International Journal of Pharmaceutics 602 (2021) 120554

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Industry 4.0 for pharmaceutical manufacturing: Preparing for the smart factories of the future

N. Sarah Arden, Adam C. Fisher *, Katherine Tyner, Lawrence X. Yu, Sau L. Lee, Michael Kopcha

Food and Drug Administration, Center for Drug Evaluation and Research, Silver Spring, MD 20993, United States

ARTICLE INFO

Keywords:
Industry 4.0
Pharmaceuticals
Digitization
Advanced manufacturing
Innovation

ABSTRACT

Over the last two centuries, medicines have evolved from crude herbal and botanical preparations into more complex manufacturing of sophisticated drug products and dosage forms. Along with the evolution of medicines, the manufacturing practices for their production have advanced from small-scale manual processing with simple tools to large-scale production as part of a trillion-dollar pharmaceutical industry. Today's pharmaceutical manufacturing technologies continue to evolve as the internet of things, artificial intelligence, robotics, and advanced computing begin to challenge the traditional approaches, practices, and business models for the manufacture of pharmaceuticals. The application of these technologies has the potential to dramatically increase the agility, efficiency, flexibility, and quality of the industrial production of medicines. How these technologies are deployed on the journey from data collection to the hallmark digital maturity of Industry 4.0 will define the next generation of pharmaceutical manufacturing. Acheiving the benefits of this future requires a vision for it and an understanding of the extant regulatory, technical, and logistical barriers to realizing it.

1. Introduction

The term Industry 4.0 refers to the fourth industrial revolution which brings together rapidly evolving technologies such as the internet of things (IoT), artificial intelligence (AI), robotics, and advanced computing to dramatically change the landscape of manufacturing. Industry 4.0 is characterized by integrated, autonomous, and self-organizing production systems. New thinking will be required to realize Industry 4.0 for pharmaceuticals and overcome the inertia of current manufacturing infrastructure, operations, and regulation. While implementing many of the advanced technologies and manufacturing approaches needed to enable Industry 4.0 may not be easy, it may well be worthwhile as they bring the potential for higher output, increased manufacturing safety, improved quality, better value, increased agility, additional flexibility, and reduced waste (Ezell, 2016; Buvailo, 2018; Baur and Wee, 2015; Clemons, 2016; Tilley, 2017).

1.1. Industry 1.0

If Industry 4.0 is the future, then Industry 1.0 is the starting point of the modern pharmaceutical industry. The application of herbal or botanical preparations as medicines has spanned the history of civilization. Only in the last two centuries have we seen dramatic changes in how materials are processed and formulated for medical use. Industry 1.0 saw the manual processing of botanical, mineral, and animal derived materials transition from simple hand-operated tools to commercial-scale machinery able to crush, mill, blend, and press larger quantities of medicines (Anderson, 2005). In the 19th century, larger-scale production of drugs utilizing non-electrical power-driven machinery emerged from two sources – individual pharmacies or the dye and chemicals industry (Sonnedecker and Urdang, 1976; Daemmrich and Bowden, 2005). This movement from laboratory-scale to wholesale production of drugs fueled the establishment of a pharmaceuticals industry in the 19th century – an industry that has seen tremendous growth over the last century. Yet, some of the early machines from the first industrial revolution, such as pneumatic mills and tablet presses, are still commonly used today.

1.2. Industry 2.0

The second industrial revolution was enabled by electricity and early electronic machines and assembly lines with pre-set controls that

* Corresponding author at: Food and Drug Administration, Center for Drug Evaluation and Research, 10903 New Hampshire Ave, Silver Spring, MD 20993, United States.

https://doi.org/10.1016/j.ijpharm.2021.120554
Received 4 February 2021; Received in revised form 12 March 2021; Accepted 25 March 2021
Available online 29 March 2021

incorporated basic automation and process controls which provided manufacturers the ability to set basic process parameters. In the pharmaceutical manufacturing industry, this manifested as electronic machine-based crushing, milling, blending and tablet pressing allowing for larger-scale production and – importantly – more monitoring of processes and quality. However, process controls were generally limited to pre-determined and static settings which only allowed for the monitoring of process performance and passive control strategies. Industry 2.0 developments led directly to machines such as modern tablet presses that can reliably produce over one million tablets per hour (Berry and Nash, 2003). Indeed, it can be argued that much of the current pharmaceutical manufacturing industry still operates in the Industry 2.0 paradigm (Lorenz Binggeli et al., 2018).

1.3. Industry 3.0

The third industrial revolution was enabled by the development and availability of computers and communication technologies, such as networked computing, the internet, and wireless communications. These technologies enable a higher degree of automation of processes and equipment, which in pharmaceutical manufacturing enabled concepts such as continuous manufacturing and active control. Human-computer interfaces aided in developing more sophisticated control strategies and higher product and process quality. Remote sensing and monitoring reduced the need for human operators on the manufacturing floor and facilitated better tracking of parameters and metrics associated with production.

Some industries are now well into Industry 3.0, but in many ways the pharmaceutical industry is still very much transitioning into it. For example, continuous manufacturing is a technology that sends materials produced during each process step directly and continuously to the next step for further processing; it has been widely adopted in other industries. For various reasons, the pharmaceutical industry has been slower to adopt continuous manufacturing (Lee et al., 2015). As a corollary, the pharma industry has also not yet achieved consistent six sigma manufacturing capability (i.e., <3.4 errors per million opportunities) which is common in other industries (Yu and Kopcha, 2017).

The third industrial revolution brought pharmaceutical manufacturing advanced process analytical technology (PAT), which aims to provide process and product quality data in near real time. Industry 3.0 also advanced model-based or Quality by Design (QbD) processes, which aim to control target product quality profiles within a defined set of quality parameters. However, to achieve the full potential of PAT and QbD, more technology advancements are needed to attain deeper process knowledge and real-time analytics to more widely enable real-time release testing with high levels of product quality assurance – especially for biotechnology products. With nearly two thirds of drug shortages resulting from quality issues, it is clear that more work is needed to improve process control and reliability (FDA, 2019a). Nonetheless, Industry 3.0 is enabling a much-improved understanding of how to capture, analyze, and secure large amounts of data associated with pharmaceutical manufacturing.

