Review Article

Adaptations of Pharma 4.0 from Industry 4.0

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ABSTRACT

Pharma 4.0 conceptualizes extremely systematic automated processes, which could be batch, continuous, or a hybrid of these, operated by an integrated manufacturing control strategy. Quality by design and process analytical technology principles are used to strengthen the hypothesis of Pharma 4.0. These provide the potential for robust, efficient, and quickproduction. Industry 4.0 is employed in medical technology, health-care facilities, and biopharmaceutical manufacturing. Digital transformation plays a major role. Pharma 4.0 provides better instruments to enforce product safety and supply chain security. This review explains the impact of data analytics technology, digitization, industry 4.0, artificial intelligence, digital twins, and continuous manufacturing and their impact on Pharma 4.0.

KEY WORDS: Artificial intelligence, Digital twins, Digitization, Pharma 4.0, Process analytical technology, Quality by design

INTRODUCTION

Pharma 4.0 is an integrated manufacturing control strategy, and it is a holistic operating model for Pharma companies. It is the next step toward smart manufacturing, and it is based on Industry 4.0, which was first introduced by the Germans. Pharma 4.0 is the digitalized operations model of a pharmaceutical organization that consists of trends such as big data, interconnectivity, collaborative robotics, artificial intelligence (AI), and distributed cloud-based architectures.[1] International Society for Pharmaceutical Engineering's (ISPE) introduced Pharma 4.0 to pharmaceutical manufacturing and in 2017 ISPE Pharma 4.0 Special interest group (SIG) was formed to come out with a working model for implementing Pharma 4.0 concepts. It is a new industrial revolution and deals with automation, digitization, paperless document, data integrity, and risk-based approach. Digitization is an important component, it creates a new level of transparency as it enables quick decision-making and provides in-line and in-time control over operations and quality,[2] by employing advanced data analytics it increases process robustness and improves quality, productivity, and profit.[3] It makes pharmaceutical production safer and more efficient.

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PHARMA 4.0 OPERATING MODEL

From moving Industry 4.0 to Pharma 4.0 ISPE's Pharma 4.0, SIG has developed an operating model.[4,5] It is a combination of digitalization and ICH Q10.[6] The operating model combines submission-based and manufacturing control strategies to create a pharmaceutical quality system and covers the complete product life cycle; the quality management process is based on ICH Q10. When both ICH Q10 and Pharma 4.0 elements and enablers are combined, they form a complete product lifecycle.[1]

Industry4.0 + ICH Guidelines = Pharma 4.0 Operating Model

ICH Q10 consists of PQS elements such as corrective action and preventive action, change management, management review, and enablers such as knowledge and Quality Risk Management. The operating model is based on digital maturity and data integrity by design. These are upgraded in the ICH Q10 PQS model. The control strategy was explained in this model across the finished product lifecycle in which the manufacturing

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and submission control strategy is composed. ICH Q10 defines critical quality attributes (CQAs), critical process parameters (CPPs), and critical material attributes as key elements of product and design. ICH Q12 identifies these parameters as established conditions. These parameters are monitored by product quality and process performance systems to detect out of trend and out of specification. Knowledge management of all sub-organizations and integration of IT systems leads to a holistic process and enables data integrity of all big data and analytical approaches for decision-making. Pharma 4.0 includes PQS elements and enablers. These have a huge impact on complete product lifecycle management and quality.

PQS elements

It includes:

- Resources: Workforce 4.0, digitalization, available, and qualified
- Information System: Holistic value network, integration, and traceability
- Organization and Processes: Holistic control strategy, and lifecycle management
- Culture: Communication and decision-making.

PQS enablers

It includes digital maturity and data integrity by design.

Pharma 4.0 Elements

Resources

It includes human resources, equipment and machinery, materials, tools, and the final product. The efficiency of mass production is increased as smart equipment adapts to multiple configurations. Process analytical technology (PAT) monitors KPPs and communicate through digital infrastructure. Reference Architectural Model Industry 4.0 (RAMI4.0) cube explains the product-quality and process performance system. The integration layer acts as a task-based interface between humans and machines. Traceability and visibility of information are enabled by communication and information layers that are sent to the manufacturer for predictive maintenance through AI. Each layer communicates with the entire value chain network throughout the company. This increases the quality and availability of products.

