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Mini-review

Industry 4.0 Elements for Pharmaceutical Development and Manufacture

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Abstract: The innovations of the Industry 4.0 revolution in the New World aim at creating a society where we can solve many problems in every sector and social life. As a condition for Industry 4.0, industrial sectors are heading towards digitalization and automation. Pharmaceutical Industry takes its share in this sense and tries to keep up with this pace in the context of Pharma 4.0 which is a hot topic. However, it is a known fact that developing safe and effective new treatments is a long, difficult, and expensive process, so FDA released the Pharmaceutical cGMPs for the 21st-century report and in this report; it specified Quality by Design (QbD) and Process Analytical Technologies (PAT) initiative to bring a solution. The introduction of the new *QbD* approach, which advocates providing the quality within the product with design instead of testing, brought an increase in the quality of the products manufactured, a decrease in costs and accelerated the market launch of the medicines. Moreover, patient safety is brought to the fore with better quality medicines and the patient accesses the drug in a shorter time.

Keywords: *Industry 4.0; pharma 4.0; QbD; PAT; pharmaceutical development; pharmaceutical manufacture*

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1. Introduction

The reform that started the industrial revolution with the English engineer Thomas Newcomen developing a machine to drain water in 1712 is now called Industry 1.0. With the discovery of electricity and its use as a power supply, the concept of Industry 2.0 emerged, and the manufacture of automobiles started. The dominance of the digital and electronic systems and information systems in the sector accelerated mass production and increased automation over time. Thus, the third industrial revolution started, and more precise, efficient, and good standards were produced thanks to computer-controlled production. With Industry 4.0 that came later, the importance of manpower became lost, cyber and physical systems came into play and the factories started to use concept of Internet of things. These physical systems made the management of factories much easier, decreased energy consumption and increased efficiency.

The innovations of the Industry 4.0 revolution in the New World aim at creating a society where we can solve many problems in every sector and social life. Thus, the future society is planned to be a super smart society where new values and services are created constantly and life is easier and more sustainable.

2. Pharma 4.0 concept

As a condition for Industry 4.0, industrial sectors are heading towards digitalization and automation. Pharmaceutical Industry takes its share in this sense and tries to keep up with this pace in the context of Pharma 4.0 which is a hot topic. The Pharma 4.0 concept promises enhanced opportunity in terms of product safety and security through digitalization, data analysis technology, Internet of Things (IoT), continuous manufacturing and artificial intelligence technology (Kumari, 2020).

Implementation of adaptive and innovative technologies from Industry 4.0 revolution will lead to establish more robust and agile production processes characterized by fewer interruptions and defects, with higher quality management levels for pharmaceutical companies. Integration of Industry 4.0 elements will also upgrade the pharmaceutical production plant to a "reconfigurable factory" which may provide mass customization of personalized drugs for different demands. Effective knowledge web across company boundaries and big data analytics can improve process monitoring performance and achieve sustainability with reducing material waste, overproduction, and energy consumption (Reinhardt et al., 2021).

3. Quality by Design (QbD) and Process Analytical Technology (PAT)

It is a known fact that developing safe and effective new treatments is a long, difficult and expensive process, so FDA released the Pharmaceutical cGMPs for the 21st-century report and in this report, it specified Quality by Design (QbD) and Process Analytical Technologies (PAT) initiative to bring a solution. The introduction of the new *QbD* approach, which advocates providing the quality within the product with design instead of testing, brought an increase in the quality of the products manufactured, a decrease in costs and accelerated the market launch of the medicines. Moreover, patient safety is brought to the fore with better quality medicines and the patient accesses the drug in a shorter time (Aksu, 2013).

As specified in the International Conference on Harmonization (ICH) Q8 guidelines, QbD is a systematic drug development approach that begins with predefined goals and emphasizes understanding of the product and process based on sound science and quality risk management (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, 2009). QbD increases knowledge on the process and helps to better understand the product, which often happens through the application of new technologies such as PAT or modelling. It enables pharmaceutical development, production and quality assurance by advocating risk-based approaches based on science and scientific data and can be considered is one of the drivers of Pharma 4.0.

Recent regulatory measures on pharmaceutical quality, such as Process Analytical Technology (PAT) Guidance by the FDA, the draft Process Validation Guidance recently released by the FDA and ICH Guidelines (Q8, Q9 and Q11), have all encouraged the use of advanced PAT technologies and QbD principles with the

aim of gaining in-depth process understanding, reducing, and eliminating the risk of releasing poor or substandard quality pharmaceutical products to the public (Wu and Khan, 2010).

