

# DIGITAL TRANSFORMATION OF THE PHARMACEUTICAL AND BIOTECHNOLOGY INDUSTRIES

**ARC Strategies**  
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The digital transformation of the pharmaceutical and biotech manufacturing industries is well under way. With advanced connectivity of data, sensors, and equipment; moving documents and data to the cloud; new analytics; and new service offerings, industry participants can improve their ability to comply with regulations while becoming more innovative. They can improve manufacturing efficiencies, respond to changing demands for drugs, and improve business models. Digital transformation represents an opportunity for pharma and biotech manufacturers to differentiate themselves and compete globally. Companies that have not yet begun to embrace digitalization risk getting left behind.

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## Executive Overview

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Compared to other consumer-focused industries, pharmaceutical and biotechnology have traditionally been slow to adopt emerging technologies. This is largely due to regulatory constraints, intellectual property issues, and a generally conservative culture. That said, most pharmaceutical and biotech companies are developing roadmaps for digital transformation and many have already started to adopt these newer digital technologies.

Digitalization allows sensors, machines, equipment, and people to communicate and collaborate, while providing real-time data to improve both plant processes and the products they create. Digitalization should enable new ap-

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*Digital transformation is beginning to disrupt the pharmaceutical, biotech, and medical device industries. Manufacturing companies are reinventing business processes and relationships and re-making legacy IT systems for better health care. This involves changes to business, engineering, supply chain, and manufacturing operations. The transformation involves modern software systems, data integrity, cloud, artificial intelligence, new healthcare sensors, robotics, connected things, and developing creative new ways to collaborate with and support patients.*

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proaches for innovation and creativity as opposed to simply enhancing or supporting traditional approaches.

For some companies, digital transformation, may just be a matter of going paperless (by digitizing paper-based data), connecting data silos, and/or implementing cloud-based solutions. But for most, digital transformation includes technologies such as cloud computing, advanced analytics, cameras, video, augmented reality, and mobility.

While the Internet of Things (IoT) connects people, processes, data, and “things” over the internet; digital transformation includes integrating information technology (IT) and operational technology (OT) and data to enable better insights, optimize processes, and create efficiencies. The Industrial Internet of Things (IIoT) extends the IoT into industrial environments.

While we’re seeing some progress in adopting digital technologies for business and manufacturing processes in the pharmaceutical and biotech industries, manufacturers still struggle to exploit the full potential of digitalization. Often, cultural inertia – rather than technology – holds them back. ARC believes that digital technology will drive value for pharmaceutical and biotech manufacturing, which – ultimately – should drive widespread adoption.

Along with newer therapeutics such as genomics and personalized medicine, the industry is evolving and adapting for the digital transformation. Production processes will evolve to support higher volumes or adapt to personalized medicine with “batches of one.” Additionally, the industry is experiencing a cultural change that includes a newer generation of workers.

### **Major Challenges for the Pharmaceutical and Biotech Industry**

In addition to operational problems, the pharmaceutical industry faces major challenges such as finding and gaining regulatory approvals for new drugs and then scaling up from laboratory to full production. The regulatory challenges demand new and improved track-and-trace solutions.

While as many as 70 percent of pharmaceutical companies are initiating pilots, ARC has not yet seen widespread expansions and scale up of digital transformation technologies across the enterprise, where the real value is to be found.

For some companies the initial strategy is to first improve cybersecurity and data integrity and move regulatory documents to the cloud. Others have begun advanced analytics initiatives and moved historian and other data to the cloud, edge, and new types of on-site devices. At least one major data historian supplier has a cloud offering that some pharma companies are using for real-time data. Other companies are implementing new enterprise architectures and platforms and scaling up digitalization, analytics, and visualization throughout the enterprise. Most of the companies that have not yet started on the digital transformation journey are now developing their initial plans and strategies.

The need for more efficient methods to produce breakthrough therapies and biosimilars, along with strategies to manufacture conventional and new drugs more economically and reliably sparks investments in more innovative methods for making drugs and biologics. The shift to personalized medicines and gene therapies will require the production of small batches. At the same time, pressure to reduce manufacturing costs and avoid shortages and recalls demands more reliable methods for ensuring the quality of large batches of conventional drugs.

Digital transformation enables manufacturing companies to allow patients to play a more active role in their own care. Some trends will impact manufacturing within the next few years, while others may take a little longer to

adapt due to the transformation that will require changes in technologies, therapeutics, people, and processes.