Information systems

It is based on economic criteria by both people and communication technology. The computerized systems are integrated throughout the value chain network. This includes data interfaces, PAT technologies are applied to continuous process verification to support process automation, and real-time release testing (RTRT) is established by predictive process controls. Areas such as preventive maintenance, environmental monitoring, automation, continuous process verification, mass serialization, real-time-release, and the batch release should have integration with IT systems.

Organization and processes

Organization refers to both the company's internal organization and value network. It collaborates internally and externally. The holistic control strategy is the key element for lifecycle management in pharmaceutical processes. To ensure high product quality, CQAs and CPPs are monitored in continued and ongoing process verification. To design the step-by-step approach and ensure the integrity and performance of holistic control strategy, cross-functional communities are established.

Culture

It covers the value system within the company and describes the collaboration. By implementing automation technologies, paperless execution came to existence. This requires a culture of the collaboration of all systems such as production process, technology, and quality. The collaborative value chain contains three elements – design, execution, and realization where tech transfers, innovation, and maintenance together form a holistic control strategy.

PHARMA 4.0 ENABLERS

Digital Maturity

The four divisions of an operating model are common to all stages of the industry, but the implementation differs. Pharma specific model is developed that allows organizations to assess holistic control capabilities, future capabilities, and operated within the parameters. An organization should provide data visibility, data transparency, predictive capacity, and adaptability to move toward Pharma 4.0. The latest technologies such as paperless execution systems, virtual and augmented reality, collaborative robotics, 3D printing, and blockchain can authorize resources if all the four divisions are equally implemented.

Data Integrity by Design

Data integrity plays a key role in Pharma 4.0, data are transparent, and it travels in horizontal and vertical directions and poses new challenges. The performance product lifecycle depends on structural capabilities. If IT should implement in an organization, there should be defined processes and data flow. Data integrity is all about data quality, the data lifecycle, and ALCOA+ principles. It requires well-defined, robust, repeatable processes, risk management principles, and critical thinking. For example, excipients used in the company should have one name and one reference number across the company to mix-ups and errors.

IMPACT OF INDUSTRY 4.0 ON PHARMA 4.0

Industry 4.0 is defined as the technical integrating of cyberphysical systems (CPS) into manufacture and organization, as well as the implementation of internet of things (IoT) and services in industrial operation. In general, Industry 4.0 deals with computer integrated manufacturing (CIM), whereas industry 4.0 consists IOT where the machines and people associate and transmit each other. It is the digitalization of production.[7] It applies machine learning and industrial IOT (IIoT). Manufacturing processes are improved by employing data and analytics and maintains internal, autonomous, communication within the factory. The data are transferred between the types of equipment, and it analyzes the data periodically to control different processes.[8] It is dependent on CPS, IoT, cognitive computing, and cloud computing. It accelerates production while reducing faults and errors and has improvements in distribution and supply chain management (SCM). In CPS, operations are monitored, coordinated, controlled, and integrated by computing. The human thought process is simulated in a computerized model using cognitive computing, whereas IT systems and cloud offer to solve problems without human assistance and aids in decision making. SCM in Pharma plays a crucial role. From country to country, the product standards, environment and temperature, packaging, and labeling requirements vary. Technologies such as cloud computing, blockchain, radio frequency identification (RFID) tags, electronic records, cognitive computing, and CPS are used to track and trace continuously. Through electronic batch record systems (EBRS) the graphic user interface captures the data automatically, exchange of batch information, batch production management, report generation and accuracy of operators. In addition EBRS will provide central storage of data to maintain data security and integrity. AI and Pharma digitalization play a crucial role in Pharma 4.0.[9] Nine technologies form the building blocks of Industry 4.0 they are discussed below:

Big Data and Analytics

Real-time decision making is supported by collecting and evaluating data from different sources such as manufacturing equipment and customer management systems (mass data analysis).

Autonomous Robots

Robots have a wide range of capabilities; they interact with humans and improves performance.

Simulation

In-plant operations, the real world is reproduced in a virtual mode to perform tests and minimize machine programming. This allows for increasing the quality and machine setup times.

Horizontal and vertical system integration

Using computer systems, clients, vendors, and manufacturers are connected, thereby provides highly automated value chains.

IIoT

The devices and sensors are connected with centralized controllers, which allow us to communicate and interact with one another and analyze data to predict failures, which result in rapid, flexible, and efficient manufacturing processes to high quality with low costs and enables real-time responses.