1.4. Industry 4.0

The fourth industrial revolution brings together advanced manufacturing technologies to enable integrated, autonomous, and self-organizing manufacturing systems that operate independent of human involvement. The experience gained in the automated and digital environment of Industry 3.0 empowers the widespread transformation into Industry 4.0 in pharmaceutical manufacturing. Whereas Industry 3.0 saw rapid advancements of individual operations and tools, Industry 4.0 promises advancements of entire manufacturing systems and infrastructures. In such an environment, performance data can be analyzed by algorithms and used for critical real-time business and operational decisions that directly impact production outputs (Fuhr et al., 2014). The journey from simple data collection to digital maturity is one in which data transforms from raw data captured from a manufacturing process, to information gained by analysis of these data, to knowledge formed through the addition of contextual meaning perhaps by artificial intelligence, and finally to actionable wisdom to inform decision-making by the contribution of insight (Fig. 1). This "wisdom" is what fuels autonomous systems and cyber-physical machines (i.e., with mechanisms controlled by computer algorithms) capable of self-optimizing, judgement/decision making, remote movement, and adaptive control (Guilfoyle, 2018).

The dawn of Industry 4.0 forces us to visualize what a fully digitized and autonomous manufacturing world would look like and how it could impact pharmaceutical operations and regulations. There will be new operating paradigms as a result of digitization, automation, and real-time data integration that should enable better than six sigma quality in pharmaceutical manufacturing - for both small and large molecule drug products. The COVID-19 public health emergency has highlighted the need for manufacturing technologies that are responsive to rapidly changing demand and reduce dependence on human intervention. For example, automated and robotics-based operations may be necessary in the face of challenges that limit humans working in close proximity to others. Here we will describe a vision of the future of pharmaceutical manufacturing and some potential regulatory, technical, and logistical challenges that need to be addressed for society to realize the full value of Industry 4.0.

2. How industry 4.0 technologies could be deployed in pharma manufacturing

The archetypal feature of an Industry 4.0 environment is the integration of connectivity, artificial intelligence (AI), and robotics to enable systems that operate with little to no human involvement (Leurent and deBoer, 2018). Integrated autonomous and robotic systems fuse real-time and online data with industrial production processes and artificial intelligence in order to optimize manufacturing and enterprise-wide management (Moore, 2018). Multiple data sources can integrate to connect both external and internal information. For example, in pharmaceutical manufacturing, external information - including variables such as patient experience, market demand, supplier inventories, and public health emergencies - could fuse with internal information such as energy and resource management, modeling and simulation outcomes, and laboratory data. Integrating internal and external data sources enables unprecedented real-time responsiveness, monitoring, control, and prediction (Fig. 2). The result is a well-controlled, hyper-connected, digitized ecosystem and pharmaceutical value chain for the

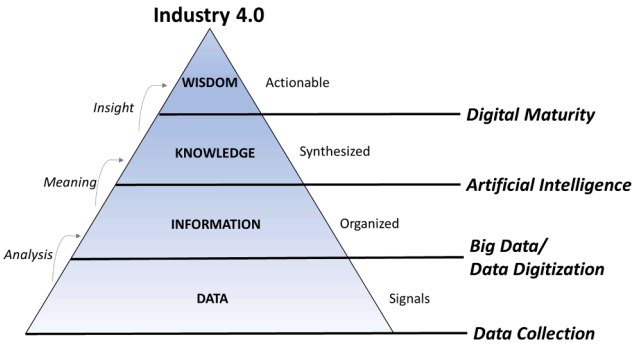

Fig. 1. The stages of data transformation on the path to realizing Industry 4.0. In these stages, data are transformed from raw signals captured from a system to full digital maturity. Data are initially collected from a manufacturing process, then organized by data digitization and analysis as Big Data into information, then synthesized into knowledge by the meaning discerned via artificial intelligence, and finally to actionable wisdom attained through the combined insights of digital maturity.

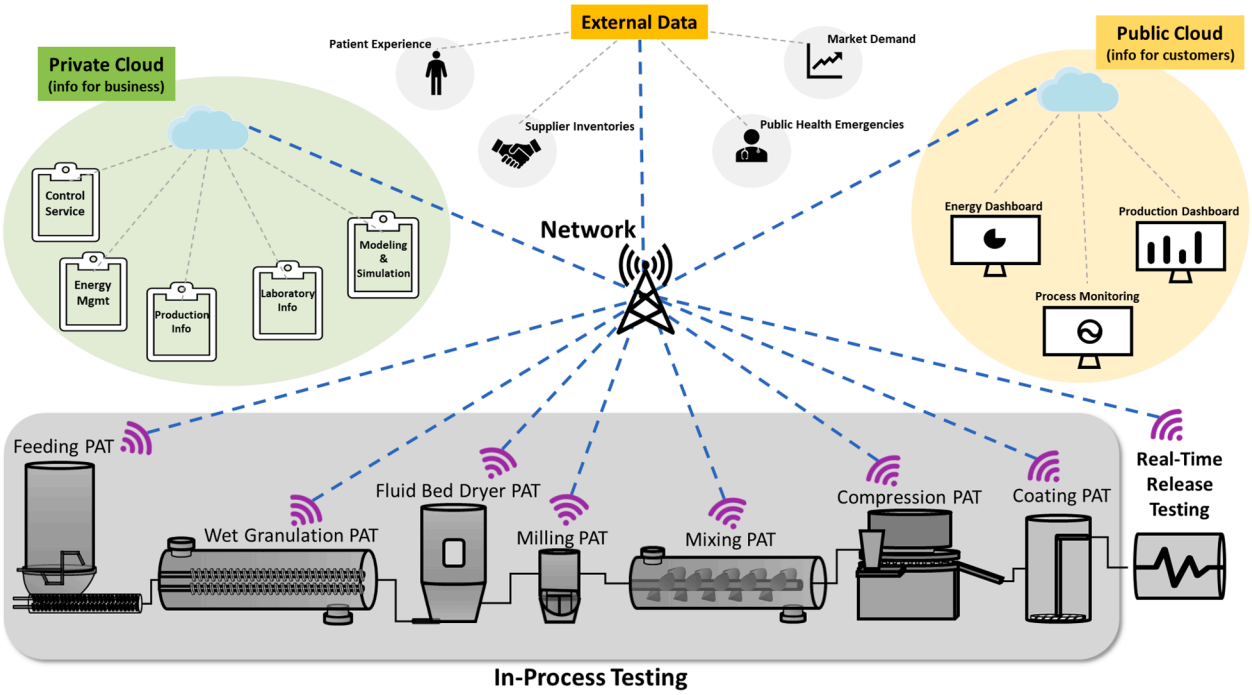

Fig. 2. A cyber-physical system (CPS) for pharmaceutical manufacturing in Industry 4.0. Key parts of a CPS include the public-cloud, private-cloud, and manufacturing floor. The public cloud contains application services for external customers. The private cloud deals with information for higher layer features such as remote monitoring systems, production, energy management, laboratory information, control service, and modeling and simulation. The public and private cloud digitally reflects the status of the physical system, thereby enabling real-time optimizations and predictions. The manufacturing floor consists of equipment, PATs instrumentation, and real-time release testing (RTRt). PAT provides control of the manufacturing process and RTRt ensures product quality based on the information collected during the manufacturing process. The operations of the process (e.g., feeding, wet granulation, fluid bed drying, milling, blending, compression, and tablet coating) connected to the local network and the cloud through the internet.

