Pharma in the Context of Industry 4.0 - Challenges and Opportunities Based on Literature Review

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Abstract

This paper aims to explore the main challenges facing the pharmaceutical industry today, as well as the potential opportunities offered by emerging Industry 4.0 technologies that can help address these challenges. To this end, a systematic literature review (SLR) based on a search with the keywords "Pharma" and "Industry 4.0" for identification, selection, and evaluation of the published research in this area, was performed. Thus, following this approach, two main questions were attempted to be answered: (i) "*What is the As-Is situation that characterize the today's pharmaceutical production*"; and, (ii) "*How technological perspective presents itself as a possible To-Be situation by the use of I4.0 concepts*". The key contribution of this research lays in the exploration of different obstacles in the current way how pharma is operating and what concepts from Industry 4.0 are in place to overcome them. The conclusion shows that the special situation in pharma due to its strong regulation by external authorities needs special ways of process design.

Keywords
Industry 4.0, Pharma 4.0, Smart Manufacturing, Pharmaceutical Production; Challenges and opportunities

1. Introduction
Today's pharmaceutical production facilities mostly allow one type of drug, active ingredient or dosage to be processed on one production line at a time (Sarkis et al., 2021). New technology makes it feasible from a technical perspective to change that in the coming years. Traditional approaches become challenged, practices and business models for the manufacture of pharmaceuticals change by new possibilities and ways of thinking (Arden et al., 2021; Reinhardt et al. 2020).

Nevertheless, every drug production has to follow the globally recognized GMP (Good Manufacturing Practice) guidelines harmonized by The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH 2000) or their national adoptions. In order to have an answer to upcoming dosage forms such as 3D printed medicines, personalized liquid active ingredients or continuous production Pharma must open up new processes and production strategies (Stegemann, 2016). Activities in process monitoring and the execution of critical work steps that were previously carried out by humans must be supplemented by technical aids or replaced by new process steps (Steinwandter et al. 2019).

Concepts like smart or workerless factories following ideas from Industry 4.0 seem to be more present in the automotive or consumer electronics sector. Advantages coming from these concepts are things like mass customization of products while keeping their prize low and thus affordable for many people. We argue that such ideas can be transferred to the pharmaceutical sector which may embrace the opportunity of producing personalized medicines. Big pharma companies could serve the market using small batch approaches as soon as their production capabilities are flexible enough to react on fluctuating demands of their customers. Small and medium sized companies could work on continuous single dose production sites for rare diseases or personalized medicines for exclusive use of one person.

To understand how a smart pharma factory could be put in place, this paper explores the current state of research concerning the possible use of Industry 4.0 (I4.0) technology and methods for upcoming tasks in pharmaceutical production. A systematic literature review provides information about what is important for future research and what possible solutions from I4.0 could be. The “As-Is” situation in pharma and the “To-Be” situation enabled by I4.0 lead to a research gap.

This paper is structured in four sections. After the introduction in section 1, section 2 outlines the methodology adopted for this research, which was based on a Systematic Literature Review (SLR). Section 3 focuses on the summary of the reviewed content and the conclusion derived from the clustering of the different topics. The conclusion and final remarks are formulated in Section 4.

2. Methodology

A Systematic Literature Review (SLR) as guided process to review the current state of the art for the combination of pharma and Industry 4.0 is the main part of this paper.

2.1 Systematic literature review

The goal of this SLR is to get the state of the art in terms of how the pharmaceutical branch and its researchers adopt Industry 4.0 theory. To understand this situation, we considered important for this research paper to contribute to the development process towards smart pharmaceutical manufacturing techniques.

The document search is performed in the Current Contents Connect section of Web of Science database because the topic is relatively new, and this database offers high quality content. The common keywords used in this field of knowledge are “Pharmaceutical Manufacturing”, “Pharma 4.0”, “Industry 4.0” or “Fourth industrial revolution”. As the search term the following expression is used in the field Topic which includes title, abstract, author and keywords. The search is not case sensitive therefore there is no need to make a distinction between upper and lower case.

"Pharma*" AND ("Industry 4.0" OR "Industry4.0" OR "Fourth industrial revolution" OR "Industrie4.0" OR "Industrie 4.0" OR "Pharma4.0" OR "Pharma 4.0")

Pharma with the asterisk will lead to results that include the term “Pharma” with all related words like pharmaceutical, pharmacology and else. The other terms are equivalents to Industry 4.0. The final search result is 44 articles in this database (Figure 1).