Challenges	Descriptions	Causes	Solutions
<b>Meeting demand with high quality at reasonable cost</b>	Preventing shortages due to demographics, better access to health care globally due to government plans	Population growth creates drug shortages for selected products. While new plants are highly automated, older plants still have islands of automation and use spreadsheets	<ul style="list-style-type: none"> <li>Pharma is investing in production management, and advanced analytics and new infrastructure. All CapEx expenditures need to justify with ROI. ROI is more important than ever</li> </ul>
<b>Compliance and regulation</b>	Meeting global regulations, automated documentation, move to paperless	Need automated documentation/validation	<ul style="list-style-type: none"> <li>Regulatory solutions, production management solutions with pharma documentation</li> <li>Blockchain/Track &amp; trace/serialization of raw materials and end products</li> </ul>
<b>Optimize production and yields</b>	Produce high-quality products quickly	Need high-quality products to meet increasing demand	<ul style="list-style-type: none"> <li>Production management, OEE, statistics, advanced analytics, and digital twin</li> </ul>
<b>Time-to-market</b>	Get new products to market as fast as possible	NPIs, faster changeovers, faster product release, and equipment availability	<ul style="list-style-type: none"> <li>Formulation management, planning &amp; scheduling, and production management</li> <li>Scale up in numbers, not in size – modularization</li> </ul>
<b>Personalized medicines, genomics, and biosimilars</b>	Many smaller batches	Batch-to-batch consistency and documentation	<ul style="list-style-type: none"> <li>Batch management</li> <li>Track and trace</li> </ul>
<b>Reduce costs faster</b>	Move to continuous processing even for biologics	Regulatory approvals for continuous manufacturing & innovation	<ul style="list-style-type: none"> <li>Move to modular design of plants</li> <li>Make batch processes continuous</li> </ul>
<b>Maintaining or improving quality</b>	Assuring high and consistent product quality, safety, and efficacy	Branding, product efficacy, and legal issues	<ul style="list-style-type: none"> <li>Quality management software</li> </ul>
<b>Reduce costs/increase profits</b>	Reduce product costs, prevent downtime	Competitive pressures from generics	<ul style="list-style-type: none"> <li>Production management</li> <li>Asset management/analytics</li> </ul>
<b>Digital transformation</b>	Transforming and using IIoT, Cloud, Data Lakes, and robotics. Executive support for cultural evolution.	Global competition needs to collaborate more	<ul style="list-style-type: none"> <li>New IIoT sensors, new data storage in Cloud, new analytics, etc.</li> <li>Moving data to the cloud</li> <li>New robotic solutions for repetitive processes</li> </ul>

#### Pharma & Biotech Industry Challenges, Causes, and Potential Solutions

## People, Process, and Culture

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While many companies view digital transformation as being technology-driven, in fact, it's more about people and processes. Digitalization enables collaboration among coworkers and partners, improves access to data and intelligence across the organization, and provides tools for remote expert support.

As digital natives, the new generation of workers tend to adapt faster to newer and often easier-to-use technologies. But where do workers fit in? The changes that digital transformation will have in the workforce are likely to be the most far-reaching and sustained effects. Not only will it change the size and profile of the workforce, it will rewrite organizational structures and how the work gets done. Managing the human element successfully can be the most difficult aspect. These transformation initiatives almost always have direct impact on humans. Often, a well-conceived and executed change management process works best to minimize impact and maximize productivity. Knowledge and expertise, hiring practices and staffing levels, teams and organizational design, reporting structures, executive support, sales and support, customer engagement, and more are all affected.

### Training

For digital transformation to succeed, training will be very important. Not just for the manufacturing employees but also for the company's customers. Manufacturing teams should be trained for new techniques, working with new technologies and ways to use them better.

Some companies are investing in and empowering digitally-minded people at all levels of the organization. These people need to help bring slower adopters on board with the new generation of technologies.

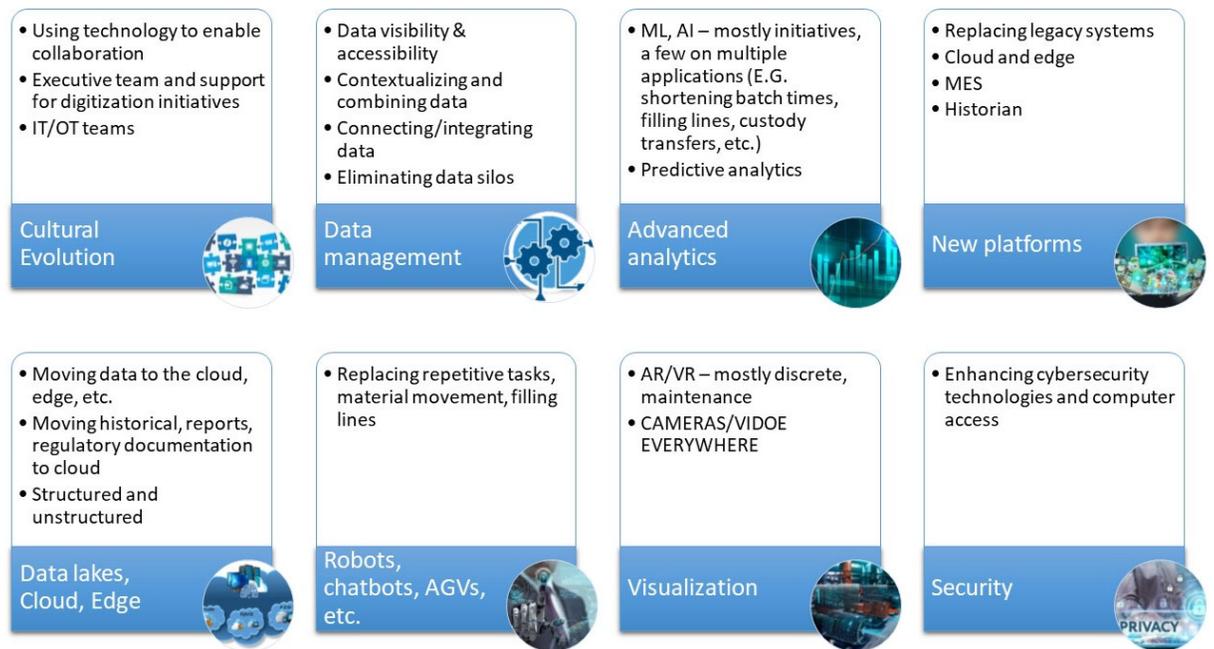
### Providing a Digital Transformation Culture

Adopting a digital transformation culture is one of the most important aspects of the digital journey. Pharmaceutical and biotech manufacturing companies need to adopt a startup approach and create a culture that inspires and embraces innovation. Some companies support failures by acknowledging them as part of process and moving on quickly. This

encourages innovation, new initiatives, and experimentation that helps determine future successes and opportunities for scaling up across the organization.