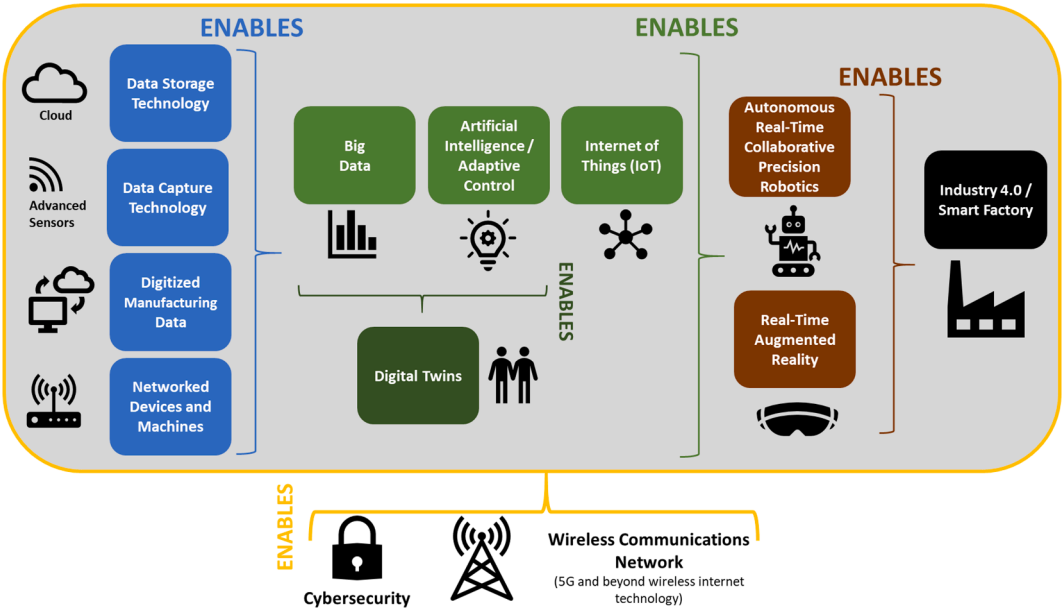

Fig. 3. The enabling technologies of an Industry 4.0 smart factory. Data from a manufacturing process are captured and stored via two key technologies: data storage technology, such as the cloud, and data capture technology, such as advanced sensors used in an operation. Data storage technology enables the long-term storage of digitized data captured from advanced sensors. This data-rich environment enables Big Data and simulations, artificial intelligence and adaptive control, digital twins, and cyber-physical systems like the internet of things. These combined technologies enable intelligent, precision, real-time, collaborative robotics and augmented or virtual reality technologies to run and manipulate manufacturing. The entirety of the smart factory is enabled by a wireless internet network and appropriate cybersecurity.

manufacturer (Markarian, 2016; Dublin S-TC, 2016).

2.1. Digitization and digital maturity

A key to implementing Industry 4.0 is the digitization of multiple complex pieces of the pharmaceutical value chain with embedded cybersecurity. A critical concept in developing the so-called "smart factory" is the industrial internet of things (IoT), which is a type of cyber-physical system comprising interconnected computing devices, sensors, instruments, and equipment integrated online into a cohesive network (IEEE, 2021). The IoT requires data digitization, which is the transformation of previously manually captured data to digital device-captured data. In pharmaceutical manufacturing this may include supply chain-related information such as raw materials variability and global tracking of materials across facilities (Sandle, 2019; Marcus Ehrhardt PB, 2016), manufacturing floor-related information such as operation procedures and operator work instructions (Jovanis, 2019), monitoring real-time operations by video (Marcus Ehrhardt PB, 2016), video-based training and centralizing quality event data for improved decision making (Jovanis, 2019). Full digital maturity, the process of gaining wisdom from these digitized data, is necessary to transform reactive operations into a fully integrated and digital ecosystem capable of proactive and predictive decision making (Grossman, 2018). This integration enables real-time connectedness both within a manufacturing facility (e.g., machine learning across unit operations) as well as outside the facility, as products "talk" back to their manufacturers using technologies that track environmental conditions, quality attributes, use, and performance of products (PwC, 2015, 2016). Together with AI algorithms focusing on machine learning and adaptive control (described below), the IoT would be disruptive in pharmaceutical manufacturing and product development (Biophorum/BPOG, 2017) (Fig. 3).

Industry 4.0 may well shift the key problem for pharmaceutical manufacturers from controlling processes to enabling human understanding of the operations. To facilitate visualization and human understanding of digitized manufacturing operations, each segment of the value chain could be divided into digital architectures; i.e., hardware, and software infrastructures that support data capture, storage, and analysis. Different types of architectures have been proposed to address this problem including digital ecosystems or digital compasses (i.e., different modes of organizing how data is collected, stored, and analyzed) that highlight 'levers' mapping to key value drivers (Baur and Wee, 2015; Hartmann et al., 2015; PwC, 2021). In order to develop cost-effective intelligent systems that merge online data with production systems and customer demand, it will be necessary to further develop powerful computing architectures (i.e., sets of rules and methods that describe functionality, organization, and implementation) and improve high-speed communications, at lower costs (Lydon, 2017). While the specific tools developed to optimize key value drivers may vary depending on the core competencies and business models of pharmaceutical firms, the development of more integrated systems will be consistent. It is the digital integration into an IoT that could produce disruptive pharmaceutical applications such as real-time, on-demand, small-scale production systems, truly personalized dosage forms, and revolutionary biosensor diagnostics (Tracy, 2017; Wilson, 2018; Woods, 2017; Banks, 2015).