QbD involves the integration of six main steps: Quality Target Product Profile (QTPP), process and product design risk assessments, DOEs, design space, control strategy, and continuous process improvement. Together with PAT tools, these cover the entire manufacturing process from the beginning to the end of the manufacturing chain along with logistics and business planning and have sought to understand processes in development over the past decade by gathering and analyzing data using multivariate data analysis methods and developing effective monitoring and control systems. They also provide a basis for the design of pharmaceutical products and manufacturing processes, thus making the products acceptable and affordable and the production lines more reliable without quality failures. If PAT and QbD approaches are used at any stage of production to assure the material and product quality, real-time release testing (RTRT) can be realized. Real-time release testing means the capability, based on process data provided by in-line, non-destructive analytical sensors, to assess and ensure the appropriate consistency of the in-process and/or final product, thus providing commercial and economic benefits for the manufacturers like decreasing in end-product release testing and removing of superfluous manufacturing scale monitoring and control (Kessler and Kessler, 2020; Mészáros et al., 2020; Shah et al., 2011).

When PAT tools such as chemometric tools, process analysers, endpoint tracking tools and information management tools are combined, the production process can be actively and adaptively controlled; also decrease in cycle times with the utilization of on-, in-, or at-line measurements and controls, elimination of raw material waste (e.g. chemicals and high-quality water), release of the products in real time, and expanded use of automation are expected to contribute to improved quality and efficiency (Shah et al., 2011).

Despite the financial result and competitive interests obtained by various industries that adopt process analytics, pharmaceutical companies are restricted in their efforts to implement PAT. The various factors restricting the implementation of PAT that have caused the current state and can be summarized into three categories: real and perceived technological barriers since the process control requires a high level of automation and highly robust sensors that can survive the industrial environment, lack of economic incentives and factors hindering licensing should be considered (Cogdill, 2008; Kessler and Kessler, 2020).

3.1. *Data Analysis*

Data analysis methodologies are also among the important QbD tools. The expanded opportunities offered by on-line/in-line/at-line PAT process analysers and material sensors progressed significantly in last 15 years used to track any specific process or material produces significantly large and complex data sets. Thus, advanced data management techniques are required for the intricacy of such complex data analysis. By using appropriate techniques including Multi Variate Data Analysis (MVDA) in the analysis of these real-time dynamic process data, we can extract material characterization, critical product/process information and knowledge, and this is essential for rationale product and process design, and process control. In addition, machine learning (ML) and deep learning (DL) principles, can infer the model function from

sample input results are used to explain the behaviour of the system instead of using physic / engineering or chemometric based models, offer new approaches to designing complex system or data-driven systems models in Industry 4.0 applications (Kessler and Kessler, 2020; Stagner and Haware, 2019; Wu et al., 2011).

4. Digitalization in the Context of Pharma 4.0

In terms of digitalization, Industry 4.0 concept includes cyber-physical systems (CPS), the internet of things (IoT), industrial internet of things (IIOT), cloud computing, 2 cognitive computing and artificial intelligence to optimise all aspects of processing over the entire product life cycle (Vaidya, 2018).

Further digitalization, the basis for the Industry 4.0 will dramatically change the structures of future development enabling the connectivity and cloud services and advanced data analysis tools which allows experts to extract and analyze enormous amount of information (*i.e.,* big data) from the supply chain, products, machines, and production lines; then the realization of Cyber-Physical Systems (CPS) that is managed or monitored by computer-based algorithms that are embedded into the Internet structure and needs a combination, respectively between physical and computational elements for the process industry (Kessler and Kessler, 2020; Reinhardt et al., 2020; Reinhardt et al., 2021).

Conclusion

It is an indisputable fact that the contributions of Industry 4.0 to healthcare technology will provide numerous benefits in the future. The relationship between technology and the healthcare sector today is evident in the establishment of health information systems in healthcare institutions to collect, store, share, transmit and manage medical data of individuals or data related to various processes.

To conclude, even though further research and a clear roadmap for execution in Pharma 4.0 is required to increase the knowledge, the implementation of Industry 4.0 to the pharmaceutical industry is promising to bring new opportunities, which can solve the problem of efficiency in manufacturing, more robust process and R&D growth, data evaluation.

Conflict of Interest

Authors declare no conflict of interest.

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