufacturing defines its ability to work according to the Pharma 4.0 model. Based on these facts, the ISPE SIG has developed an assessment model, with which organisations determine where they are, and based on this, define holistic management strategies for their journey to Pharma 4.0.

Achieving digital maturity is a key factor that enables a pharmaceutical organisation to become agile, which means it is data and information-based. Figure 6 (Ding, 2018; Schuh et al., 2017;), tells us that the computerisation and connection of processes (islands of automation) were the basic characteristics of Pharma 3.0. In order for the organisation to work according to the Pharma 4.0 model, it is necessary to achieve data visibility and transparency, as well as their predictability and adaptability. Advanced technologies such as paperless work order management systems (MES), 3D printing, collaborative robotics, blockchain virtual reality (VR), augmented reality (AR), and other technologies can contribute to a faster path to the Pharma 4.0 model, as illustrated in Figure 4.

Industry	**1.0**	**2.0**	**3.0**	**4.0**
Resources	*Mechanically*	*Electric*	*Digitisation*	*Visibility*
Information system	*Individual work*	*Manufacturing process*	*Computerisation*	*Transparency*
Organisation and processes	*Craft manufacturing*	*Taylorism*	*Connectivity (Islands of Automation)*	*Prediction*
Culture	*Internal focus, adaptive behaviour*	*Internal focus, stabilising behaviour*	*External focus, stabilising behaviour*	*External focus, adaptive behaviour*

Figure 6: Digital Maturity Model for Pharmaceutical Organisations
Adapted according to: (Ding, 2018; Schuh et al., 2017)

It is important to point out that the integrity of patient safety data was just as important in the era of classic information systems, as it is today when we talk about the Pharma 4.0 model. For these reasons, it is always the focus of regulatory agencies (Ding, 2018; Mustapä et al., 2022). In the Pharma 4.0 model, data is spread throughout the entire value chain, so managing its integrity is a particular challenge. The data flow must be transparent, with a clear process flow to which it relates. In the

Pharma 4.0 model, the performance of business processes in the life cycle of a pharmaceutical product depends on the structural capabilities of the organisation. For example, if the organisation is strictly divided into organisational units, there is a high probability that the business-technical information systems are designed so that each unit forms its own "island".

The Pharma 4.0 model, based on a holistic strategy, overcomes this problem. Most often, we find that in a pharmaceutical organisation, as a rule, business processes are not fully defined and/or documented. It is important to point out that to work on the Pharma 4.0 project you must have defined processes and data flows. As a rule, this means that you have to start implementing an ERP (enterprise resource planning) model as well as an MES (work order management) model. In this case, it is important to point out that the MES model must be based on a well-structured, documented and validated software system, which is part of the Pharma 4.0 model. Ensuring data integrity is a prerequisite for ensuring good process traceability in the organisation. So, it is about the quality of the data, its content, the life cycle of the data and adherence to the principles of ALCOA $^{+}$ (a set of principles for ensuring the integrity of data for GMP) (Ding, 2018; U.S. Food and Drug Administration, 2016). That's why data integrity requires well-defined, robust and repeatable (but flexible) processes. The principles of risk management should also be applied, which must include basic knowledge about the structure and architecture of data. When defining a risk map in the ICH Q9 model, the most important step is risk identification. This process requires extensive experience, a clear view of risk and anticipation of possible disruptions. It is extremely important in this process to have available prior knowledge, in a structured form. "Resources" in this model refer to intangible and physical resources. This includes employees and their knowledge (human resources), machinery and equipment, tools, materials and the final product. Therefore, Cyber-Physical Systems (CPS) in Pharma 4.0 are rapidly adaptable and capable of producing diverse products with mass manufacturing efficiency (Manzano, 2018). Smart equipment "including products" has the ability to create different manufacturing configurations, thanks to the Pharma 4.0 model. Thus, PAT will monitor all KPP online and communicate using digital infrastructure with different partners in the manufacturing network, where new value is created. Also, new methods of process validation will enable continuous process improvement in the pharmaceutical organisation, especially in manufacturing (MES). Each product quality and process performance monitoring system in a pharmaceutical organisation can be explained by the RAMI 4.0 model, Figure 7 (Plattform Industrie 4.0, 2016).