Cybersecurity

The systems and production lines are fully interconnected with one another should be protected from cybersecurity threats such as hacking, industrial copyright, personal data, and privacy.

Cloud

The industry adopts cloud solutions powered by blockchain and other technologies. These challenge data storage, data integrity, privacy, and protection. The information is coupled with analytics and integrated with the end consumer information and feedback, which allows good quality and effective products. The cloud technologies gather the data from all over the production systems and store it.

Additive manufacturing

3-D printing is the latest technology, which prototype and produce customized products in small batches. Raw materials, stocks, and transport distance are reduced.

Augmented reality

These support a variety of services and send information directly to mobile devices. It gives real-time information to workers to enhance decision-making and work processes.[10]

AI

It is an emerging technology used in Industry 4.0. In regulatory perceptive AI creates difficult questions because many algorithms are used for product manufacturing, then the validation of the product becomes difficult. AI affects the industry, so the Pharma industry must focus on it, and the changes should be managed.[11] Pharmaceutical companies and health-care organizations adopt AI for early drug discovery, clinical trial optimization, and business intelligence. In delivering novel drugs to market, AI is assisted in clinical development and go-to-market activities. In operational tasks, AI manages external innovation projects, clinical

trials, and risk assessment. Innovations such as predictive analytics, and big data analytics create a digital plant. This improves production processes. Using AI new drugs are designed. Pharma companies must build internal digital capabilities to continuously monitor the risks.[12] Big Pharma adopts AI to encourage drug discovery. Drug target identification, validation, target-based and phenotypic drug and polypharmacology discovery, drug repurposing programs, biomarkers development, and biomedical, clinical, and patient data are included.[13] AI-powered digital twins used to predict and detect deviations. By running potential simulations and using data, the design and development of drugs take place, which leads to manufacturing drugs. In digital twin technology, advanced sensor data are used; it creates digital representations of existing assets. However, by implementing the standards and emerging technologies such as AI and digital twins, the industry can find a way to move effectively into this new arena of manufacturing.[14]

PHARMA DIGITALIZATION

There are two reasons for adopting digitization. First, the information in a variety of formats can be collected and processed with the same efficiency. Second, the smart factory is achieved where the operations are carried with minimal manual intervention, high reliability, and flexibility. The automated workflow, synchronization of assets, tracking, and scheduling increases yield and quality and reduces the cost.[15] In this digitalized concept, machines collect process and product data and communicate with other machines through IIoT. AI plays a key role in the industry and no human intervention, so the chances of errors are less.[16] Equipment, raw materials, and finished products are transported through collaborative robots, autonomous mobile robots. Robotics eliminates repetitive and manual activities and improves safety and control. Pfizer and Sanofi are beginning a digital transformation.[11] Pharma digitalization facilitates health-care transformation. Transformation drivers include health-care market challenges, complex regulatory requirements, and increasing operational challenges. By adopting digitalization, the health-care transformation leads to evolving new therapies and increased patient-centric care.[17] In wearable technology, wearable devices are used which are continuously monitored by health-care facilities. It provides a continuous data stream which decreases risk levels and helps the drug companies for better understanding of the medical conditions. The quality of life increases and expenditure decreases. In personalized care, 3D printers are used for personalized treatment. Spritam levetiracetam is the first product produced using 3D printers. IoT and cyber systems play a prominent role.[18] Now Pharma companies are adopting new technologies and innovations to improve medicine development and health care. The data play a prominent role in medication efficacy and decreases the risk factors. Pharma digitalization transformation drivers are health-care market challengers, complex market regulations, and increasing operational challenges.

Health-care Market Challengers

It includes as follows:

- Innovations and competition of the Pharma business
- Expanding price pressure generated by the strengthening price regulations in the market and patent expiries of major blockbuster medicines
- Demand for enrich data on the prescription potency and patient standard of life
- New business models and ecosystems are challenging the current way of business.

Complex Market Regulations

It includes as follows:

- Distinctive and speed changing global regulating in drug manufacturing and supply chain conformation are exacting infrastructure changes over ongoing fitness and abilities
- USFDA's perception for the 21st-century pharmaceutical quality manufacturing requires effective, acute, and flexible production that faithfully generates high-quality drugs.