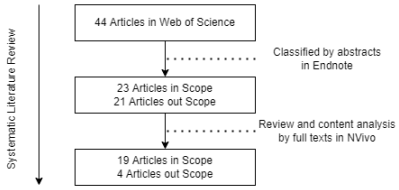

Figure 1. Systematic Literature Review Process

The dataset was exported as Full Record to Endnote 20. Next, an unstructured review of the titles and abstracts was performed. Papers that contained information about pharma production and organization related topics with orientation towards Industry 4.0 were considered relevant, while papers related to more general healthcare or medical devices sector were considered out of scope, as these are not within pharma business. Also, not relevant were papers about research in the sector of drug substances or ingredients, as these could not be related to the general manufacturing design processes. Modern manufacturing of drugs with 3D printer approaches was a different field of research that focused on material processing within a printer unit and not on general process design.

The application of the beforementioned criteria resulted in 23 relevant results and 21 were excluded. The remaining documents were exported to NVivo with their full text. In this software the coding procedure was carried out. The texts were analyzed based on their relevance and the information was structured as follows.

Papers were sorted after their methodology and research question as well as the main two questions as they are "As Is" in pharma and "To Be" with I4.0 concepts. Four articles did not fit within these questions and were excluded. This full-text review resulted in 19 articles with relevance for the research question.

Eight papers discussed frameworks for smart factories, while all others focused on particular questions from the field of implementing I4.0 technology. Nine documents used Case Study as methodology, five were set up as a Literature Review, three followed the concept of a quantitative research, while the other papers had unclear methodology.

Figure 2 shows the 19 relevant articles summed up according to their year of publication. The bar graph shows the number of papers per year indexed on Web of Science. The constantly increasing number shows that the research topic is relevant and in focus of the researching community. First articles with the chosen keywords appear in 2015 which shows that the topic is recent.

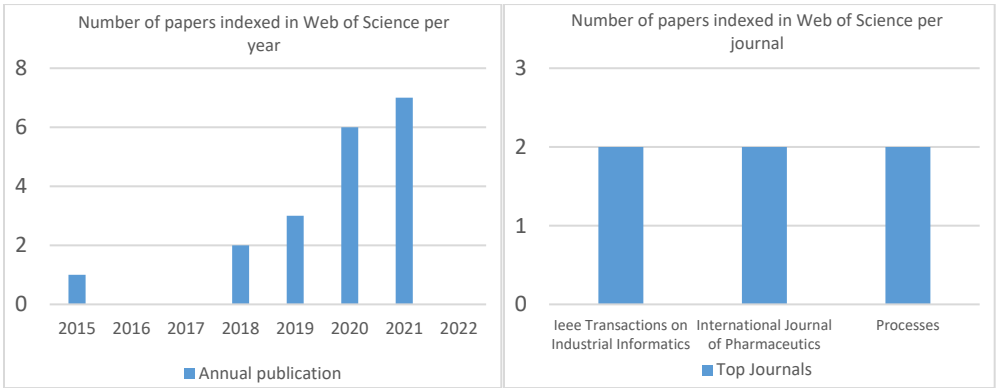

Figure 2. Annual publication and top journals

An evaluation concerning top authors and journals in this sector is noticeable. There is no data which point to leading authors. There are three journals that published more than one article (Figure 2).

3. Systematic Literature Review results

This section focuses on the information gathered while reviewing the articles chosen by the SLR process. The key statements are structured within two categories. One part focuses on the challenges for pharmaceutical production, the other on concepts from Industry 4.0 perspective with potential to solve the identified challenges. The individual sections result in a synthesis of the reviewed elements.

3.1 Contemporary Challenges for Pharmaceutical Production

The pharma world faces similar challenges as other high-tech industries around the globe, e.g. by being connected through a global supply chain with all its disadvantages in these uncertain times, by competing for the one of the most valuable resources among all, humans with education in highly specific areas.

However, something special for the Pharma Branch are its regulatory authorities, e.g. FDA (US Food and Drug Administration) or EMA (European Medicines Agency). They constantly work on regulations that secure drug quality and continuously improve the way how development, production and supply of pharma products is handled and can be monitored by the involved stakeholders. And also, they put in place specific constraints in pharmaceutical production which may delay or even hinder pharmaceutical innovation.