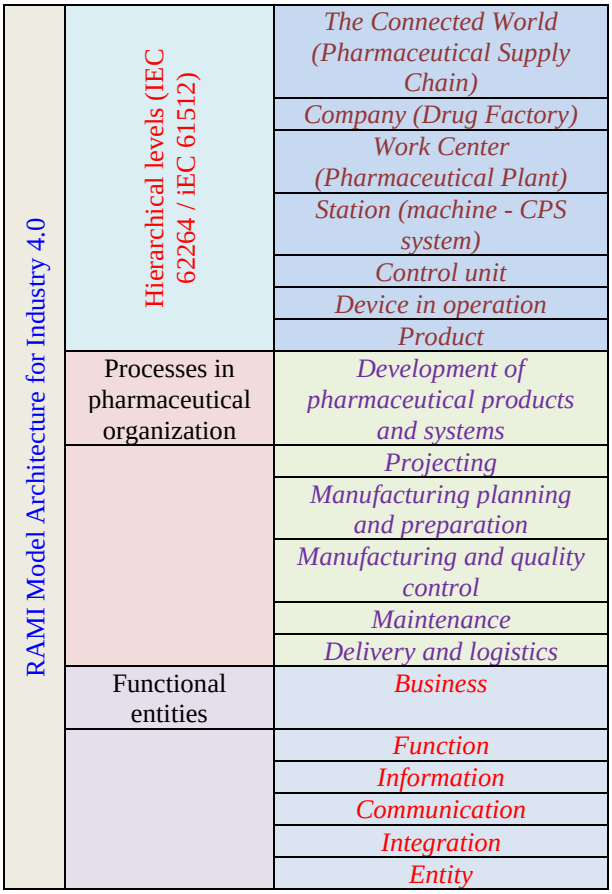

Figure 7: RAMI model architecture for Industry 4.0 and Pharmacy 4.0 (Plattform Industrie 4.0, 2016)

The integration layer in the RAMI model acts as an interface between the digital and physical worlds (i.e. the human-machine interface). The traceability and visibility of information are realised through the communication and information layer, which is used for predictive maintenance using VR with the support of AI. Each layer communicates through the value chain network via a single location throughout the pharmaceutical organisation (Arden et al., 2021). By designing, implementing and transferring information along all axes of the model, delay is reduced, product quality is improved and the business profit of the pharmaceutical company is increased. In the part of the model where we have information-rich nodes, the model helps the new human-machine communication, in terms of data collection and reporting on different bases. The

information system is the basis for the integration of all computer systems in the Pharma 4.0 model, both vertically according to the functions of the pharmaceutical organisation, and horizontally according to the network of the supply chain and the life cycle of the pharmaceutical product.

Process automation through data linking provides continuous process verification (CPV) using the PAT model, which monitors and predicts process parameters in real-time (Wölfle et al., 2022). This model has already been applied by some of the big pharmaceutical companies, forming their "data lake" through which they got a "single source" for system integration and ad hoc real-time reporting. In the Pharma 4.0 model, integrations include: predictive maintenance, environmental management, energy management, manufacturing automation (MES), continuous process verification (CPV), mass sterilisation, real-time performance monitoring, batch release and tracking, as well as traceability. For these reasons, ERP and MES systems must be integrated with equipment (CPS). The presented integration model must comply with global technical standards: Good Manufacturing Practice (GAMP) automation, ISO and IEC. Also, product development must be in line with the automation of manufacturing processes. In this context, a thorough understanding of data and information, a broad knowledge base and extensive experience are paramount for good decision-making at all levels (Amrich et al., 2022). Fulfilment of regulatory requirements, the application of a holistic management strategy, risk management, and well-defined business and manufacturing processes are key elements for managing the life cycle of a pharmaceutical product. Starting from these facts, the instructions for process validation given by ICH and FDA recommend flexible pharmaceutical manufacturing processes, including continuous process verification, by monitoring CQA and CPP parameters, thus ensuring high product quality (ISPE, 2024). In Pharma 4.0, however, the quality assurance concept must be adapted to the cross-functional business processes of the pharmaceutical organisation. In addition, the tasks and responsibilities of the system, the owner of cross-functional processes and the owner of their content must be redefined. A long chain of decisions is typical for pharmaceutical organisations, at the beginning of the development of the Pharma 4.0 project, it refers to specialised teams, which work according to the needs of the value chain network (Herve et al., 2013; Rawashdeh, et al., 2023).