Increasing Operational Challenges

It includes as follows:

- Pharma companies are facing increasing challenges in production flexibility, competent resources, time-to-market, and operational costs
- Global production is highly distributed and non-standardized
- A value network is very complex, with lot of partners and suppliers
- Information paradox: There is a lot of it, but not accessible or usable.[17]

Benefits of Digitization

- Process control is assured continuously
- Used to quickly detect any deviations
- Due to automatic monitoring, there is continuous data which is validated against regulatory guidelines
- Man-hours are decreased by generating annual reports automatically.[19]

In digitalization, digitalization ecosystem plays a significant role. Pharma IoT and Pharma Industrial Internet are the two digital ecosystems in Pharma digitalization. It elucidates the product lifecycle and product supply network.

Pharma IoT

IoT influences quality control, supply chain traceability, and overall supply chain efficiency. The

digitalization of Pharma products and processes with acute connected medical devices and IT services and patient care are conceptualized in Pharma IoT. It is market for utilizing; analyzing the Pharma products and deals with patient care data.[17] IoT is based on smart devices such as "Organ in a Chip" this allows us to run real-life diagnostics. The output from these devices is clubbed with Big Data analytics, thereby increases R&D productivity. IoT helps Pharma companies by saving costs, improved quality, better compliance adherence, and lesser time to market. "Chip in a Pill" is an ingestible pill on the consumption sensor that gets activated. Stomach fluids powders sensors. Sensor communicates health status using body's physiological response system. The wearable device captures the physiological response from the sensor and sends information to smart devices. The smart devices are synced with the cloud ecosystem. These IoT drive improvements are making operations more efficient and robust.

Internal Systems

Drug efficacy data and health information received are sent to R&D. The data can be fed to the analytics engine, and results are used in pharmacovigilance to identify adverse events.

External Environments

Health statistics are directly shared with health-care professionals. Hence, this information is used to control drug dosage and intensity levels.

Regulatory Submissions

Regulatory bodies receive the data directly; this can be helpful in clinical trials and post-drug launch. Using these smart devices, it decreases time-to-market drugs, errors are detected, and regulatory compliance is improved. Personalized medicines are prescribed by HCPs from the wearable devices data 4, it improves drug efficacy and decreases treatment period.

IoT Application Across Pharma Value Chain

These are applied in various stages they are drug discovery and development: Organ chip devices to run real-life diagnostics, wearable devices with sensors for real-time health reporting, sensors, and devices are used to monitor clinical sites, subjects, and real-time monitoring.

Manufacturing and supply chain

Auto-ID with AIDC is used for smart serialization. Report parameters, smart warehousing, and routing, predictive maintenance of equipment are captured using RFID and sensors.

Sales and marketing

It includes drug interaction checker.

Patient access

Wearable devices chip in a pill, smart pill with dose serialization, drug usage tracking, and medication compliance.

Advantages of IoT

- It increases manufacturing efficiency and operational efficiency in the warehouse
- It maintains desired storage conditions
- It ensures product integrity and traceability across the supply chain
- It optimizes inventory costs and maintains drug quality during transit.[20]

Pharma industrial internet

The digitalization evolution of product supply infrastructures from manufacturing to dispensing the medicines to patients is conceptualized. It manufactures and supplies to market.

- Infrastructures and capabilities
- Implementation of intelligence in manufacturing
- Execution of software in packaging control
- Implementation of integration supply chain
- Exploit back-end IT cloud-based services (XAAS) that use the data from the product supply [Figure 1].[17]

Digitization and Automation in QC Lab

Digitization and automation ensure better quality and compliance by decreasing manual errors and variability, allows faster, and effective resolution of problems. As Pharma labs incorporate digital and automation technologies, there is a drastic change. The manufacturing line is connected with high accuracy digital sensors. The evolution of Pharma labs – digitally-enabled labs, automated labs, and distributed quality control.