In this section, and given the particularities of this type of industry, some of the main challenges that the pharmaceutical industry faces today will be presented and discussed.

3.2 New demand for personalized medication

The past decade brought new technological possibilities to development and manufacturing of drugs. Cell based therapeutics and vaccines offer a reasonable potential for personalized medication based on the specific disease structure of a single patient (Sarkis et al. 2021). This approach also meets market requirement as for example the number of old people with chronic diseases is increasing and with that the need for more tailored pharmaceutical products becomes relevant. Stegemann (2016) derived from this tendency that there will be a shift in the production approaches of modern pharmaceutical companies such as “combined medication regimes for specific populations, or even “zero lag” real-time production for individual demand”. To have the possibility to produce drugs “on demand” in an economically reasonable manner there is a need for switching operation from batch based to continuous manufacturing (Lee et al. 2015). Creating new value from individual drug therapy is a motivational factor for the pharma branch. Value in form of revenue (Stegemann 2016), environmentally sustainable processes for example through waste reduction (Gernaey et al. 2012) or shorter time-to-market with less effort for scale up of commercial production (Jelsch et al. 2021; Lee et al. 2015).

3.3 New ways of product distribution by changes in the pharma supply chain

The behavior of the society in terms of purchasing consumer goods changed the past century by given new opportunities like online shops and same day delivery. These convenient ways to purchase products also affect the Pharmaceutical Supply Chain (PSC) as things change from traditional wholesale and pharmacies structure to Online Shop based supply. Ding (2018) stated main challenges in this topic such as “additional human involvement, end-to-end collaboration, sustainable issues, safety and disastrous consequences if there are any mistakes”. To keep up with these challenges and see them as opportunities pharma need to implement a smart and sustainable PSC with a holistic view of the product life-cycle (Narayana et al. 2014). Decentralization of pharmaceutical production affects the PCS directly by changing the process and distribution network adding a new level of complexity to it but on the other hand also new capabilities to solve current problems and meet future demands (Sarkis et al. 2021). New players like Amazon or Google have the potential to disrupt the branch through their lead in high tech innovation (Baines et al., 2020). Distributed and on-demand manufacturing could also be a key element for new ways within the PSC. Drugs with individual dosage and shape can be produced by a 3D printer with low effort for a small number of products. This could improve the accessibility of special drugs in pharmacies, emergency rooms or ambulances (Norman et al.,2017) and minimize the need for complex supply chain monitoring. These possibilities directly affect the PCS because it seems that there is no need for large centralized pharma production facilities for drugs with ingredients that can be handled by such additive manufacturing equipment.

3.4 New operation paradigms

The technological innovation during the past years in terms of computational power, machine learning and digitalization enable new ways of production and therefore change the way production is organized and carried out. New paradigms bring the necessity of new skills which results in knowledge and training gaps if not introduced well (Arden et al. 2021). New operation paradigms include the fundamental change from batch based to a more continuous form of production with close-loop control of the process and on-line quality measurement and management (Lee et al. 2015). Continuous production is defined as a system that gets constantly supplied with raw material and products are continuously discharged from the system (Leuenberger 2001). To enable such concepts, new production design and control strategies have been introduced by regulatory authorities like FDA. O'Connor et al. (2017) describe a way how Quality-by-Design can change the way how manufacturers set up production steps and equipment according to science- and risk-based approaches to identify critical quality attributes (CQA) and critical process parameter (CPP). Jelsch et al. (2021) discuss how these identified attributes can be transferred to a new control strategy named Quality-by-Control (QbC) that could lead to more robust processes and less product quality variations using real-time data. Using such modern monitoring and control technics could lead to better quality than the current six sigma target (Arden et al. 2021). These new ways of operation also enable concrete patient-specific therapeutics scenarios that can not be produced using current large batch manufacturing concepts (Sarkis et al. 2021). These methods seem to be in a research state and not shared or implemented across the whole industry. The reviewed literature lacks examples for already implemented solutions.