Pharma 4.0 is a project that has multiple interconnected entities using IoT, requiring a pharmaceutical company to establish cross-functional teams, that will define step-by-step data integrity and determine the performance of a holistic management strategy. The application of Pharma 4.0 and the strategy of holistic management provides an integrated approach to the design and management of business processes, especially at the plant level (MES), without paper, in digital form. This means a new culture of cooperation between organisational units responsible for the manufacturing process, technology and quality. Due to these facts, some regulatory bodies are now looking for a defined strategy to manage the digitalisation of the pharmaceutical organisation, which makes sense given that the implementation of a holistic management strategy requires IoT solutions and other elements of Industry 4.0 (Dhingra, et al., 2020; ISPE, 2024). For these reasons, the organisational culture should be defined in such a way as to understand the importance of each element in the management strategy of the Pharma 4.0 model, and (ISPE, 2024): (i) clearly defined values of critical parameters, with which process disturbances will be detected, (ii) evidence-based risk is a key element for its management, and (iii) improvements of the Pharma 4.0 model in implementation should involve all interested parties, thus building the overall culture of the pharmaceutical organisation.

CONCLUSIONS AND FUTURE RESEARCH

When we summarise the results of the current application of the Industry 4.0 model in a pharmaceutical organisation, we can derive the following facts (Rawashdeh, et al., 2023; Swami, et al., 2022; Wanjul, et al., 2023; Wölfle, et al., 2022): (i) Pharma 4.0 is an Industry 4.0 model for the pharmaceutical manufacturing organisation, extended with regulatory regulations in the field of drug manufacturing, (ii) based on the previous characteristic, it erases borders, or more precisely, it connects the pharmaceutical industry, regulators, health care and other interested parties, (iii) as a new business model of a pharmaceutical organisation, it is the best framework for the manufacturing of new generations of drugs, (iv) applied PQS (Pharmaceutical Quality System) is a prerequisite for starting the Pharma 4.0 project in an organisation (Yu & Kopcha, 2017), (v) it is important to emphasise that Pharma 4.0 is not an IT project, because the operational model of Pharma 4.0, in addition to IT, includes: organisational and

cultural elements, processes (business, manufacturing) and from all aspects the resources of the pharmaceutical organisation, (vi) the Pharma maturity model 4.0 enables the harmonisation of the operational model of the organisation for innovative approaches to manufacturing, networking of suppliers and outsourced processes and bringing them to the required state, (vii) the application of the Pharma 4.0 model is not necessary (whereas digitalisation of the pharmaceutical organisation is), but is a competitive advantage of the organisation in the pharmaceutical industry.

Pharma 4.0 is the promising present and secure future of the pharmaceutical industry. Nevertheless, we can conclude that a greater application of AI and ML/DML than currently is inevitable, considering the following facts (Bhattamisra et al., 2023; Coglaiti & UpDyke, 2022; Haleem et al., 2023; Manufacturing Chemist, 2024): (i) thanks to BDA analysing processes in the pharmaceutical industry, its operations will be more predictable than ever before, primarily due to the application of deep learning models. Moreover,(ii) previous facts have a great influence on the development of the Industry 5.0 model, which means that this area will also move towards Pharma 5.0, as the pharmaceutical factory of the future.