Digitally Enabled Labs

Digitally enabled labs are 100% available nowadays, 80% of paperless operations are achieved, and 90% of testing is done in labs. Technologies such as automated data transcription between equipment and systems, advanced data analytics for real-time data insights, and optimized schedules are used. The labs are transitioned from manual data to automatic data transcription between equipment and General Laboratory Information Management System (GLIMS). To track trends and to prevent out-of-specification, real-time data analytics and process verification are used. Digital tools like smart glasses are employed they create a digital twin of the lab to identify impacts before making changes. In production operations, these eliminate 80% of manual documentation work and increase personnel, equipment, and material utilization. These employ smart glasses, advanced

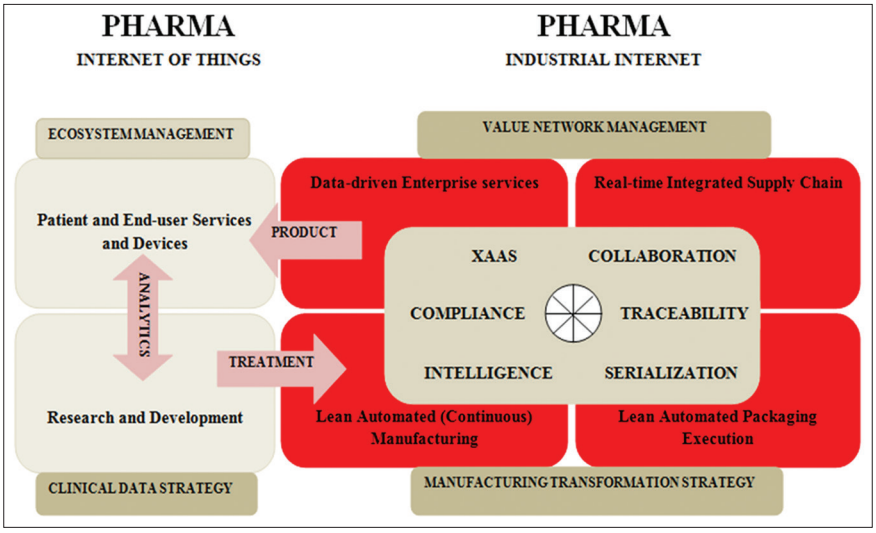

Figure 1: Pharma digitalization

analytics-enabled lab planning and schedule, digital management, GLIMS interface, advanced analytics problem solving, and real-time trending.

Automated Labs

To perform all tasks advanced automation technologies are used and predictive maintenance technologies are used to plan for infrequent tasks which lead to decrease downtime and reduce costs. 70–80% is available, 60–80% testing is done in labs, and 20–40% twisting on the shop floor. It employs automated compendia testing, automated settle plate handling, robotic process automation, automatic sample preparation, and processing.

Distributed Quality Control

In the production line, routine product testing occurs, enables RTRT. AI capabilities are adopted for equipment and robots. The adoption of PAT and RTRT is slow because of regulatory filing and approvals. In the future, operations should collaborate with R&D to improve quality control for new products and manufacturing sites. Distributed quality control can enable 0-20% testing in labs and 80-100% online real-time testing. Automated transcription of testing and product-quality-relevant process data is used, artificial-intelligence-enabled equipment and robotic technologies are used. 50–60% is available. In future Pharma manufacturing line instantaneous microbial detection of water and air, parametric real-time release, automated AI and machine learning are enabled for process and product parameter control.[21]

Advantages of Industry 4.0

- It increases profits
- It is applied in the medical device sector. For example, it becomes an integral part of Aesculap AG's Innovation Factory, which manufactures sterile containers
- Siemens AG's electronics plant in Amberg produces printed circuit boards are the digital company
- Piston filling machines for liquid pharmaceuticals such as cough syrup are manufactured by Bosch. This machine is a part of the digital network
- ESCAD Medical GmbH entered Industry 4.0. This company specializes in endoscopy. It adopted a storage system called endoSTORE® which improves endoscope processing. Endoscopes are registered with barcodes; this prevents disinfected endoscope to reach near patients.[7]

PHARMA 4.0 APPLIED TO PHARMACEUTICAL MANUFACTURING

Pharma 4.0 is the future of pharmaceutical manufacturing. The advent of the internet changed every industry. In Pharma 4.0, there is a huge demand for personalized products and it creates the increased pressure on R&D for the production of new drugs. Pharma 4.0 creates a single virtual network that connects human data and machines. Using IoT and big data analytics, it gathers real-time data. Quality and productivity are improved due to interconnectivity and automation. The manufacturing process is real-time monitored to identify any error that may occur in the future. In manufacturing, Pharma 4.0 transformed from batch to continuous process because it is a lengthy and time-consuming process. To overcome this continuous process is developed. This is a flexible and precise process where there is no need to stop in-between the process during manufacturing. Fully integrated components are adopted in an assembly line where the materials are supplied; there is no shut down of equipment and no human error. Many