3.5 From quality control to deep process understanding

A reasonable number of articles in this literature review show that digitalization is an often-discussed task within the pharmaceutical branch. The authors link this topic to challenges like a shift from "controlling processes to enabling human understanding of the operations" (Arden et al. 2021). This can be supported by visualization of data and segmentation of digitized manufacturing operations (Arden et al. 2021). Digital process modeling helps to understand dynamic production effects caused by material properties or operation conditions. Based on such models, analysis and optimization can be performed. The task here is to get all the knowledge necessary to set up sufficiently accurate process models (Chen et al., 2020). Such process design concepts will be key to effective process control and reliable quality (Ding 2018). According to the US Food and Drug Administration (2004) Process Analytical Technology (PAT) and Real Time Release Testing (RTRT) deliver relevant data sources for process model evaluation and process control. Also from authority perspective deep process understanding is also a way to improve product quality based on scientific approaches and quality risk management (EMA 2017).
The circumstance that FDA published its implementation guideline for PAT and RTRT in 2004 which technics are still stated as "under development" and implementation in a reasonable number of articles shows us that there is a need for further support for the pharmaceutical branch in understanding and implementing such methods.

3.6 Regulatory authority

A circumstance that makes the pharmaceutical industry unique is its strong regulation by national authorities. Some of them have more guiding character like the EMA (Leal et al., 2021) others such as the FDA act more as a control instance with the ability to lock down complete production facilities. This results in a serious problem for the whole branch when it comes to the adoption of newer technologies. The lack of precedent within pharma companies lead to regulatory uncertainties and this could be a reason for companies to not invest in new technology. Pharma firms tend to follow a "first to be second" approach which means that they observe their competitors new manufacturing technologies and wait how regulators respond to them (Arden et al. 2021). Changing approved or implemented processes or products need a regulatory registration and acceptance which is another challenge for the adaption of new methods and technologies (Sarkis et al. 2021). The latest implemented technologies such as continuous manufacturing or adaptive control systems challenged the process validation procedure as their aim is to collect data that is capable to show that a process can run stable under certain conditions. These technologies depend on continual change of the monitored parameters which makes regulatory oversight a challenge (Arden et al. 2021).

As the national authorities around the globe do not have the same set of rules and guidelines it is a task for the pharma companies to launch their products within the regulatory authority of each country. Europe has its EMA that is a central agency and lowers the barrier to market access and eases regulatory measures (Leal et al. 2021). To have a worldwide applicable guideline for development, production and distribution of drug products the ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human use) was founded (Steinwandter et al. 2019).

From our perspective it is necessary to have this kind of common regulation for the whole branch to lower the burden for investments in new equipment. Pharma companies need security that innovative products related to latest technology will be accepted in all of their sites independent under which regulatory influence they are.

3.7 Organizational structure and data handling

Pharma companies are often organized in a department-based structure with dedicated competences and specified interfaces and relationships in-between each other. These different expert groups use tools and databases that fit best to their task. Quality management uses special tools that are valid for pharmaceutical quality management. Project manager use different project management systems. Sometimes production documentation is still paper based. This variety of data storage methods is an obstacle for process monitoring or optimization approaches that need to have the "big picture" to take into account all relevant parameters (Finelli & Narasimhan, 2020). The transfer of historical data to an active support or decision-making system by the use of artificial intelligence can only be successful if the existing data is structured, available and valid for such a task (Arden et al. 2021; Z. S. Wang et al. 2021).

In the context of digital transformation pharma companies have to overcome their data silos and need to implement shared and accessible data models to enable data-driven applications. Without this data structure most machine learning projects need time-consuming manual efforts to extract relevant datasets out of the distributed sources (Finelli & Narasimhan 2020). Such a system for data sharing between company organs needs to make sure that the quality of data is always given and controlled. Quality in this context means that there are transparent mechanisms for data capture, governance and compliance to ensure the data authenticity. The implementation of the ALCOA principle is one way to proof the quality of pharmaceutical relevant data. This mechanism stands for data that is attributable, legible, contemporaneous, original and accurate (Leal et al. 2021).

3.8 Environmental challenges

The production of pharmaceutical products includes different process steps with demand for different forms of process energy such as heat, cool, vacuum or pressured air. Other process materials can be clean water, clean air or other process gas. Packaging material such as cartons, labels or foil also have direct impact on the carbon footprint that is generated during production. Their current main focus is to get the highest possible product quality and not that they are used in a resource efficient manner (Steinwandter et al., 2019). Industry relevant documents like the ICH Guideline Q8 (2017) indicate that producing pharma companies shall implement ways of developing high quality medicines in most resource efficient ways. Optimization in terms of waste management and organizational changes within pharma companies could help to improve more environmentally friendly drug production (Bamakan et al., 2021). Besides the possibility of efficiency improvement during production there is one more important way to impact environmental challenges. Expired or unused drugs that are disposed by private households is pharmaceutical waste the gets uncontrolled into the local waste water with unpredictable effects (Shah et al. 2016). US and EU enacted regulations that should take care of these drawbacks but they do not focus on low-carbon processes and are not relevant in developing countries (Ding 2018).