## IT and OT Reporting Structures

While an increasing number of automation and control organizations in manufacturing now report to IT, some organizations are deploying IT people that report to manufacturing. Manufacturing IT people and OT people need to see eye to eye. Manufacturing leaders believe that IT needs to better understand manufacturing's issues, processes, technologies, and culture. Without alignment and executive support for manufacturing, a cultural transformation would be very difficult.



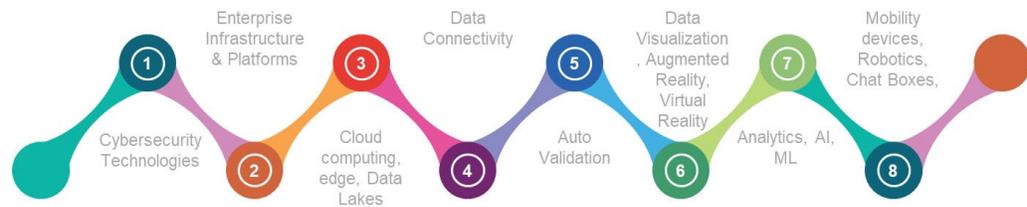
Some Digital Transformation Initiatives

## Technology Adoption

Digitalization, combined with new manufacturing processes, automation, and therapeutics and personalized medicine have the potential to transform the pharmaceutical and biotechnology industries in new and exciting ways.

Digitalization represents a significant opportunity for companies to become more competitive globally. Many companies have already started on their digital transformation journeys with cybersecurity initiatives and new platforms; moving data to the cloud; and adopting new technologies such as additive manufacturing, robotics, analytics, mobility and wearables.

Automated validation testing of scripts and regulatory documents and data are being moved to the cloud. Companies are adopting advanced analytics to help them optimize their processes. While not as widely adopted, augmented reality (AR) and virtual reality (VR) are also helping optimize processes. Similarly, simulation and digital twins are being used to make faster changeovers and to help determine process bottlenecks ahead of time.



**Some Digital Transformation Technologies in Pharma**

## Enhancing Cybersecurity and Secure Computer Access

Because cybersecurity is a huge concern, there is a major effort to improve the security of manufacturing technology. Without proper attention, business systems, factory systems, machines, tools, and sensors, and engineering systems could be vulnerable to cyberattacks. Companies are using multi-prong approaches to cybersecurity including upgrading to the latest security system, adding endpoint protection for older systems that can't be upgraded, and locking down firewalls on the factory floor.

Most manufacturing companies today rely on software to automate processes, manage supply chains, and facilitate research and development, which could increase cyber-crime risk. All stakeholders should be vigilant in implementing cybersecurity measures. The supply chain has become an increasingly attractive target for cyber-criminals. However, attacks against many manufacturing companies tend to be targeted at stealing intellectual property (designs and customer lists), or interrupting operations. Even small- and medium-sized manufacturing businesses should not assume that their size precludes them from threats. Mastering IT security issues provides a foundation for successful implementation of the digital enterprise.

The US Food and Drug Administration's (FDA) 21 CFR Part 11 regulations require secure access to computer systems. Many companies have invested in two-factor authentication approaches, including biometric finger scans, hand scans, eye scans, and facial recognition.

## **Data Connectivity and Data Management**

Many manufacturing facilities have already been connecting their manufacturing data silos and most suppliers' APIs or SDKs to make it easier to integrate data sources. As companies digitize, more data silos will be connected. However, the different organizations within a manufacturing enterprise (manufacturing, engineering, finance, marketing, etc.) store data in different environments. Many suppliers have discussed master data management, but most manufacturing companies still have at least some data silos.

Master data can leverage technology and business processes to present data in a consistent, contextual, and timely manner. However, if stored in the cloud, execution would often be too slow for many manufacturing processes. In this case, the master data is located in the manufacturing facility or close to the process.

Data and technology can enable a radical shift in a company's business models and methodologies, but planning is critical. A crucial component to digital transformation is dealing with staggering amounts of data. This makes data management, contextualization, integrity, interoperability, and synchronization critical. Audit trails regarding changes, physical location, and time stamps of changes are other issues that companies must deal with.

Digital transformation provides an opportunity for companies to work with data experts and business innovators to leverage new technologies and develop new insights that can increase efficiency for operational excellence.

## **Data Integrity for MHRA and FDA Compliance**

FDA's data integrity guidance emphasizes the need and requirements for "secure computation system access." Controls must be in place to restrict the ability to alter specifications, process parameters, or manufacturing or testing methods. Other computer changes must be restricted, possibly by limiting permissions to change settings or data.

Data integrity is a critical focus area for both the FDA and Medicines and Healthcare Products Regulatory Agency (MHRA). This is because without basic data integrity controls the agencies cannot rely on that company's data or records to determine compliance, quality, or safety risks to consumers and patients. Data integrity is the cornerstone of FDA compliance, since data and documentation provide the only reliable information to determine a company's actions and intent. FDA trains investigators to detect signs of data problems who look closely for signs of altered and doctored records. MHRA's "GXP Data Integrity Guidance and Definitions" publication describes the core elements of a compliant data governance system for manufacturing.