In the context of the previous facts, the directions of future research can be: (i) decarbonisation of pharmaceutical manufacturing in the direction of regulatory requirements and their application in the Pharma 4.0 model, (ii) development of different platforms for the Pharma 4.0 model, according to the types and volume of pharmaceutical manufacturing, and (iii) personalised manufacturing of innovative medicines on previous platforms (Wanjul, et al., 2023).

REFERENCES

Adhikari, A., Maddulety, K., & Riaz, S. (2022). A study to identify the Pharma 4.0 influencing factors within the pharma supply chain. *SSRN Electronic Journal*. https://doi.org/10.2139/ssrn.4050444

Amrich, P., & Damayanti, R. (2022). Pharma 4.0 quality management challenge: A literature review. In *Proceedings of the International Conference on Industrial Engineering and Operations Management* (pp. 606–615).

Arabi, A. A. (2021). Artificial intelligence in drug design: Algorithms, applications, challenges and ethics. *Future Drug Discovery*. https://doi.org/10.4155/FDD-2020-0028.

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.

Bakator, M., Đorđević, D., & Ćoćkalo, D. (2019). Developing a model for improving business and competitiveness of domestic enterprises. *Journal of Engineering Management and Competitiveness*, *9*(2), 87–96. https://doi.org/10.5937/jemc1902087B.

Barenji, R. V., Akdag, Y., Yet, B., & Oner, L. (2019). Cyber-physical-based PAT (CPbPAT) framework for Pharma 4.0. *International Journal of Pharmaceutics*, *567*, 118448. https://doi.org/10.1016/j.ijpharm.2019.06.036.

Basset, H., Tunnah, P., & Spong, A. (2013). *The digital pharma industry*. In H. Basset, D. Stuart, D. Silber, & F. Boutin (Eds.), From Science 2.0 to Pharma 3.0 (pp. 97–148). Chandos Publishing. https://doi.org/10.1016/B978-1-84334-709-5.50004-1.

Bhattamisra, S. K., Banerjee, P., Gupta, P., Mayuren, J., Patra, S., & Candasamy, M. (2023, March 1). Artificial Intelligence in Pharmaceutical and Healthcare Research. *Big Data and Cognitive Computing*. MDPI. https://doi.org/10.3390/bdcc7010010.

Binggeli, L., Heesakkers, H., Wölbeling, C., & Zimmer, T. (2018). Pharma 4.0™: Hype or reality? *Pharmaceutical Engineering*, *38*(4), 40–44. https://www.ispe.org/pharmaceutical-engineering/july-august-2018/pharma-40-hype-or-reality

Coglaiti, H., & UpDyke, D. (2022). *Beyond Pharma 4.0: Pharma Manufacturing and Industry 5.0*. Manufacturing Chemist. https://manufacturingchemist.com/beyond-pharma-4-0-pharma-manufacturing-and-industry-5-0-207433

Dhingra, P., Gayathri, N., Kumar, S. R., Singanamalla, V., Ramesh, C., & Balamurugan, B. (2020). *Internet of Things–based pharmaceutics data analysis. In V. E. Balas, V. K. Solanki, & R. Kumar (Eds.), Emergence of pharmaceutical industry growth with industrial IoT approach* (pp. 85–131). Academic Press. https://doi.org/10.1016/B978-0-12-819593-2.00004-2.

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.

Ephlux. (2024). *Industry 4.0 solution for the pharma industry*. https://www.ephlux.com/industry-4-0-solution-for-the-pharma-industry-pharma4-0/

European Parliamentary Research Service - EPRS. (2022). *Artificial intelligence in healthcare: Applications, risks, and ethical and societal impacts (PE 729.512)*. Brussels. https://doi.org/10.2861/568473.