After all, process efficiency is one thing but reducing the number of unused products to a minimum seems to be way more effective to us. On-demand production with low process energy input sounds very promising to solve the already relevant environmental challenges.

3.9 Synthesis of key elements

The described challenges for pharmaceutical manufacturers showcase a strong relation to digital transformation and show the need for structural changes to enable the use of new technology and processes. Caused by the wait-and-see behavior as development concept of the pharma production branch and the relationship between producing companies and regulatory agencies need new ways of communication to speed up innovation. New production and distribution methods are necessary to keep up with customer requirements and to lower environmental impact. Data is acknowledged by researchers and companies to be the main driver for future optimization and product innovation. Therefore, data needs be treated as important source of information for holistic production planning and monitoring and shared among different stakeholders that can trust the quality and use it for decisions.

3.10 Industry 4.0 concepts with potential to address pharma challenges

The core topic of the fourth industrial revolution is described as a smart factory that brings together intelligent automation systems on hard- and software level (Barenji et al. 2019). New concepts in Industry 4.0 context depend on data that is linked to a purpose and communicated with highest quality standards. The combination of advanced manufacturing technologies and advanced regulatory systems enable real time quality measurement and assure production performance within the pharmaceutical industry (Arden et al. 2021). The use of information in digital and structured form enables process modelling and simulation or decentralized decision making which are necessary for new pharma production concepts (Coito et al. 2020). New technology will help to establish more robust and agile processes with higher level of quality (Tjahjono et al. 2017) and supports the concept of mass customization for personalized drugs and fast reaction to changing demand (Qin et al. 2016). Innovation in the pharma branch needs to take the human nature in to account as he needs to be ready for such a change and needs to accept new ways of acting (Reitze et al., 2018). As regulatory agencies are involved in all the main actions from product development to supply chain mechanisms of the final product this must be considered for every concept with relation to Industry 4.0 topics. Documentation during the development of equipment and system design that allows regulatory insights will increase the acceptance for new technology (Steinwandter et al. 2019).

3.11 Real Time monitoring and Data analysis

With Industry 4.0 concepts arrived for extensive data analysis with possibilities to ensure product quality by defined critical control points and product acceptance criteria. With that production processes can be continually optimized by changing parameters without influencing product quality. Process validation can then happen possibly simultaneously to production which is relevant for reconfigurable processes (Arden et al. 2021). Continuous and automatic optimization can have positive effects to product cost and energy management which contributes to environmental impact measures (Ding 2018). Statistic process models and soft sensors that combine different measurable values and physical laws to unmeasurable values to predict cause, effects and countermeasures based on real time data. This information can help to influence production parameters or to make general decisions with better decision options (Jelsch et al. 2021). Data needs context and quality to be able to support decision making.

ALCOA compliance and data integrity checks close to the data source ensure relevance and significance (Leal et al. 2021). As the numbers of relevant measured values and their impact on process control systems constantly grows new approaches in data analysis are used. For single values it can be sufficient to use the traditional approach by assigning upper and lower control limits to a parameter with an OoS (Out of Specification) event in case that these limits are exceeded. For multivariate systems it can happen that a process can be OoS even if all measured values are in range. Tools to implement such systems are in the field of multivariate statistics and can be principal component analysis (PCA), partial least squares (PLS) or squared prediction errors (SPE) (Steinwandter et al. 2019). Real-time monitoring and analysis can be key to smart manufacturing in the pharmaceutical environment as it provides the necessary data for PAT and RTRT. Its implementation can also be beneficial for innovative process validation actions that can be parallel to production and thus allow reconfigurable processes.