2.2. Artificial intelligence

AI involves the integration of digital data and computational analysis for the purpose of making decisions normally made by humans (McCarthy and Thomason, 1989). Tasks that rely on computer-based intelligence may involve reasoning, problem solving, learning, and decision-making among others. The application of AI in pharmaceutical manufacturing has already begun with examples including the use of machine vision technology (Forcinio, 2019; Veillon, 2020; Yadav, 2020) to replace human visual inspection of packaging, caps and vials; predictive equipment maintenance to reduce disturbances, risks, and production downtime (Otto, 2019; Markarian, 2020); and automated quality control enabling seamless scheduling of analytical testing (Han et al., 2019), continuous process quality assurance (Chapman, 2019), and enhanced data integrity (Powers, 2019).

AI includes a spectrum of sub-disciplines which take varied approaches to designing computer intelligence depending on the desired features and tasks to be performed. Such approaches involve handling large and disparate datasets with specific algorithms. Within the field of AI, and due to the advancements in available technology and software programming, machine learning (ML) and artificial neural networks (ANN) have emerged as two of the more advanced methods for prediction and risk management. In the hierarchical relationships of AI, ML is a sub-discipline of AI, and ANNs are a sub-discipline of ML.

ML primarily involves the ability of computers to learn a task by monitoring data and using statistical tools in order to derive some general knowledge from these data (via the development of mathematical relationships) without external input or prompt (McCarthy et al., 2004). It is worthwhile to note that ML algorithms can fall into one of three categories depending on how input data are utilized: supervised learning, unsupervised learning, and reinforcement learning. Supervised learning can include methods such as ANN or multivariate regression and classification analysis, which learn from and connect input data and outcomes. Supervised learning methods are commonly associated with process design and controls. Unsupervised learning draws inferences from input data without using outcomes to learn. Unsupervised learning approaches, such as dimension reduction or cluster analysis, are useful in identifying trends and anomalies associated with an operation. Reinforcement learning correlates actions with delayed outcomes so that decisions are associated with desired outcomes in the future. Reinforcement learning can be used where complex dynamics are involved; for example, plant operations, or logistics. While each of these ML approaches has the potential to enhance pharmaceutical manufacturing operations, supervised learning approaches are typically viewed to have less risk and uncertainty and have thus far gained the most traction.

Supervised learning ML approaches such as ANN have seen steady progress in advanced manufacturing applications (Peres et al., 2016; Arinez et al., 2020). ANNs are modeled after the connectivity between the neurons and synapses of the human brain which utilize data-driven algorithms to determine a mathematical relationship between input and output variables. The design and structure of the ANN is such that individual nodes in one layer are connected via weighted connections to individual nodes in subsequent layers. ANN models can be developed and applied independently or, as is often the case, utilized in conjunction with other modeling techniques. ANN has been used for prediction and control in pharmaceutical development (Ekins, 2016; Korteby et al., 2016) and recently to perform risk-based analysis of biomanufacturing processes (Shirazian et al., 2017; von Stosch et al., 2016a, 2016b), develop control schemes and perform fault detection for complex dynamic processes (Montague and Morris, 1994; Shimizu et al., 1998; Stanke and Hitzmann, 2013; Takahashi et al., 2015), and to predict outcomes for therapeutic drug pharmacokinetics and pharmacodynamics (Atobe et al., 2015; Lin et al., 2015; Pavani et al., 2016; Yamamura, 2003). A significant advantage of ANN models is their utility in pattern recognition within a dataset – even with noisy or complex data with missing data points.

Computer vision quality control, digital twins, predictive maintenance, real-time augmented reality, and collaborative robots are tools better enabled by AI (Fig. 3). AI should generally improve and optimize manufacturing processes while also reducing human intervention in the production of pharmaceuticals. Computer vision-based quality control uses images (for example, images of packaging, labels or glass vials) that are analyzed by software to detect deviations and to ensure images match the requirements of a given quality attribute of a product.

Collaborative robots (i.e., cobots: groups of robots programmed to work together) act in collaboration through one or more integrated software programs in order to achieve a desired outcome through a series of steps such as packing, moving and sealing a box or taking a sample of material from process machinery, moving it to a different location, analyzing it, and sending information back to the process machinery controls (Fig. 3). The use of augmented reality may be useful in the areas of customer experience, discovery and research, maintenance, quality assurance, safety, packaging and training (Biophorum/BPOG, 2017; Stracquatanio, 2018; Fassbender, 2017).

A digital twin is a digital replica of a physical process such as an operation, machine or activity used to better understand, evaluate, predict, and optimize its performance (Fig. 3). Digital twins can be based on empirical data (data-driven models) or integrate both empirical and mechanistic simulations to provide high resolution models together with real-time or near real-time data from which to assess process performance. Such models outperform traditional process models both in terms of resolution and real-time feedback. For example, some companies outside pharma have employed digital twins in smart factories (Wilson, 2020; GE, 2020) and inside pharma in smart processes (InSilico, 2020). Digital twins enable humans to better understand how deviations or disruptions may impact performance, and how related risks can be mitigated.

2.3. Full automation

Complete process automation includes the capture of all process performance data via integration of cloud-connected PAT technology, followed by the analysis of that data into organized information, the application of AI based algorithms to convert that information into knowledge, and finally the use of that knowledge to gain insight about the process and to enhance process control (Fig. 1). A useable IoT requires the capacity for individual units to connect to the cloud in order to send and receive data (Fig. 3). Within the current landscape of pharmaceutical manufacturing, process controls are typically segregated from process performance. This leads to an inherent delay in applying modifications to control systems, for example in a situation where process performance trends out of specification. This challenge may be mitigated by the application of AI algorithms employing ML or ANN approaches using process data to detect and predict when measured parameters are trending out of specification and making changes before they do so. ANN models can be utilized for such adaptive control of processes due to their ability to learn, predict, and forecast process states based on current and historical data. The application of these concepts will enable the real-time capture of process performance parameters and trends in the data, which can further be applied to predict product quality attributes further down the process pipeline. This adaptive control strategy enables the additional opportunity for real-time process optimization via the application of digital twins (Fig. 3).

3. Challenges to realizing industry 4.0 in pharmaceutical manufacturing

Achieving Industry 4.0 will require adopting advanced manufacturing technologies and overcoming regulatory, technical, and logistical challenges. Each step-change on the path to an Industry 4.0 manufacturing environment should lead to more autonomous manufacturing systems with enhanced process controls and more mature quality management. These changes should reduce variability across lots and produce consistently available products. While the foundational tools of PAT and QbD are readily used by many pharmaceutical manufacturers, fewer are prepared to take the next steps to adopt advanced technologies in support of smart manufacturing. A major reason for the delay in adopting newer technologies is related to the vast institutional and regulatory knowledge accrued on existing platform technologies. The lack of precedent in the industry, the costs associated with development, and perceived regulatory uncertainties leave many firms keen on a “first to be second” approach by observing how competitors approach new manufacturing technologies and how regulators respond.