Any evidence of misrepresented data or problems with records related to current good manufacturing practices (CGMP) found during an inspection could lead to further investigation. Here, FDA would focus on the greatest sources of risk to patients. Inaccurate or falsified data threatens FDA's efforts to streamline regulatory processes. Companies with perfect quality systems will benefit from less FDA interference. Data integrity issues have real consequences. ARC believes that some of these risks can be reduced or eliminated using automated systems in conjunction with adequate procedures, standards, and enforcement policies.

Excellent quality data has always been important to FDA because data integrity issues can lead to serious CGMP violations. Dealing with poor data slows down FDA inspections and costs both the agency and the business, money. Unfortunately, data integrity issues are not uncommon and enforcement in this area is increasing.

FDA's *Data Integrity and Compliance with CGMP Guidance for Industry*, clarifies the role of data integrity in CGMPs for drugs. The guidance covers the agency's current thinking on creating and handling data in accordance with CGMP requirements. FDA believes that ensuring data integrity is an important component of industry's responsibility to ensure the safety, efficacy, and quality of drugs, as well as its own ability to protect public health. This is a key part of the digital transformation in these industries. ARC believes that it is in everyone's best interest for pharmaceutical companies to implement effective strategies to manage their data integrity.

All therapeutics shipped to the US must be produced under processes that comply with US FDA CGMPs and all computer systems used to produce a therapeutic must be validated and meet 21 CFR Part 11, which includes the

accuracy, reliability, integrity, availability, and authenticity of required records and signatures. Other global regulations such as those of the European Medicines Agency and MHRA also apply for companies that ship products to those countries. However, the US FDA tends to have the most stringent policies. While promising, the movement toward global regulations has been in the works for many years.

## **Enterprise Architecture and Integration**

Consider the Internet of Things (IoT) platform as the middleware. Most IoT platforms include a communication network and software for monitoring, troubleshooting and administrating the connected devices and managing the network and data management.

Some IoT platforms have software for translating or analyzing the data and support for developing apps. The IoT platform is the connector between the data collected from the “things” – devices or sensors at the edge and the user facing applications.

Pharmaceutical companies are updating automation systems to adapt to the digital transformation. Many of the systems in older pharmaceutical manufacturing facilities have not changed in over two decades. Many were implemented for Y2K and are now getting a major update to adapt to newer standards and the digital transformation. A lot of older systems are being replaced, since platforms older than 10 years often experience issues with support, maintenance, integration, and security.

Pharmaceutical and biotech companies are beginning to make use of the cloud to store, access, and connect all their data from research to clinical trials to manufacturing to the supply chain. Their cloud-based infrastructure will enable participants in the pharmaceutical and biotech industries to connect all ecosystems and enable real-time communication between globally disparate production systems.

## **Moving Manufacturing Data to the Cloud**

Much manufacturing data is being moved to the cloud. Typically, this includes non-mission critical data, such as historical or aged data. But data from historians, recipes, LIMS, MES, PLM, etc. are also being moved to the cloud. Most of the data is in on- or off-premise private clouds. With the

appropriate controls in place, data can be distributed across a cloud's hardware in several geographic locations.

While hesitation around cloud adoption in the pharmaceutical industry continues, current cloud technologies (even public clouds) can be more secure than what the companies can provide internally. This is particularly true for smaller companies with limited IT resources.

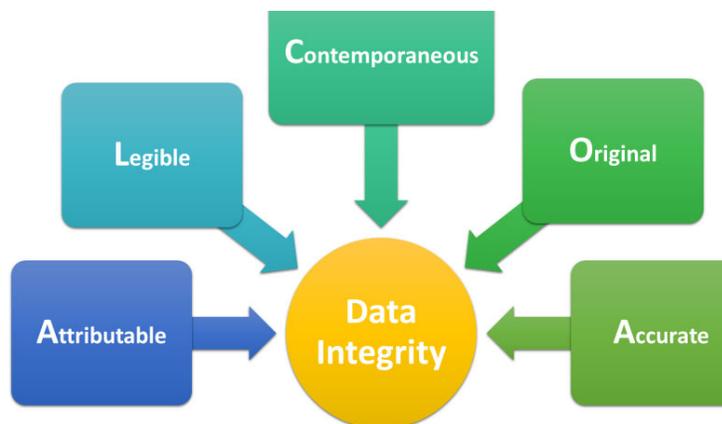
## Moving Regulatory Documentation to the Cloud

After cybersecurity, the movement of regulatory documentation to the cloud is currently the largest focus area for the digital transformation in the pharma and biotech industries. Many regulatory documentation technologies are being deployed in the cloud. Users want fast uploads to transfer GMP data and the ability to query, access, and make data available later.

FDA's recently updated guidance for industry, *Data Integrity and Compliance with CGMP*, mentions cloud infrastructure as being part of computer systems. This enables the use of cloud for regulatory documentation, including the documents required to validate the manufacturing process.

## Data Lakes and Big Data Investments

Companies are starting to invest in data lakes to store, manage, and analyze data. Some are putting structured and unstructured data in the cloud. This



**Data Should Be Attributable, Legible, Contemporaneously Recorded, Original, or a True Copy and Accurate (ALCOA)**

includes GMP data, with unstructured data dumps for non-GMP data. Some are using data historians to feed data into the cloud. Others are using semantic graph technology to help analyze dissimilar data. In concept, this allows IT and end users to combine diverse sources of structured and unstructured data including videos and images, internal and external into a vast data knowledge network. However, data integrity needs to be ensured and all data must be attributable, legible, contemporaneous, original, accurate, accessible and subject to easy change management.