3.12 Digital Twin

The digital representation of a physical process, operation, machine or activity is named Digital Twin (DT) or Cyber Physical System (CPS). Such twins are generated through empirical data or a combination of empirical and mechanistic simulation data for precise models. Its purpose is mostly to better understand, evaluate, predict, simulate and optimize the real behavior of its physical counterpart (Arden et al. 2021). During production a DT can reflect characteristics and behavior of real systems and enable real-time optimization and predictions for autonomous decisions (Ngo et al. 2018). A DT consists of a physical component, a virtual component, an automated data communication with data management system. The stable data communication between real and virtual part is a challenge that can be addressed by the use of common interface protocols like OPC UA or MQTT. In a pharma context a DT can assist material tracking, serialization and quality assurance (Chen et al., 2020). Researchers are working on system design frameworks for DT systems in different branches with the goal to have the best possible structure for horizontal and vertical integration of the needed system components (Coito et al. 2020). Production planning systems gain positive effect from the use of DT in terms of precision and forecast periods (Reitze et al. 2018). Digital representation of manufacturing equipment allows systematical and low-cost experimentation platforms for product development and pharmaceutical manufacturing (Bano et al. 2018). Constantly updating the knowledge represented by a DT allows implementation of Advanced Process Control (APC) strategies with sufficient accuracy as they are able to reflect changes in the physical system during runtime (Steinwandter et al. 2019). The use of APC includes

Direct Control Decisions (DCD) based on desired quality parameters of the product and simulation of different impact scenarios performed by a virtual production system represented by digital twins (Z. S. Wang et al. 2021).

3.13 IOT and Cloud Computing

Internet of Things (IOT) is a set of technology including novel modes of automated and wireless communication between machines, devices and data processing systems. Cross communication between analytical equipment, maintenance systems, adaptive process control systems and quality control needs software and hardware compatibility between different vendors (Arden et al. 2021). Devices can be conducted by cloud working approaches or in a service-oriented manner. Connected sensors and executors have unique identifier to set up machine-to-machine communication without human intervention (Barenji et al., 2019). One of the most promising data transfer protocols is OPC UA with its latest improvements to use publish a subscription methods towards a deterministic and Time Sensitive Networking (TSN) capability (OPC 2019). Data send by IOT devices should be processed in a manner that contributes to decision making on process station level with low latency for actuators or robots (Coito et al., 2020) as well as with a bigger picture of the whole organization (Barenji et al., 2019). This combination can be made possible with powerful cloud computing hardware that gets preprocessed data from devices close to the manufacturing area (Coito et al., 2020). In an Industry 4.0 environment cyber security will gain a new level of relevance. Pharma companies need to implement risk mitigation approaches to eliminate network vulnerabilities. The system architecture needs to be fortified against disruptions or threats (Arden et al. 2021).

IOT concepts will help to organize the pharma shopfloor in ways that contribute to the overall idea of a smart and reconfigurable production. Within a regulated environment such as a drug producing facility outsourcing data and computational power to distributed cloud systems seem to be problematic.

3.14 Blockchain

The concept of Blockchain as a way of data storage that provides a single source of truth for actions that happen in a chronological order which is promising for logging pharmaceutical relevant data (Bamakan et al., 2021). These data-blocks are connected through shared information that include the nature of the data. If any change in one of the blocks would happen the chain of data artifacts gets inconsistent. Therefore, the Blockchain will not accept any change caused by an attack for example (Leal et al. 2021; Pandey & Litoriya 2021). Data that cannot be manipulated is relevant in pharmaceutical context for cold chain monitoring (Bamakan et al. 2021) decentralized trusted networks (Kshetri, 2018) or serialization and tracing (Jochumsen & Chaudhuri 2018). This concept allows transparency without the need for middlemen to proof data authenticity to regulatory authorities (Bamakan et al., 2021). Storing data in a form that does not allow manipulation seems to be a promising approach for future pharmaceutical production and supply chain concepts. Data access regulations and the underlying necessary IT infrastructure need to be constantly reviewed in the design phase of a new concept.