3.1. Regulatory challenges

With respect to regulatory barriers, operating in existing regulatory frameworks can be a perceived or corporeal challenge for technological innovation. Lack of regulatory precedence can lead the industry to maintain conventional processes even when new processes may reduce the overall regulatory burden and increase quality over the long run. Even existing implemented Industry 3.0 technologies such as continuous manufacturing technologies and adaptive control systems for product release have challenged the current process validation paradigms of the last half century. Another regulatory challenge is the burden of filing regulatory applications across multiple global jurisdictions that have varying regulatory expectations, especially for new manufacturing technologies. International regulatory convergence on advanced manufacturing technologies can potentially lessen this uncertainty for manufacturers.

The U.S. FDA has been driving toward increasingly performance-based regulation for over a decade (Yu et al., 2015). Performance-based regulation is based on measurable desired outcomes rather than prescriptive processes, techniques, or procedures (US Nuclear Regulatory C). In many ways, Industry 4.0 and performance-based regulation are complimentary, and perhaps mutually enabling. Performance-based regulatory systems focus on a defined set of results so that regulatory actions can then focus on identifying performance measures that ensure an adequate safety margin and offering incentives to improve safety without formal regulatory intervention (US Nuclear Regulatory C; Yu and Kopcha, 2017). The extensive data and analysis made possible by Industry 4.0 will enable manufacturers and regulators to identify the fundamental set of critical control points which can fully ensure that the critical quality attributes of products meet the predefined acceptance criteria. Because of this, the production system can continue to evolve and improve by continually optimizing different parameters while still reliably producing quality product. A key challenge for regulators will be monitoring risks associated with the continual change of these parameters with little or no active regulatory oversight. In an Industry 4.0 environment, performance-based regulation may need to be realized by bringing together advanced manufacturing technologies and advanced regulatory systems to enable real-time assurance of production system performance.

Current process validation approaches aim to collect data to demonstrate that a process is under a state of control and capable of consistently producing quality products for the commercial market throughout the lifetime of a given drug product (FDA, Guidance for Industry). To achieve this, after process design (stage 1), validation exercises are initiated by a set of process qualification (stage 2) runs at the beginning of the product-process lifecycle. Such exercises provide a snapshot of process performance at the stage of process launch with continued process verification (stage 3) driving process improvement over the lifecycle. In an Industry 4.0 environment, all three stages of process validation can potentially happen earlier - and possibly simultaneously - due to the availability of large data sets and the ability to continue to collect quality data with high frequency (e.g., via PAT during commercial production) (Lorenz Binggeli et al., 2018). Process validation may well transition from an intermittent continual activity to an ongoing continuous activity enabled by model or AI-based process designs that better capture data on process variations, associated failure modes, and risk mitigation. Ideally, Industry 4.0 process validation approaches will provide a higher level of confidence in production system performance and accelerate product release by reducing time to market. Here again, a key challenge will be regulating continuous process

validation with little or no active regulatory oversight, especially given the large amount of data associated with AI, models, and digital twins.

As mentioned above, the pharmaceutical industry is still very much transitioning into Industry 3.0 by adopting continuous manufacturing and employing advanced PAT. Of course, some manufacturers are content sticking to the Industry 2.0 paradigm. A key challenge will be regulating an industry in which some pharmaceutical manufacturers stick to Industry 2.0 principles as others transition to Industry 4.0, and the rate at which manufacturers make this transition will vary. This will set up a situation in which regulated industry will simultaneously comprise Industry 2.0, 3.0, and 4.0. The co-existence of old and new technology paradigms (perhaps even within the same company) will require regulatory frameworks that are flexible or amenable to all technology paradigms in order to enable the adoption of novel technologies while not negatively impacting the supply of products still made with older technologies. Indeed, the FDA has launched an effort to identify and implement needed changes in the regulatory structure; for example to handle the management of data-rich environments, the evolving concepts of process validation, and miniature, mobile manufacturing platforms for the manufacture of essential drugs near or at the point of care (FDA, 2019b).

3.2. Technical challenges

Many, if not most, challenges related to Industry 4.0 implementation will be the technical challenges uncovered and navigated by early adopters. While some manufacturers may not be keen to embrace these challenges, the current manufacturing paradigm is not without its technical limitations, including inflexible process parameters, the application of extensive offline testing (especially for sterile products), and the use of regular human involvement in manufacturing operations. Some of these limitations may be attributable to current regulatory frameworks and the lack of applicable technologies. For instance, analytical technologies can be limiting and inadequate to support the real-time release of drug products. However, advanced PAT coupled with a cloud-based infrastructure and advanced computational power to implement artificial intelligence may enable end-to-end automation and customer demand-driven manufacturing, operations, and even dispensing.

Most industries are now beginning to navigate the world of “Big Data” which requires capturing, processing, and retrieving large amounts of stored and real-time data. Handling Big Data and transforming it from an unstructured format into organized information, then contextual knowledge and finally insights (Fig. 1) provides the outputs necessary for rapid and reliable monitoring, decision-making and actionable results for a given system (Fig. 3). Manufacturers’ assessments of their process performance in Industry 4.0 requires an advanced data and computing infrastructure that integrates software and hardware to rapidly provide the necessary information about a process or product. A challenge of Big Data is deciding what to do with knowledge and insights gained from it, which could be used for internal auditing purposes, product release decisions, marketing, and/or sharing with regulatory agencies. In an IoT, Big Data is the source from which machines and devices interact, communicate, and learn from each other (Matthews, 2017; Byrne, 2018; Witkowski, 2017). Determining and communicating the data’s purpose will be a key technical challenge in Industry 4.0.

Of course, data alone is incapable of solving problems. Something must link the value chain, status updates, sensor data, and process controls. Wireless communications protocols are continually being developed, including novel modes of automated communication between networked machines and devices which will significantly reduce and/or eliminate the need for human intervention for numerous tasks, thus reducing risks associated with human error. For instance, analytical testing, equipment maintenance, adaptive process control systems, and quality control testing will need to be compatible across software and hardware elements and will rely on communications across networked devices to accomplish the full integration and digitization of a smart facility (Fig. 2). Industry may no longer need human user interfaces and dashboards to monitor and control systems, but it may need hardware and software that are compatible in a plug-and-play nature. The ease of sharing digital information could theoretically lead to higher levels of collaboration and knowledge transfer across the industry and lower the burden of preparing information to share with regulators (Strategy&, 2018).