Additionally, data lakes are working with existing enterprise data warehouses for an integrated approach to data. They cost less to operate than enterprise data warehouses for most applications. Pharmaceutical and biotech companies are using these for research and clinical trial data and starting to use data lakes for manufacturing too. Many companies are using data lakes to pull data from multiple sources as a research dashboard with analysis and visualization.

Data is usually stored in their native format and then contextualized when needed. Real-time and relational databases are typically managed as part of the data lake to make it easier to access some of the data sources. Because the data are stored in their raw, uncontextualized format, it's easier for users to reproduce what actually occurred if they do not know what they are looking for ahead of time or the interrelationships

On the other hand, some of the real-time automation data or relational databases that require time stamps, more specialized historians, and/or faster insights will still be used in conjunction with the data lakes and cloud technologies. This is because historians are more efficient at aggregating, contextualizing, and storing real-time data, including all the metadata for time-stamped data such as alarms, limits, and values that are also part of the data store. Other companies are "on the fence" about data lakes because they believe that once the volume of data gets high enough – it may be difficult to analyze the data or take too long to analyze.

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While cloud and edge both play a big role, early adopters of digital trends tend to be the smaller and medium-sized companies due to the cost savings from having someone else manage IT and cloud.

By moving data to the cloud, manufacturers can connect, interact, integrate, and collaborate on an unparalleled level. Some companies are enabling their OEMs to maintain the equipment or the systems so that they are always up to date and prevent any potential downtime. Collaboration will ultimately enable safer therapeutics.

A cloud-based environment can connect all the data from the various data silos and seems to represent an ideal method to manage, deploy, access, and maintain this critical data. Cloud also enables a paperless manufacturing environment for documentation including regulatory documentation.

## Continuous and Automated Validation

Digitalization is making the validation process easier and faster. Documentation is electronic, and some solutions automate software development, testing, and documentation. This means that as developers write code, they can also write scripts to test each piece of code. A good overall test automation program will include thousands of units, integration, and other tests for validation. By simultaneously writing the validation scripts along with the code and deploying those tests into a framework that executes at regular intervals, the application is being tested at every stage of development. Defects surface immediately and can be addressed closer to the point of origin. This would also enable continuous validation of applications. Auto testing and documentation will revolutionize the validation process—what used to take months can now be accomplished in days, or even minutes.

Installation qualifications (IQs) operational qualifications (OQs), and performance qualifications (PQs) can be updated as needed in the cloud or on the edge.

Validation lifecycle management using available automated testing solutions can automatically create a trace matrix, validate updates, and manage changes in cloud-based systems to support regulatory compliance. These solutions include workflow engines that support the preparation of required regulatory documentation that include IQ/OQ/PQ and change management. Other available software testing tools can accelerate application testing and software development.

By integrating cloud with automated validation technologies, life sciences manufacturers can automatically validate any updates or changes to cloud-based solutions. This provides confidence of compliance with FDA and helps ensure properly working systems.

## Data Visualization and Accessibility

By improving data visualization, accessibility, and collaboration, digital transformation enables companies to improve product quality, empower operators, and adhere better to regulations.

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How well the information is used to improve the manufacturing process will become critical to the survival of pharmaceutical and biotech companies. Most companies have

connected different plants or sites, but not yet embarked on an enterprise-wide initiative for data visibility.

Modern MES solutions are often employed to share data-based manufacturing intelligence across the enterprise in a secure and intuitive manner. The ability to visualize the metrics at a glance enables users to uncover actionable insights quickly. Even though different pharma manufacturers have different products and processes, they often track many of the same key metrics. These typically include:

- Sales and product demand
- Quality
- Regulatory performance and compliance issues
- Production output and yields
- Safety
- Downtime and maintenance
- Rejects and scrap
- Material and product costs

### **Advanced Analytics, AI, and ML**

Pharmaceutical companies are adopting a range of advanced analytics. These include descriptive analytics for condition monitoring of machines and production equipment, predictive analytics to determine what will happen, and prescriptive analytics to determine how to fix recurring problems. Some of these advanced analytics are self-service tools for engineers and workers that make it easier to analyze the data. Others integrate AI and machine learning to be self-learning. Some of these tools are being used by, integrated with, or built into other solutions. While analytics are not new, newer technologies make it quicker and easier to analyze real-time data to support timely decisions.

Predictive analytics and machine learning are an important part of the digital transformation for life sciences manufacturers. ARC has spoken with several pharmaceutical companies that are applying predictive analytics solutions for a variety of challenging applications. These range from reducing the time for clean in place to determining optimum bioreactor end points. All have strong value statements resulting in better use of equipment, materials, improved time to market, and reduced manufacturing costs. Other pharmaceutical companies discussed examples of how they are using predictive analytics solutions for maintenance to prevent downtime.

Another class of industrial analytics, marketed as artificial intelligence (AI), gets much of the attention today. This class, a subset of AI, uses algorithms that mimic the human brain to replicate human capability for recognition. Machine learning (ML), natural language processing, and chatbots are examples of this AI subset.

As it ingests large amounts of data, ML can identify discriminative patterns and identify the probability of a behavior occurring. ML techniques can adapt to incorporate new behaviors and data sets without being explicitly told what to look for. However, in most cases in the pharmaceutical industry humans are still involved to make the final determination.

### **Additive Manufacturing/3D Printing**

Additive manufacturing (AM) will have a significant impact on the manufacture of future pharmaceutical and biotech manufacturing processes. AM technology is currently being used to manufacture or print pills and to make artificial limbs and prototypes in the medical device industries. AM will continue to expand and enable more consistent and error-proof manufacturing for both personalized and continuous processing of pharmaceuticals.