companies switched to a continuous process to catch up with Pharma 4.0. For example, cystic fibrosis drug is manufactured using a continuous process. Meeting the requirements of GMP in Pharma 4.0 is a big challenge. Pharma 4.0 enables smart manufacturing with the help of integrated systems and software. The gap between manufacturing and automation is bridged by various technologies such as AI, big data, and cloud computing. For example, in manufacturing process sensors are fitted in every component, these sensors predict any failure or risks. The quality is relayed on real-time data exchange. For publishing and submissions, organizations rely on electronic submission experts. Cloud-based systems are highly used. For example, in the life sciences, GxP-critical information is managed. The data are stored in electronic format and located in the cloud. Storing the data in the cloud gives the manufacturers to access the data directly.[22] Digitalization and automation play a prominent role in the manufacturing of pharmaceuticals. CIM and computer-aided manufacturing were included in product development and manufacturing activities. Intelligent, virtual, and internet controlled manufacturing is advanced manufacturing.[23] There are four evolutionary stages of manufacturing. They are

- First stage – Mechanization, water power, and steam power
- Second stage – Mass production, assembly line, and electricity
- Third stage – Computer and automation
- Fourth stage – Cybersystems.[19]

Based on autonomous, computerized processes, Pharma 4.0 deals with digitalization and automation of the manufacturing world. To sustain the internal, self-governing, communication within the factory machine learning and IoT involved. Data are transferred and monitored continuously. For example, apart from the Pharma industry semiconductor industry implements Industry 4.0.[24] Intelligent networks were created by connecting machines and systems. For example, machines predict failures and trigger maintenance process autonomously. Decentralized intelligence creates independent process management, which represents a new aspect of the manufacturing process. EMI, cloud computing big data analytics, CPS, machine to machine communication, and automation concepts are explored. IT department plays an important role; it ensures necessary connections are made and maintained. Communication technologies like CPS will detect the defects and production failures early and increase productivity, quality. It should avoid problems; otherwise, it leads to expensive production outages.[19]

- Digitalization is employed in the pharmaceutical manufacturing process. Various PAT and
- Advanced process controls are used to enhance the quality and effectiveness of products. Robotic and integrated manufacturing control is essential for a continuous manufacturing system. Real-time data are consigned to control the system by PAT. Instead of fed-batch reactors perfusion technology used.

Nowaday's, Pharma companies support modernization. These technologies provide the capability for robust, effective, and quick manufacturing.[11] Pharma 4.0 allows the industry with smart tools, which leads to drug safety. IIoT impacts pharmaceutical manufacturing technologies to improve the efficiency of complex manufacturing operations. The Pharma companies adopt digital technologies to improve the process efficiencies, increase profits, and decrease efforts. Pharma companies face several challenges in regulatory standards, so it is mandatory for companies to implement digital technologies. By digitization, product quality is enhanced, process efficiency is improved, decrease cycle times, scrap and rework, and reduce downtime. During manufacturing, all the information and data regarding machines, materials, operators should be recorded. Real-time reporting and IIoT play a prominent role in continuous monitoring of equipment, personnel, and assembles the requisite data. By Supervisory Control and Data Acquisition or Manufacturing Execution Systems or Distributed Control Systems, the equipment is connected and controlled. By enabling informed decisions through data connectivity, the effectiveness of processes is improved. By full automation of plant, it enables faster time-to-market for products.[25] In Pharma 4.0, continuous manufacturing and continuous process verification play a major role. These two processes are highly digitalized to produce a robust process.