3.15 Artificial Intelligence and Machine learning

The use of Artificial Intelligence (AI) in Industry 4.0 concepts comes with the opportunity of automated decisions based on historical and real-time data. Autonomous units that are able to deliver highest possible outcome can be controlled by algorithms without a need for human interaction (Steinwandter et al., 2019). Machine learning (ML) as a subset of AI is able to find correlation between input signals with minor variance and is therefore already relevant for drug R&D (W. Wang et al. 2021). Data from process monitoring can be used to forecast process behavior using AI that can be used to generate alerts before deviations from the desired quality level happen (Leal et al. 2021). Key enabler element for data driven AI approaches is labeled historical data. Some of the relevant concepts for the pharmaceutical branch are computer-vision based quality control, predictive maintenance, real time operator support systems and collaborative robots. These AI approaches mostly follow the concept of supervised learning which is classified to be one of the low-risk methods using the above-mentioned historical data. More complex scenarios like forecast of process deviations based on real-time data and predicting correct measures to prevent the system from out of specification process performance can be solved by Artificial Neural Networks (ANN) (Arden et al. 2021).
Such concepts seem to be very promising for modular or distributed processes where human decision making is not available at all spots at all time. The use of AI or ML in pharmaceutical production scenarios needs careful revision in terms of how to qualify equipment or how to validate processes in which such concepts are involved.

3.16 Modular process design

A smart and reconfigurable factory needs objects with a special purpose that can be rearranged based on the current need of the ongoing process. The standardization of such modules can have positive effect on the process quality and production costs by flexibly adjusting the number and type of used equipment (Reitze et al., 2018). Implementation of such process design should follow the concept of a holistic product lifecycle approach from R&D to commercial production. The implementation roadmap for a modular production needs to be reviewed by business representatives to ensure that the planed output capacities match the market fluctuation and needs (Mothes, 2015). Successful reconfigurable production is enabled by data communication between different units, whole plants and feedback information from various distribution channels (Sarkis et al. 2021). Self-organizing units with independent and flexible control strategy are of great significance for modular equipment concepts. These units need to be described in terms of interfaces, properties and resources in classes to proof their inner structure according to their specification (Wan et al. 2019). Such modules with independent logic and control systems with the possibility to decide on their own within their domain are named Agents and a group that forms a process is called Multi-Agent-System (MAS) (Leitao et al., 2016). Relevance for the reconfigurable smart factory in pharma context is clear. Implementation under cGMP regulations is challenging and needs further research.

3.17 Synthesis of key elements

The described technologies are enablers for a smart and reconfigurable factory of the future. These elements seem to be in close relationship to each other. Modular and flexible production design needs agents with possibility to make own decision that can be based on AI components. Data for these decisions come from IOT devices with real-time monitoring capabilities. Evaluation and simulation of the decisions are supported by process knowledge represented by digital twins. To have an evaluable log of the ongoing process and the decisions made by the agents a blockchain seems to be beneficial for this kind of data storage with security measures in a world that knows the value of its data and needs to protect it against outside attacks.

4. Final remarks

4.1 “As-Is” situation in pharma

Pharma companies are often more cautious when it comes to the use of new technologies than their counterparts in automotive or consumer electronics are (Arden et al. 2021). The historical roots of the rules governing the whole drug producing industry show the relevance for cautious behavior. The rules established over time can be summarized as the current good manufacturing principles (cGMP) (ICH, 2000). They are designated to be strict which is sometimes interpreted as counterproductive for new ways of thinking processes.

But Industry 4.0 can change the way how production processes are designed. Digitalization has impacted some companies and pharma researcher work with these ideas according to the rising number of articles published in this sector. Regulatory agencies also contribute to such new concepts for example by new guidelines for continuous manufacturing of drug substances and products (ICH, 2021).

Trust in process optimization and process control mechanisms enabled through data gathering and machine learning scenarios seem to be basis for further implementation strategies. Intralogistics, product handling and packaging are parts of the production that seem to be already good automated. This production concepts are designed for the common way to produce drugs. Today drug manufacturing is mostly organized in batches which means the production of a certain number of same products is done by a set of single purpose machines. All process steps are aligned one following another. According to cGMP regulations after the batch is produced, all machines get inspected and cleaned up to make sure that no product residues are influencing the next products running on the same equipment (ICH, 2000). This process step comes with manual documentation of the produced goods and quality issues that can come up during end-of-line control.

4.2 “To-Be” steps towards Pharma 4.0

Following the concept of a smart factory that can produce a single unit of a product according to its specifications the pharma industry will be able to serve demands in personalized drugs. To achieve a high utilization of modular designed equipment, it can be necessary to run different products in parallel on the same equipment.

In such scenario there is limited time to clean machine parts and to verify that there are no debris from the last products handled. In order to avoid human actions, all process steps are constantly monitored on product level. Every anomaly will be recognized by the system and decisions according to an action plan with respect to a risk analysis are carried out automatically.