AM could be a game changer, particularly in personalized medicine and genomic based products. Therapeutics could be manufactured in the hospital right beside the patient. Additionally, AM can be used for clinical trials and to improve product development processes to support high volume manufacturing. AM could also reduce validation efforts required for new products.

### **Support for Mobile Workers**

Mobile computing devices including smartphones, tablets, still and video, cameras, smartwatches, etc. are widely used today. They have transformed a lot of manufacturing processes that were previously performed manually or required an operator to remain at a console and enter data - sometimes writing notes on a clipboard so that he or she would remember to input the right data. Tablets and smartphones are being used for data collection. Cameras and wearables are being adapted to track operators entering data and facilitate physical security. Some tests will be linked to mobile phones equipped with biochips and will initiate new pharmaceutical products for different patients.

Employees want to work remotely and be able to both get and input the right information. This includes scanning and inputting information about incoming materials and finished products to improve product tracking throughout its lifetime. Electronic data entry via mobile devices speeds data capture and improves accuracy. However, it's important that mobility and cybersecurity be considered together.

## Robotics and Automated Guided Vehicles (AGVs)

Robotics already play an important role in pharmaceutical manufacturing, and are commonly used for filling, inspection, packing and in the warehouse. Many pharmaceutical and biotech companies are investing in robotics be-

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*Robotics will play an even larger role in process manufacturing in the future. Future pharmaceutical employees will work beside the next generation collaborative robots in the manufacturing process. Areas that have repetitive processes will be initiated first. Additionally, there will be more robotic-based systems, which will be able to manufacture some products without workers.*

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cause of the obvious business value. One large pharma company, for example, is using a robot on a bottling line to place dispenser caps onto bottled medications. Robots and robot-like bioprocessing equipment are also being used to produce personalized medicines, such as the antigen needed to trigger a cancer patient's immune system and target the tumor.

Robots are also being used in cleanrooms to minimize human contamination and in laboratories for repetitive procedures such as cleaning. Automated guided vehicles (AGV), combined with robotics and fully automated cage washing systems, can simplify operations and overall logistics.

New robots will incorporate more haptics technology, enabling them to "touch" and "feel." This makes them more sensitive and ARC expects their use to increase to support future modular production concepts.

Advances in sensor technologies, artificial intelligence, haptics, and real-time connectivity within the factory make human-robot interaction (HRI) possible. Collaborative robots, or "cobots," autonomously learn new work steps/processes and how to interact safely with their human colleagues. This enables humans and robots to work together in close physical proximity without being separated by physical cages. Cobots can be used in multiple functions – from providing single parts, to loading machines, to autonomous assembly. This can free human workers from having to perform tedious repetitive tasks. New robots will be used where conventional robots had been

prohibited in the past due to their size, immobility, and low-level protection mechanisms.

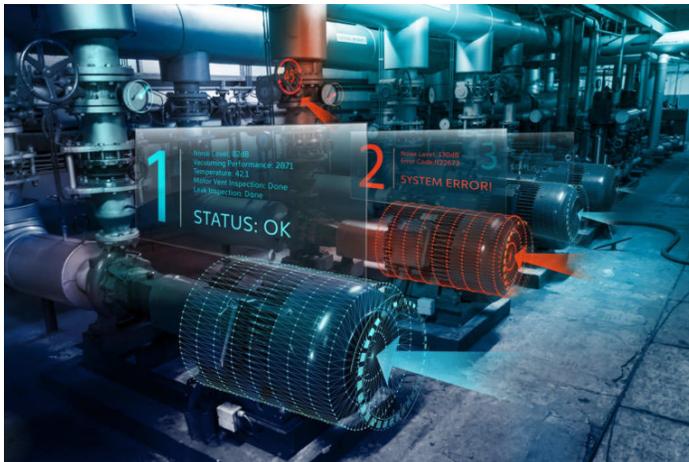
These changes will open enormous potential for more efficient manufacturing and new supplier services. ARC believes that “robots as a service” will be part of the digitalization future.

## Chat Boxes and AI

Many companies use chatboxes, a form of AI, because of their ability to increase production and assimilate more information from human workers.

## Virtual Reality and Augmented Reality

Virtual reality (VR) can be thought of as a mirror image of the equipment or machine. With augmented reality (AR) screen overlays or a smart device



**Augmented Reality Provides Workers with Helpful Contextual Information (Image: Siemens)**

overlays a digital image of real systems. Both give additional information or instructions or identify problems or repairs to the operator or user. VR/AR and mixed reality can be very appealing to the new worker generation or someone without extensive experience with the automation system.

Virtual reality is being used in operations and maintenance for training, troubleshooting, and to gain a better understanding of the process. VR enables remote experts and engineers to

provide assistance. Although more training today is done via interactive computer video, future training will be more virtual since it can accelerate the learning process. VR can be used to identify the source of a problem, adjust settings, and more. Individuals can drill down and see what something looks like, which can be very helpful.

## Process Simulation and Digital Twin

Digital twins are being used to optimize new product and manufacturing processes before investing in physical prototypes and assets. A digital twin is a virtual representation of a physical product, process, manufacturing

facility, or value chain that can be used to help predict the physical counterpart's performance characteristics. MES can be based on a model of the plant

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*Digital twins can help determine the impact of design changes, new product lines, usage scenarios, environmental conditions, and other endless variables – eliminating the need for physical prototypes, reducing development time, and improving quality of the finalized product or process.*

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or a digital twin of the process and used throughout the product lifecycle to simulate, predict, and optimize the product and production system – starting from before any investment has been made in physical prototypes and assets.