CONTINUOUS MANUFACTURING

Industry 4.0 technologies are executed by the Pharma industry. The batch manufacturing process is used, but it is a lengthy process, and in each step, the product is stopped and tested for quality. Sometimes the product is stored in the container and kept under hold times to complete the manufacturing process. This leads to an increase in the chance of defects and errors. FDA delivered a blog entry in 2016, states that it is promoting manufactures to metamorphosis from batch to continuous production. Nowadays, manufacturing of personalizing medicine is coming into existence. In continuous manufacturing, the process is done in the same installation without interruption, hold time between different stairs is eliminated, and the assembly line consists of fully

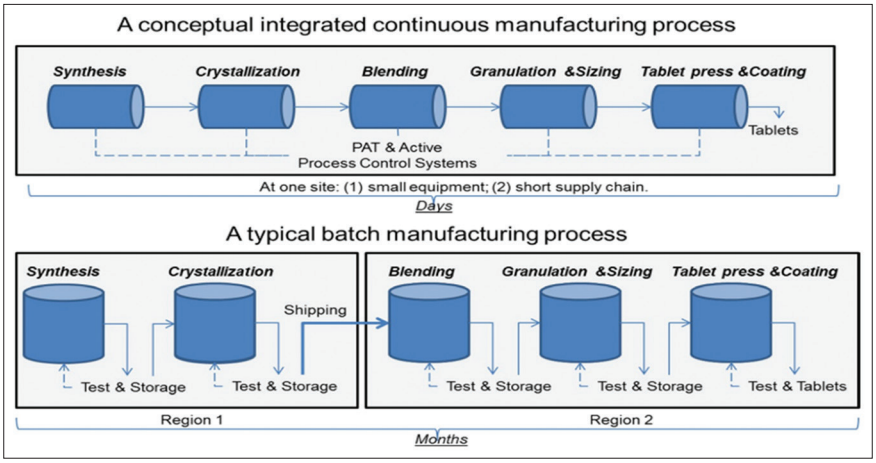

Figure 2: Continuous manufacturing versus batch manufacturing

Table 1: Examples of pharmaceutical industries adopted continuous manufacturing

Johnson and Johnson's	In 2016, FDA approved the Janssen drug unit to transit to continuous production[26]
Vertex	In July 2015, continuous the manufacturing process is used for producing cystic fibrosis drugs[27]
Eli Lilly	Formulated a compound for Phases I and II clinical trials in Eli Lilly's Ireland site by adopting continuous production[28]
GSK	In 2014, commenced an upper providence continuous pilot plant[29]
Pfizer	Unlocked a recent tablet production, continuous manufacturing plant in Freiburg in May 2017. Due to regulatory orders, manufacturing was stopped[30]

integrated components in which materials are fed. It saves time and abolishes human error [Figure 2 and Table 1].[24]

CONTINUOUS PROCESS VERIFICATION

CPV is adopted by all pharmaceutical companies, in every stage of the product development, the data are captured, analyzed, and reported continuously and validated to ensure that they are within the parameters. By digitization, CPV can be achieved using four ways.

Analytics

Statistical process control and statistical methods are used to collect data, and these procedures are used to compute and estimate the process stability and process capability.

Risk-based Real-time Approach

It verifies all CQAs and control strategy requirements of process materials.

In-line, On-line, or At-line Controls

Process performance and product quality are supervised.

Quality attributes

Incoming materials, in-process materials, and finished products are monitored.[19]

PHARMA 4.0 TECHNOLOGIES AND APPLICATIONS

Industry 4.0 has an immense influence on Pharma 4.0, where industries move from automated process control (APC) with reactive reporting to a true predictive analytics capability across the supply chain. APC tells what has gone wrong, whereas Pharma 4.0 predicts what will go wrong, and how to handle and avoid it. Both of these synchronize digital and physical value streams of product planning, production and assembly, quality assurance, packaging, and logistics. By adopting Pharma 4.0, the industries go beyond automation and using machine learning; IoT improves productivity, ensures regulatory compliance and drug safety, reduces unplanned downtime, and identifies complex business KPIs.[31] Advanced process controls such as smart equipment and PAT are used in process modeling. For example, smart equipment improves process control and efficiency by reducing waste in biopharma manufacturing. For example, the smart mixer is utilized for buffer solutions it estimates pH continuously and using acid and base pumps automatic titration is done. This saves time compared to manual titration. In real-time, PAT measures CQAs and employed in upstream bioprocessing, it takes time to employ in downstream and manufacturing. Mass spectrometry employs multi-attribute methods as PAT. The data are collected by sensors and PAT. This data are used to analyze what is happening in the process and if any changes are given it will identify what impact the changes will happen in a process. Using simulation algorithms, the process optimized. By enabling these processes, we gain greater knowledge of the process before performing the actual process.[16] The areas that can benefit the Pharma industries with high predictability, interconnectivity, and automation are listed below:

Regulatory Compliance and Traceability

FDA compliance through visibility into the factory, production lines, processes and machines, and track and trace solutions through barcodes, it increases revenue and market growth.