Guilfoyle, P. (2018). Northwest Analytics, *Pharma 4.0:*

Industry 4.0 applied to pharmaceutical manufacturing. Pharmaceutical Processing World. https://www.pharmaceuticalprocessingworld.com/pharma-4-0-industry-4-0-applied-to-pharmaceutical-manufacturing/.

Haleem, A., Javaid, M., Singh, R. P., & Suman, R. (2023). Exploring the revolution in healthcare systems through the applications of digital twin technology. *Biomedical Technology*, *4*, 28–38. https://doi.org/10.1016/j.bmt.2023.02.001.

Hariry, R. E., Barenji, R. V., & Paradkar, A. (2021). *From Industry 4.0 to Pharma 4.0*. In C. M. Hussain & P. Di Sia (Eds.), Handbook of Smart Materials, Technologies, and Devices (pp. 1–22). Springer. https://doi.org/10.1007/978-3-030-58675-1_4-1.

Hariry, R. E., Barenji, R. V., & Paradkar, A. (2022), Towards Pharma 4.0 in clinical trials: A future-oriented perspective. *Drug Discovery Today*, *27*(1), 315–325. https://doi.org/10.1016/j.drudis.2021.09.002.

Hazrat A., Junaid Q., Tanvir A., Mowafa H., Zubair S., *Healthcare Transformation with Informatics and Artificial Intelligence*, Studies in Health Technology and InformaticsEbookVolume 305: Healthcare Transformation with Informatics and Artificial Intelligence, J. Mantas et al. (Eds.), 2023, 10.3233/SHTI230533.

Herve P., & Joe, C. (2013). Information systems for enterprise integration, interoperability and networking: theory and applications. *Enterprise Information Systems, Taylor & Francis*, *7*(1), pp.1-6. https://doi.org/10.1080/17517575.2012.684802

Herwig, C., Wölbeling, C., & Zimmer, T. (2017). A holistic approach to production control: From Industry 4.0 to Pharma 4.0. *Pharmaceutical Engineering, 37*(3), 44–49. http://hdl.handle.net/20.500.12708/146557.

ISPE (2024). *Pharma 4.0™.* https://www.ispe.org

Juthuri, P. K. (2023). Role of enterprise applications for pharmaceutical drug traceability. *Universal Journal of Pharmacy and Pharmacology*, *2*, 41–46. https://doi.org/10.31586/ujpp.2023.812

Kagermann, H., Wahlster, W., & Helbig, J. (2013). *Securing the future of the German manufacturing industry: Recommendations for implementing the strategic initiative Industrie 4.0*. Final report of the Industrie 4.0 Working Group. Acatech – National Academy of Science and Engineering. https://www.acatech.de/wp-content/uploads/2018/03/Final_report__Industrie_4.0_accessible.pdf.

Karabegović, I., & Majstorović, V. (Eds.). (2024). *Industry 4.0: Digital transformation shapes the future.* Academy of Sciences and Arts of Bosnia and Herzegovina.

Khan, M. I., Haq, M. A. U., Khan, M., Ghouri, A., & Farooqi, R. (2024). *Industry 4.0 or Pharma 4.0?: Assessing suitability, benefits, challenges, and opportunities for healthcare supply chains*. In H. Kohl, G. Seliger, & F. Dietrich (Eds.), Manufacturing driving circular economy (pp. 319–341). Springer. https://doi.org/10.4018/979-8-3693-1363-3.ch012.

Khan, S., Tomar, S., Fatima, M., & Khan, M. Z. (2022). Impact of artificial intelligent and Industry 4.0 based products on consumer behavior characteristics: A meta-analysis-based review. *Sustainable Operations and Computers*, *3*, 218–225. https://doi.org/10.1016/j.susoc.2022.01.009.

Kolluri, S., Lin, J., Liu, R., Zhang, Y., & Zhang, W. (2022). Machine learning and artificial intelligence in pharmaceutical research and development: A review. *AAPS Journal*, *24*(1), 19. https://doi.org/10.1208/s12248-021-00644-3.