Next-generation platforms will enable simulation-based processes for manufacturing that accelerate and validate the design prior to manufacture. This will help optimize and accelerate the roll out for new products. Simulation will enable production processes, machines, and other production equipment to be easily validated prior to startup.

As factories digitize, they will rely upon a complete digital representation (“digital twin”) of the entire physical value chain. This seamless integration of data along the value chain will be critical to maintain competitiveness. New smart manufacturing and digital production require complex digital capabilities and in-depth understanding of how they interact.



**Steps for Process Optimization Using Digital Twin**

increase efficiency. The goal of the digital twin is for synchronous, real-time mapping of all processes in the virtual and real worlds.

In the future, digital twins will enable workers to simulate a manufacturing line and run through the execution and model changes using a virtual environment before actual changes are integrated to help optimize production. This will

### **New Sensors for Industrial IoT**

Pharmaceutical and biotech companies are partnering with their automation providers to bring their production systems into a smart, connected environment. This involves the use of intelligent sensors, equipment, and robotics with intelligent edge connectivity and computing.

We're seeing a variety of new IoT sensors in pharma. These include acoustic and vibration monitoring sensors for equipment condition monitoring and infrared sensors to verify chemical composition prior to packaging. We're also seeing connected cameras and videos everywhere.

### **Blockchain for Track and Trace**

By 2023, every company in the US pharmaceutical supply chain is required to meet the regulations outlined in the Drug Supply Chain Security Act, which outlines steps to build an interoperable electronic system to identify and trace certain prescription drugs. Part of the requirements include data collection on supply chain, transport, and product storage temperatures.

New blockchain technology offers considerable potential to improve track and trace capabilities across the industry. "Going digital" involves securing the supply chain. And blockchain can build a connected record for the pharma supply chain and products. Blockchain enables one party to prove to another that it has received an item without disclosing anything other than the specific details required. Serial numbers or other data can be verified and kept private. An interoperable system, blockchain requires an ecosystem and network and involves multiple companies. The future will include managing chain of custody for personalized medicines, raw material certification, cold chain, and more.

## **Business and Manufacturing Processes**

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Digital transformation of the pharma and biotechnology industry will also drive and/or support new business and manufacturing processes.

### **From Batch to Continuous Processing**

Moving from batch to continuous processing may not seem like a major issue, but in the pharmaceutical and biotechnology industries this has been a major step forward. Most pharma companies still rely on batch processes despite the potential benefits and cost savings from continuous processing. Continuous processing works fine in most high-volume industries with well-known processes. But pharma is a highly regulated, largely batch-oriented industry that does not regularly lend itself to continuous processes.

Unanswered questions surround issues such as handling feedback control and electronic batch records for continuous manufacturing and how to work with machine learning and AI applications. (Most of the manufacturing examples still involve a human and the AI application does not move an actuator.)

That said, the use of novel science and technologies for continuous manufacturing can also lead to innovative pharma and biotech products and help pharma companies resolve some long-standing cost, quality inspection, supply chain, and even cold chain issues. Well over a decade ago, the pharma and biotech industries started looking at producing products in continuous processes, rather than in batches. While most industry participants agreed that for high-volume, high-demand specialty drugs produced chemically in batches, the move from batch to continuous processing could work well. To avoid contamination issues, the process is usually run using disposables. The need to change the mindset and adopt new technologies has resulted in slow adoption of continuous manufacturing.

Although some companies have already received approvals from both the European Medicines Agency (EMA) and US FDA, the additional regulatory approvals required can increase risk for some companies. Currently, only a handful of companies have received approvals to produce in a continuous manner.

According to an article in the Wall Street Journal, Johnson & Johnson wants to manufacture 70 percent of its high-volume products on continuous processing lines within eight years. Amgen already uses continuous manufacturing processes at its Singapore plant and GSK has built a \$29 million continuous manufacturing plant in Singapore. Most of the projects under way are for the processing of finished products from active pharmaceutical ingredients (API).

### **Smaller Batches for Personalized Medicines**

At the other end of the production spectrum, because of the move to personalized and individualized medicine, ARC expects to see more smaller batches being produced, right down to batch sizes of one. It's likely that medicines for some rare diseases and individualized medicines would continue to be produced in batches, rather than in continuous processes. FDA has approved the use of additive manufacturing to manufacture pills and this could potentially benefit customized production.

The shift to a personalized, gene-based research approach that prevents and even cures diseases will impact how future products are manufactured. Additionally, newer therapeutics will be developed faster using data and analytics to determine outcomes. And this will affect manufacturing, with batches of one or cellular manufacturing becoming the norm. Some predictions include hospital-based manufacturing units for individual therapeutic production based on individual patients' DNA.

Emerging CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) genome engineering technology, for example, enables scientists to easily and precisely edit the DNA of any genome.

Dozens of therapeutics are waiting for FDA approvals, with more predicted for 2019. Some of these technologies will be manufactured in vaccines that modify DNA while others will be done on an individual basis. It's likely that CRISPR will transform healthcare and the pharmaceutical industry and manufacturing as we know it today.

Scaling up for clinical trials, production, documentation, and validation will be critical for companies adopting this technology. Manufacturing processes will range from very small to high volume production.

### **Future Role of Patients in Manufacturing**

While healthcare professionals will continue to represent the relationship between patients and the pharmaceutical and biotech industry, digital trends include increasing patient feedback and their access to other resources. Feedback from connected patients will improve the efficacy of medications and treatments and play a major role in manufacturing and product changes in the future.