While the easy sharing of large amounts of information could be clearly beneficial, sensitive digital information will need to be well-protected. Issues such as standards around data capture, storage, analysis, and transmission may be needed. Third-party data management may also be required and may need to be closely controlled, particularly as processes become autonomous and controls can be adaptable based on machine learning algorithms. These issues are part of larger vulnerabilities that are inherent to fully digitized systems and ultimately present risks to product and process security from cyberthreats. In an Industry 4.0 setting, companies will need to develop risk mitigation approaches to reduce or eliminate network vulnerabilities. The future will require that data and system architectures are fortified against disruptions or threats to operations involving networked devices and manufacturing equipment.

3.3. Logistical challenges

Industry and regulators will face logistical barriers to the implementation of Industry 4.0, and in some cases they may be competing with each other for the same scarce resources. The path to full adoption of Industry 4.0 approaches will require cultural changes and innovations by manufacturers and regulators addressing multiple data, computing, and automation risks. Knowledge and training gaps will need to be addressed in adopting a new paradigm and industry infrastructure based on digitized and inter-connected enterprise systems that rely on computational power, communications technologies, cybersecurity, and advanced controls in order to achieve optimization. A number of skills beyond the traditional biology, chemistry, and process engineering will be needed to adopt AI in pharmaceutical manufacturing. For example, this may require data scientists, computational and systems engineers, IT specialists, and AI experts. Regulators and industry may be competing for the same small pool of talent in these areas, at least initially. Certainly, new labor force training requirements are on the horizon and robust training programs will be needed.

A key feature of Pharma 4.0 is the application of AI-based mathematical models. The pathway towards making the concept of AI control a reality begins with the accumulation of historical data gathered from advanced manufacturing approaches such as continuous manufacturing. This is due to the necessity that AI-based strategies rely on model training with real data, much like humans learn from a young age from examples. For instance, in order to develop an AI-based digital twin for a biological or chemical process, the model must be trained with adequate historical data relating process control parameters with process performance parameters. In this regard, relevant data must be collected from individual process units for the development of an overall process. Machine learning may be easier if manufacturers adopt collaborative, precompetitive, or open innovation models to share these historical process data. This presents a shift from the current paradigm of a “closed” business model wherein all data and knowledge are stored internally within each company (Balasegaram et al., 2017; Schuhmacher et al., 2013). In this regard, intellectual property and intellectual property rights are a limitation that may need to be addressed. Ultimately, realizing the benefits of Industry 4.0 may require extensive cooperation and communication among and between manufacturers and regulators.

4. Conclusions

Industry 4.0 technologies have the potential to transform pharmaceutical manufacturing and logistics platforms through digitization, autonomous systems, robotics, and computing advancements. In particular, the pharmaceutical supply chain, production processes, distribution, and inventory frameworks could see significant improvements. The smart factory of the future will take on autonomous features enabling more production flexibility and agility. The path to full adoption of Industry 4.0 will require advancements and innovations addressing multiple data, computing, and automation risks and challenges. Both industry and regulators are developing competencies in preparation for smart manufacturing systems: modeling and simulations, sensor systems, data management, data analytics, computational and control engineering approaches needed to support autonomous systems, artificial intelligence, and computing infrastructures. Enterprise-level systems such as quality management and training may need to be re-envisioned. We are beginning to identify known or latent risks associated with these new approaches, recognize dissonance with existing approaches to regulatory compliance, and ultimately develop regulatory frameworks that support Industry 4.0.

The adoption of the advanced manufacturing technologies of Industry 4.0 may pose challenges to the current regulatory framework, because most regulations were developed in an Industry 2.0 paradigm of traditional batch manufacturing. The U.S. FDA has launched an effort to identify and implement needed changes in the regulatory structure to enable new technologies. For example, new policy and regulatory topics related to Industry 4.0 include the management of data-rich environments, the evolving concepts of process validation for advanced manufacturing systems, and the regulatory oversight of post-approval changes for such systems (FDA, 2019b). International regulatory convergence will be useful in encouraging industry adoption of new manufacturing technologies. For example, an effort is underway now to develop a guideline on continuous manufacturing of drug substances and drug products for both small-molecule and biological products (i.e., ICH Q13), which will help ease the burden of achieving global regulatory acceptance of these technologies (ICH, 2018). This type of cooperation and communication may be necessary to realize the promised benefits of Industry 4.0.

Of course, in addition to the regulatory, technical, and logistical challenges related to a new pharmaceutical manufacturing revolution, financial investment will also be required. The initial investments directed towards both capital and operating expenses to convert facilities or create new ones may pose barriers to entry for some. As with any investment, Industry 4.0 may not provide immediate returns. Yet, the long-term value of this new manufacturing paradigm should make the business case for adopting new technologies - more control, fewer errors, more responsiveness, and fewer drug shortages. In the future, additional, more accessible, and real-time product quality information will be generated, and it may become more transparent to purchasers, payors, healthcare providers, and patients - impacting demand. Such transparency would further incentivize investment in technologies that can consistently manufacture high quality products. The ultimate winner of Industry 4.0 in pharmaceutical manufacturing, though, should not be drug manufacturers or regulators, but rather the patients who will benefit from higher quality drugs with more reliable supply chains less prone to shortage.

CRediT authorship contribution statement

N. Sarah Arden: Conceptualization, Visualization, Writing - original draft. **Adam C. Fisher:** Conceptualization, Visualization, Writing - review & editing. **Katherine Tyner:** Writing - review & editing. **Lawrence X. Yu:** Conceptualization, Writing - review & editing, Supervision. **Sau L. Lee:** Writing - review & editing. **Michael Kopcha:** Writing - review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

No external funding for this work.

DECLARATIONS: This publication reflects the views of the authors and should not be construed to represent FDA's views or policies. Technologies and their applications addressed herein do not imply recommendation or endorsement nor best use for intended purpose.