Manufacturing Chemist. (2024). *Pharma 5.0: Regular news and updates on manufacturingchemist.com.* https://www.manufacturingchemist.com/introducing-pharma-5-0-the-future-of-pharmaceutical-innovation.

Manzano, T., & Langer, G. (2018). *Getting ready for Pharma 4.0: Data integrity in cloud and big data applications*. Pharmaceutical Engineering, September–October, 72–79. https://ispe.org/pharmaceutical-engineering/september-october-2018/getting-ready-pharma-40.

Mukhlas, A., Talip, B., Mustapha, J., & Ismail, S. (2022). Industry 4.0 (IR 4.0) for pharmaceutical industry: An exploratory review. In *2022 International Visualization, Informatics and Technology Conference (IVIT)* (pp. 103–109). IEEE. https://doi.org/10.1109/IVIT55443.2022.10033386.

Mustapä, T., Nummiluikki, J., & Viitala, R. (2022). Digitalization of calibration data management in the pharmaceutical industry using a multitenant platform. *Applied Sciences*, *12*(15), 7531. https://doi.org/10.3390/app12157531.

Pansare, M., Pansare, J., Dashpute, S., Erende, S., Sonawane, P., Jadhav, S., & Patil, D. (2023). Digital advancement and transformation in pharma sector – a review. *International Journal of Scientific Development and Research*, *8*, 1110–1122. https://www.ijsdr.org/.

Plattform Industrie 4.0. (2016). *Reference architectural model Industrie 4.0 (RAMI 4.0)*. DIN SPEC 91345:2016-04. https://ec.europa.eu/futurium/en/system/files/ged/a2-schweichhart-reference_architectural_model_industrie_4.0_rami_4.0.pdf.

PRISMA. (2024). *Systematic reviews and meta-analyses: PRISMA statement*. https://www.prisma-statement.org/.

Rawashdeh, O., & Jawabreh, O., & Ali, B. (2023). Supply Chain Management and Organizational Performance: The Moderating Effect of Supply Chain Complexity. https://doi.org/10.18576/isl/120351

Reinhardt, I. C., Oliveira, J., & Ring, D. (2020). Current perspectives on the development of Industry 4.0 in

the pharmaceutical sector. *Journal of Industrial Information Integration, 18*, 100131. https://doi.org/10.1016/j.jii.2020.100131.

Schneider Electric. (2024). *Pharma 4.0 for plant manufacturing: A roadmap to the future.* https://www.se.com/rs/sr/download/document/Pharma4.0_eGu_/

Schuh, G., Anderl, R., Gausemeier, J., Kagermann, H., Krüger, A., Hompel, M., ... & Harland, T. (2020). *Industrie 4.0 Maturity Index: Managing the digital transformation of companies – Acatech study (Rev. ed.)*. Munich: Herbert Utz Verlag. https://www.en.acatech.de/publication/industrie-4-0-maturity-index-managing-the-digital-transformation-of-companies/.

Sethu, A., Durai, T. A. K., Beeraka, N. M., Pujar, G., Singh, M., HS, A., & Meduri, B. (2021). Machine learning and deep learning in data-driven decision making of drug discovery and challenges in high-quality data acquisition in the pharmaceutical industry. *Future Medicinal Chemistry, 14*. https://doi.org/10.4155/fmc-2021-0243.

Sharma, D., Patel, P., & Shah, M. (2023). A comprehensive study on Industry 4.0 in the pharmaceutical industry for sustainable development. *Environmental Science and Pollution Research, 30*, 90088–90098. https://doi.org/10.1007/s11356-023-27957-7.

Soni, Sanket & Patel, Ankitkumar. (2024). Digital transformation and industry 4.0 in pharma manufacturing: the role of iot, ai, and big data. Journal of Integral Sciences. 1-8. 10.37022/jis.v7i4.92.