Minimize Unplanned Downtime

With smart predictive maintenance, capital asset management, it increases revenue and decrease in cost.

Monitor and Predict Complex Business KPIs

KPI metrics, predictive analytics, and big data, it increases revenue.

Eliminate Manual Processes

Automated actions based on predictive and reactive alerts. It reduces costs.

With Pharma 4.0, the companies can not only rely on real-time updates but also real-time production monitoring with predictive ability to identify faults and failures before they occur. When there is a fault in the production line, there is no need to throw out entire batches. If the shop floor is in sync with ERP, it can track any upcoming equipment service requests and inventory requirements. It provides real-time updates, auto inventory adjustments, automated testing results, shop floor and ERP in synch, no manual updates, and real-time production manufacturing. For example, the manufacturing line of tablets is fully automated and connected to IoT and Machine learning algorithms. The line has captured the data through sensors and generates service requests at various checkpoints. By predictive analysis of finished tablets, machine breakdown, the company can reduce the man-hours.[31] Pharma 4.0 adopts new technologies for ensuring product quality and patients safety. Technologies such as robotic process automation, digital twins, data analytics, drug development, and discovery play a key role.[18] These things accelerate the growth of digital transformation. These reduce risks and ensure quality through real-time analytics.[12]

Robotic Process Automation

It is also known smart manufacturing or APC which consists of IoT, machine learning, data analytics by AI, computing, cloud technologies, etc., some companies like Pfizer are shifting toward "connected manufacturing plants" that makes data visible and available. Collaborative robots augmented reality and paperless operations in their manufacturing site are employed by Sanofi. Merck connects "smart factories" for responsive and adaptive manufacturing.[18]

Digital Twins

Digital twins provide real-time data about the condition of a process of equipment.[12] Digital twin goes beyond traditional modeling. A generic digital representation of an asset type was created. Multiple attributes of an asset are captured by twins from sensor data, and this data are used for the detection of problems. Digital twins are used to estimating accurately the continuation and interruption; plans for process enhancements, and develop substitute plans in case of disruption without terminating the manufacturing process.[11] By employing this technology, new problems are identified and analyzed. From patient care to production, radical transformation is established in many areas of the pharmaceutical industry.[18] For example, digital transformation is engaged in Sanofi to simulate the biopharma production process. The digital plants have digital twins, which are connected directly to sensors. A real-time view of plant operation is given to managers by circulating the data to these digital twins. By analyzing this data potential, deviation recognized and rectified. Using process control strategies, yield is improved and by optimizing maintenance activities, downtime is reduced, which ultimately increases the overall output.

Advantages

- Intense asset
- Operation robustiousness
- Root-cause analysis is used to reduce cost
- Risks can be diminished proactively.

Data Analytics, Drug Development, and Discovery

Pharma companies employ advanced analytics across the research and development, development, regulatory and safety, manufacturing and supply chain, market access, commercial, medical, and enabling functions.[32] Digital analytics provides the relationship between raw material variability and process performance during manufacturing.[12] Pharmaceutical companies can use data analytics in the following ways to advance drug discovery and development, optimize and enhance the efficacy of clinical trials, target specific patient populations, improve safety and risk management, and improve insight into marketing and sales performance.[33] From incoming raw materials to the finished product, a single outlook is provided. It shows all the critical parameters and reports any issues that affect the product under manufacture. A green or red dashboard is used where operators can rapidly check which parameters require observation so they can prevent errors and improve the manufacturing, and finally, it leads to increase product quality and profitability.[19]

CONCLUSION

Pharma has typically been a disinclined industry; regulators encourage stimulating it into the Pharma 4.0 approach. Pharma 4.0 helps industries

to maximize productivity. By implementing the Pharma 4.0 holistic control strategy across the value network, it improves product safety, quality, transparency, flexibility, and productivity. Advanced analytics, robots, sensors, and automation of complex decisions change the efficiency, speed, response, and quality of processes. By employing these technologies, it increases productivity, shift economics, and fastens the industrial growth. The obstructions will fall, in time, and Pharma 4.0 will become a new standard in the upcoming period. Even after these advancements in Pharma 4.0 still, there is scope for innovation and advancement in the development of pharmaceuticals.

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