References

Anderson, S., 2005. Making Medicines: A Brief History of Pharmacy and Pharmaceuticals. Pharmaceutical Press.
Arinez, J., Chang, Q., Gao, R., Xu, C., Zhang, J., 2020. Artificial Intelligence in Advanced Manufacturing: Current Status and Future Outlook. J. Manuf. Sci. Eng. 142 (11), 16.
Atobe, T., Mori, M., Yamashita, F., Hashida, M., Kouzuki, H., 2015. Artificial neural network analysis for predicting human percutaneous absorption taking account of vehicle properties. J. Toxicolog. Sci. 40 (2), 277–294.
Balasegaram, M., Kolb, P., McKew, J., et al., 2017. An open source pharma roadmap. PLoS Med. 14 (4), e1002276.
Banks, L., 2015. 10 Disruptive Technologies that will Transform Pharma. Pharmaphorum.
Baur, C., Wee, D., 2015. Manufacturing's Next Act. McKinsey & Company. https://www.mckinsey.com/business-functions/operations/our-insights/manufacturings-next-act. Accessed.
Berry, I.R., Nash, R.A., 2003. Pharmaceutical process validation. In: Nash, Robert A., Wachter, Alfred H. (Eds.).
Biophorum/BPOG, 2017. Automated Facility https://www.biophorum.com/wp-content/uploads/2017/07/Automated-Facility.pdf. Accessed.
Buvailo, A., 2018. The Why, How and When of AI in the Pharmaceutical Industry. Forbes.
Byrne, A., 2018. Why Industry 4.0 will Require us to Change the Way we Think of Managing 'Big Data'. Global Manuf.
Chapman, J., 2019. How AI Tools Will Transform Quality Management In The Life Sciences. Pharmaceutical.
Clemons, J., 2016. Creating value from smart manufacturing. Pharmaceut. Manuf.
Daemmrich, A., Bowden, M., 2005. Emergence of pharmaceutical science and industry: 1870–1930. Chem. Eng. News. 83.
Dublin S-TC, 2016. Industry 4.0: Surfing the wave of the next Industrial Revolution. https://www.tcd.ie/mecheng/research/stam/partnerships/ceramicx_god_interview.php. Accessed.
Ekins, S., 2016. The Next Era: Deep Learning in Pharmaceutical Research. Pharm. Res. 33 (11), 2594–2603.
Ezell, S.A., 2016. Policymaker's Guide to Smart Manufacturing. Information Technology & Innovation Foundation.
Fassbender, M., 2017. More Than Entertainment: Augmented Reality in the Pharmaceutical Industry. Outsourcing Pharma Web site. https://www.outsourcing-pharma.com/Article/2017/12/14/Augmented-reality-in-the-pharmaceutical-industry. Accessed.
FDA, 2019a. CDER Conversation: Assuring Drug Quality Around the Globe. https://www.fda.gov/drugs/news-events-human-drugs/cder-conversation-assuring-drug-quality-around-globe. Accessed.
FDA, Guidance for Industry. Process Validation: General Principles and Practice.
FDA, 2019b. Safeguarding Pharmaceutical Supply Chains in a Global Economy. In. House Committee on Energy and Commerce, Subcommittee on Health. https://www.fda.gov/news-events/congressional-testimony/safeguarding-pharmaceutical-supply-chains-global-economy-10302019.
Forcinio, H., 2019. New Machine Vision Technology. PharmTech.
Fuhr, T., Gonce, A., Positano, L., Rutten, P., Tepis, V., 2014. Flawless—From Measuring Failure to Building Quality Robustness in Pharma. In: McKinsey & Company Chicago, IL.
GE, 2020. Digital Twin. https://www.ge.com/digital/applications/digital-twin. Accessed.
Grossman, J., 2018. The Four Stages Of Digital Maturity: How Does Your Organization Rank? Forbes.
Guilfoyle, P., 2018. Pharma 4.0: Industry 4.0 Applied to Pharmaceutical Manufacturing. Pharmaceut. Process. World.
Han, Y., Makarova, E., Ringel, M., Telpis, V., 2019. Digitization, Automation, and Online Testing: The Future of Pharma Quality Control. https://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/digitization-automation-and-online-testing-the-future-of-pharma-quality-control#. Accessed.
Hartmann, B., King, W.P., Narayanan, S., 2015. Digital Manufacturing: The Revolution Will Be Virtualized. https://www.mckinsey.com/business-functions/operations/our-insights/digital-manufacturing-the-revolution-will-be-virtualized. Accessed.