Swami, A. R., Shafi, S., Hangargekar, S., Ugale, P., Paratkar, G., & Dharashive, V. (2022). Artificial intelligence in pharma sector: Applications and future scope. *International Journal of Pharmaceutical Research and Applications, 7*(5), 1064–1071. https://ijprajournal.com/issue_dcp/ArtificialIntelligenceinPharmaSectorApplicationsandFutureScope.pdf.

Tetteh, M. G., Jagtap, S., & Salonitis, K. (2023). *Pharma 4.0: Revealing drivers of the digital transformation in the pharma sector. In H. Kohl, G. Seliger, & F. Dietrich (Eds.), Manufacturing driving circular economy. GCSM 2022. Lecture Notes in Mechanical Engineering (pp. 528–535).* Springer. https://doi.org/10.1007/978-3-031-24823-8_62.

U.S. Food and Drug Administration. (2011). *Q8, Q9, and Q10: Questions and answers (R4)*. ICH Revision 1. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/q8-q9-and-q10-questions-and-answers-r4.

U.S. Food and Drug Administration. (2016). *Data integrity and compliance with current good manufacturing practice: Guidance for industry*. Center for Drug Evaluation and Research. https://www.fda.gov/files/drugs/published/Data-Integrity-and-Compliance-With-Current-Good-Manufacturing-Practice-Guidance-for-Industry.pdf.

U.S. Food and Drug Administration. (2018). *Process validation: General principles and practices. Guidance for Industry.* https://www.fda.gov/media/71021/download.

Vora, L. K., Gholap, A. D., Jetha, K., Thakur, R. R. S., Solanki, H. K., & Chavda, V. P. (2023). Artificial intelligence in pharmaceutical technology and drug delivery design. *Pharmaceutics, 15*(7), 1916. https://doi.org/10.3390/pharmaceutics15071916.

Wanjul, P. B., Parshuram, M. S., Laxman, G. V., & others. (2023). Future directions of AI in pharma: Innovation in pharmaceutical industry. *International Journal for Multidisciplinary Research (IJFMR)*. https://www.ijfmr.com/papers/2023/3/3098.pdf.

Wölfle, R., Saur Amaral, I. A., & Teixeira, L. (2022). Pharma in the context of Industry 4.0 – Challenges and opportunities based on literature review. In Proceedings of the *5th European International Conference on Industrial Engineering and Operations Management*, Rome, Italy, July 26–28, 2022 (pp. 1038–1051). https://ieomsociety.org/proceedings/2022rome/207.pdf.

Yu, L., & Kopcha, M. (2017). The future of pharmaceutical quality and the path to get there. *International Journal of Pharmaceutics, 528*(1–2), 354–359. https://doi.org/10.1016/j.ijpharm.2017.06.039.

Zhavoronkov, A., Vanhaelen, Q., & Oprea, T. (2020). Will artificial intelligence for drug discovery impact clinical pharmacology? *Clinical Pharmacology & Therapeutics, 107*(4), 780–785. https://doi.org/10.1002/cpt.1795.

KA FABRIKAMA BUDUĆNOSTI U FARMACEUTSKOJ INDUSTRIJI

Industrija 4.0 je dostigla svoju zrelost u proizvodnji, nakon više od decenije primene. S obzirom na to da predstavlja ključni element za digitalizaciju privrede i javnih usluga širom sveta, danas je reč o primeni ovog koncepta u različitim oblastima, uključujući farmaciju, a pre svega farmaceutsku industriju. Cilj ovog rada je da čitaocu pruži najnovije informacije o stanju razvoja modela Pharma 4.0 (primena modela Industrija 4.0 u farmaceutskoj industriji na putu ka pametnoj fabrici), koji je počeo da se razvija u drugoj polovini druge decenije ovog veka. Rad se sastoji iz nekoliko delova, i to: (i) analiza okvira modela Pharma 4.0, (ii) detaljan prikaz modela Pharma 4.0 i (iii) neka zapažanja o budućem razvoju ovog modela u primeni.

Ključne reči: Industrija 4.0; Farmaceutska industrija; Pharma 4.0; Pametna fabrika.