A holistic production control strategy takes care of the horizontal and vertical integration of all technological and regulatory parts involved. Different flexible product transport systems work together with robots and special purpose equipment to provide all necessary production technologies. Sequencing the different production steps and navigating the product through the process is under control of a special manufacturing planning and execution system.

Continuous monitoring and real time release testing are parts of the quality ensuring system that takes care of every single product using special sensor combinations that generate self-testing data. Documentation of every single process step is made possible by constant data analysis and automated reporting. All technological parts together follow a "quality by design" approach. Together with the use of cyber physical systems (CPS) for every product and production step this led to "data integrity by design".

4.3 New design framework as proposed solution

Industry 4.0 is a concept that addresses technological solutions to tasks coming from the market demand for "mass customization". For us there is no doubt that personalized medication would be a great achievement for society and environment. To implement such concepts in real world pharma environment within a reasonable timeframe to support short time-to-market approaches for new drug formulations a new way of design and process description is necessary.

The design framework could be the basis for modular production planning as well as for qualification and validation processes according to cGMP. The design process and its outcome need to be transparent for equipment manufacturer, pharma companies and regulatory agencies to achieve trust in every process step. Iterative development cycles shall be reduced to a minimum to save cost and time for innovative production concepts.

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Biography

Roland Wölfle as an engineer with passion for technology and human creativity, he is committed to future-proof concepts in the field of pharmaceutical production. He acquired the necessary technical knowledge through training and studies while working full time in the fields of mechatronics and robotics as well as working in the research and development department of a family-run medium-sized company in the south of Germany. The special R&D environment with freedom to think out of the box and the company's distinctive team culture make him want to continue working on himself and his skills. An increased interest in human interaction and the urge to look beyond the engineer's horizon lead him to complete the International Business Management and Leadership course (MBA) at the Professional School of Business and Technology in Kempten. With Industry 4.0 as a field of research and his role as an innovative thinking leader, Roland is able to make his vision of man and machine as partners, complementing each other with their respective strengths to form an effective and resource-saving unit, become reality. This vision comes to live within a PhD program at the University of Aveiro, Portugal. The research focuses on the interconnection between pharmaceutical production and regulations, engineering tasks and design methods with focus towards Pharma 4.0.

Irina Saur-Amaral has a PhD in Industrial Management (International R&D in Pharmaceutical Industry), a MSc in Information Management and a BSc in Business Affairs. She has been teaching in higher education since 2006, in areas linked to Management, Marketing, Strategy, Innovation, Business Intelligence and Methodology in Social Sciences, in all levels of higher education and in executive training (postgrad & in-company). She is currently Coordinator Professor at Universidade de Aveiro - Instituto Superior de Contabilidade e Administração (ISCA-UA), Director of CIMAD (Center for Market Research and Data Analysis) and Researcher at NECE – Universidade da Beira Interior. She founded and managed for 4 years an academic R&D Unit and she led and was member of several research projects with competitive funding. She was Director of a Higher Education Institution. She was a consultant for more than 10 years, working closely with Portuguese companies to increase their competitiveness. She has more than 100 publications in journals, conference proceedings and book chapters, and she authored 8 books. She was the unique Portuguese member of the Advisory Board of EUWIN - European Workplace Innovation Network.

Leonor Teixeira graduated in Industrial Engineering and Management, received a MSc. degree in Information Management, and a PhD in Industrial Management (Information Systems area), in 2008, from the University of Aveiro, Portugal. She is currently an Associate Professor of the Department of Economics, Management, Industrial Engineering and Tourism (DEGEIT) at the University of Aveiro. She is also a researcher (Integrated Member) at the Institute of Electronics and Informatics Engineering (IEETA-LASI) and collaborator at research unit on Competitiveness, Governance and Public Policies (GOVCOPP) of University of Aveiro. Her current research interests include Industrial Management in general, and in Information Systems applied to Industry in particular. She has over 200 publications in peer-reviewed journals, book chapters and proceedings, and has several communications at international scientific conferences, some of which as invited speaker. She serves as a member of Program Board and Organizing Committees for several Scientific Committees of International Conferences and has collaborated as reviewer with several journals. She is associated with IIIS, IEEE Society and APSI/PTAIS.