ICH, 2018. Final Concept Paper: ICH Q13: Continuous Manufacturing of Drug Substances and Drug Products dated 14 November 2018. https://database.ich.org/sites/default/files/Q13%20Concept%20Paper.pdf. Accessed.
IEEE, 2021. Industrial Internet of Things. https://spectrum.ieee.org/telecom/internet/the-industrial-internet-of-things. Accessed.
InSilico, 2020. https://www.insilico-biotechnology.com/. Accessed.
Jovanis, M., 2019. Digitizing to Modernize Manufacturing. Pharm. Technol. 43 (4), 63–65.
Korteby, Y., Mahdi, Y., Azizou, A., Daoud, K., Regdon Jr., G., 2016. Implementation of an artificial neural network as a PAT tool for the prediction of temperature distribution within a pharmaceutical fluidized bed granulator. Eur. J. Pharmaceut. Sci.: Off. J. Eur. Feder. Pharmaceut. Sci. 88, 219–232.
Lee, S.L., O'Connor, T.F., Yang, X., et al., 2015. Modernizing pharmaceutical manufacturing: from batch to continuous production. J. Pharmaceut. Innov. 10 (3), 191–199.
Leurent, H., deBoer, E., 2018. The Next Economic Growth Engine Scaling Fourth Industrial Revolution Technologies in Production http://www3.weforum.org/docs/WEF_Technology_and_Innovation_The_Next_Economic_Growth_Engine.pdf. Accessed.
Lin, B., Lin, G., Liu, X., et al., 2015. Application of back-propagation artificial neural network and curve estimation in pharmacokinetics of losartan in rabbit. Int. J. Clin. Exp. Med. 8 (12), 22352–22358.
Lorenz Binggeli, H.H., Woelbeling, Christian, Zimmer, Thomas, 2018. Pharma 4.0 Hype or Reality? Pharmaceut. Eng.
Lydon, B., 2017. The New Era of Automation Architectures: What does it mean for users? Automation Web site. https://www.automation.com/automation-news/article/the-new-era-of-automation-architectures-what-does-it-mean-for-users. Accessed.
Marcus Ehrhardt PB, 2016. Digitization in Pharma. Strategy&. https://www.strategyand.pwc.com/gx/en/insights/2016/digitization-in-pharma/digitization-in-pharma.pdf. Accessed.
Markarian, J., 2016. The Internet of Things for Pharmaceutical Manufacturing. PharmTech.
Markarian, J., 2020. Optimizing Machine Health. PharmTech.
Matthews, K., 2017. What is Big Data's Role in the Fourth Industrial Revolution? Big Data Made Simple.
McCarthy, J., 1989. Artificial Intelligence, Logic and Formalizing Common Sense. In: Thomason, R.H. (Ed.), Philosophical Logic and Artificial Intelligence. Springer Netherlands, Dordrecht, pp. 161–190.
McCarthy, J.F., Marx, K.A., Hoffman, P.E., et al., 2004. Applications of machine learning and high-dimensional visualization in cancer detection, diagnosis, and management. Ann. N. Y. Acad. Sci. 1020, 239–262.
Montague, G., Morris, J., 1994. Neural-network contributions in biotechnology. Trends Biotechnol. 12 (8), 312–324.
Moore, M., 2018. What is Industry 4.0? Everything you need to know. TechRadarpro.
Otto, S., 2019. The Case for Predictive Maintenance. Pharma Manuf.
Pavani, A., Naushad, S.M., Kumar, R.M., Srinath, M., Malempati, A.R., Kutala, V.K., 2016. Artificial neural network-based pharmacogenomic algorithm for warfarin dose optimization. Pharmacogenomics 17 (2), 121–131.
Peres, R.S., Jia, X., Lee, J., Sun, K., Colombo, A.W., Barata, J., 2016. Industrial Artificial Intelligence in Industry 4.0 - Systematic Review, Challenges and Outlook. IEEE 4.
Powers, J., 2019. Data Integrity in the Trenches: A Look into Quality Control Lab. Pharmaceut. Eng.
PwC, 2015. Next Manufacturing: Industry 4.0. https://www.pwc.com/us/en/industries/industrial-products/next-manufacturing.html. Accessed.
PwC, 2016. Industry 4.0: Building the Digital Enterprise. https://www.pwc.com/gx/en/industries/industries-4.0/landing-page/industry-4.0-building-your-digital-enterprise-april-2016.pdf. Accessed.
PwC, 2021. Manufacturing's next big act: Building an industrial digital ecosystem. https://www.pwc.com/us/en/industries/industrial-products/library/industrial-digital-ecosystem.html. Accessed.
Sandle, T., 2019. Becoming Pharma 4.0: How Digital Transformation Is Reshaping Pharmaceuticals. BiopharmaTrendcom.
Schuhmacher, A., Germann, P.G., Trill, H., Gassmann, O., 2013. Models for open innovation in the pharmaceutical industry. Drug Discovery Today 18 (23–24), 1133–1137.
Shimizu, H., Yasuoka, K., Uchiyama, K., Shioya, S., 1998. Bioprocess fault detection by nonlinear multivariate analysis: application of an artificial autoassociative neural network and wavelet filter bank. Biotechnol. Prog. 14 (1), 79–87.
Shirazian, S., Kuhs, M., Darwish, S., Croker, D., Walker, G.M., 2017. Artificial neural network modelling of continuous wet granulation using a twin-screw extruder. Int. J. Pharm. 521 (1–2), 102–109.
Sonnedecker, G., Urdang, G., 1976. Kremers and Urdang's history of pharmacy. Lippincott.
Stanke, M., Hitzmann, B., 2013. Automatic control of bioprocesses. Adv. Biochem. Eng. Biotechnol. 132, 35–63.
Strategy&, 2018. Global Digital Operations Study Digital Champions. https://www.strategyand.pwc.com/media/file/Global-Digital-Operations-Study_Digital-Champions.pdf. Accessed.
Stracquatanio, A., 2018. Harnessing Augmented Reality in Pharmaceutical Manufacturing. Pharmaceutical Online Web site. https://www.pharmaceuticalonline.com/doc/harnessing-augmented-reality-in-pharmaceutical-manufacturing-0001. Accessed.
Takahashi, M.B., Leme, J., Caricati, C.P., Tonso, A., Fernandez Nunez, E.G., Rocha, J.C., 2015. Artificial neural network associated to UV/Vis spectroscopy for monitoring bioreactions in biopharmaceutical processes. Bioprocess Biosyst. Eng. 38 (6), 1045–1054.
Tilley, J., 2017. Automation, Robotics, and the Factory of the Future. https://www.mckinsey.com/business-functions/operations/our-insights/automation-robotics-and-the-factory-of-the-future. Accessed.
Tracy, R.B., 2017. Disruptive Pharma: 4 Innovation Trends to Watch. EtQ.
US Nuclear Regulatory C. Performance Based Regulation. US Nuclear Regulatory Commission. https://www.nrc.gov/reading-rm/basic-ref/glossary/performance-based-regulation.html#:~:text=Performance%2Dbased%20regulation-,Performance%2Dbased%20regulation,results%20are%20to%20be%20obtained. Accessed.
Veillon, R., 2020. 40 Years of Visual Inspection: Where Do We Go from Here? PDALetters.
von Stosch, M., Hamelink, J.M., Oliveira, R., 2016a. Toward intensifying design of experiments in upstream bioprocess development: An industrial Escherichia coli feasibility study. Biotechnol. Prog. 32 (5), 1343–1352.
von Stosch, M., Hamelink, J.M., Oliveira, R., 2016b. Hybrid modeling as a QbD/PAT tool in process development: an industrial E. coli case study. Bioprocess Biosyst. Eng. 39 (5), 773–784.
Witkowski, K., 2017. Internet of Things, Big Data, Industry 4.0 - Innovative SOlutions in Logistics and Supply Chains Management. Procedia Eng. 182, 763–769.
Wilson, C.J., 2018. Pharma's path to Adopting AI and Other Emerging Technologies. Pharma R&D Today.
Wilson, G., 2020. GE Digital: Optimising Manufacturing with Smart MES. Manufacturing.
Woods, T., 2017. Will Google Become the Next Big Pharma? Disruption.
Yadav, V., 2020. Vision Inspection Using Machine Learning/Artificial Intelligence. ISPE.
Yamamura, S., 2003. Clinical application of artificial neural network (ANN) modeling to predict pharmacokinetic parameters of severely ill patients. Adv. Drug Deliv. Rev. 55 (9), 1233–1251.
Yu, L.X., Kopcha, M., 2017. The future of pharmaceutical quality and the path to get there. Int. J. Pharm. 528 (1–2), 354–359.
Yu, L.X., Baker, J., Berlam, S.C., et al., 2015. Advancing Product Quality: a Summary of the Inaugural FDA/PQRI Conference. AAPS J. 17 (4), 1011–1018.