Social media is a powerful communication tool and most companies are investing in social media feedback and care for the patients who are their customers. Pharmaceutical and biotech companies will focus on customer experience as a differentiator and any ways that manufacturing can enhance that experience will become part of the digital journey. Digital technologies are making it easier for companies to access and track patient outcomes and the good news is this will continue as technologies become more interoperable and connected. "Digital" will be the catalyst for changing the future of manufacturing and healthcare. Patients will have a more active role in

healthcare and manufacturers will be more flexible in redesigning and re-engineering processes to meet new needs.

### **24/7 Virtual Care**

Doctors have begun to use digital care for some patients and, in the future, 24/7 virtual care for patients could become the norm. The industry is starting to see new sensors like watches that monitor heart beats and even produce EKGs, or injectable sensors that give continuous biofeedback data to doctors and others involved in the patient care. Google has partnered with Novartis and Sanofi and Descom to provide new connected technologies that monitor glucose levels and insulin in real time using the cloud to alert the patient before a problem occurs. NeoCare Solutions from Aetna provides on-demand assistance from neonatal nurses after patients return home with their infants. New sensors, apps, and other technologies will allow for better, more individualized patient care and better and faster feedback for the pharmaceutical company and manufacturing.

Some companies are investing in a digital ecosystem of sensors, applications, and therapeutics to obtain better data and better patient outcomes. This digital pharmaceutical ecosystem will combine biophysical information such as heart rate, blood pressure and other measurements that are possible to obtain on smart phones today and can be combined with other data to accurately assess patient response.

For pharma and biotech manufacturers, the changes in digital expectation and experience will result in a more customer-centric environment – even for manufacturing.

### **Regulations and Innovation**

Regulations and documentation have taken their toll on the US pharmaceutical manufacturing industry by inhibiting innovation and use of new technologies. However, FDA is now “on board” and issued guidance in 2017 to help pharmaceutical manufacturers implement various technological advances. We are also seeing similar activity by the European regulatory agencies.

FDA is trying to encourage manufacturers to be more innovative and thus can no longer be held responsible for limiting pharma manufacturing

production. The pharmaceutical industry is responding by embracing digital transformation.

## Ecosystems of Partnerships

Partnerships and OEMs that help improve efficiencies and processes by providing access to data, systems, equipment, and applications will lead to safer, more consistent, and higher quality products. Enhanced connectivity and collaboration will enable workers to improve efficiencies and make better data-based decisions. Several companies are implementing SaaS offerings using analytic tools to analyze data, networks, processes, and more.



**The Cloud Will Improve Collaboration Across an Extended Ecosystem**

By integrating cloud-based systems with an ecosystem of key stakeholders that includes contract manufacturers, distributors, OEMs, and other experts, manufacturers will improve efficiencies, reduce downtime, and reduce costs. Cloud technologies will enable secure access for experts who can help manage and maintain data, systems, equipment, and other things remotely. By migrating data, applications and systems to the cloud, companies can collaborate securely within an ecosystem of key stakeholders to improve pharmaceutical processes across the value chain.

## Critical Digital Transformation Initiatives

The main challenge of digital transformation is determining how to balance and prioritize the many organizational areas, technologies, and systems that will all need to be transformed. Some pharmaceutical and biotech companies face disruptive challenges from top to bottom, inside and out. In addition to substantial changes in products and services (such as for personalized medicines), companies in this sector should expect a series of transformational changes in their technologies, culture and organizational structure, business systems, corporate culture, IT, engineering and design systems, and production systems.

Pharma and biotech manufacturers should recognize that digital transformation extends to their culture, people, documentation, regulatory compliance, product quality, assets, supply chain, business processes, operations, lifecycle services, and even patients. In the future, pharmaceutical companies undergoing a digital transformation will store more data in the cloud and mine the Big Data using machine learning and artificial intelligence to identify patterns and behaviors that were not apparent previously. This will extend from research to clinical trials to manufacturing to the supply chain and right out to the patient. All will provide better patient outcomes. Eventually some manufacturing processes will be autonomously validated, tested, and operated.

A majority of pharmaceutical and biotech executives maintain that the digital transformation and a smart, connected-sensor environment in factory production systems are important to their competitiveness. These executives understand the value from the transformation starting with research and clinical trials through manufacturing and support. Additionally, new supplier service offerings will enable pharmaceutical companies to focus on what they do best.

### **Research and Clinical Trials and PLM**

Engineering technology (ET) systems are another key enabler for digital transformation in manufacturing. Often referred to as product lifecycle management (PLM) systems, these systems enable pharmaceutical and biotech manufacturing companies to design new manufacturing lines with new technologies and machines to manufacture new products. While used more often to design medical products and components, PLM is also being used for pharmaceutical drug manufacturing.

The ecosystem or environment in which the patient will use the product should also be evaluated, if possible, simulated. A digital twin of the product must be created to operate in the simulated environment. All entities involved in operating and supporting the product must be considered when establishing the real-time data monitoring requirements for product performance, output, and patient health. It will be important to understand the customer's day-to-day experience and how he or she interacts with products in an intelligent, connected environment. Social media and social media-like intelligence about the product may help improve product quality in the future.

Creating and supporting intelligent connected products requires collaboration among engineering disciplines, such as computer-aided design, engineering, and manufacturing (CAD/CAE/CAM); sourcing; materials science; and computer-aided process planning. Data needs to be accessible and easy to analyze. In addition, manufacturing, procurement, sales, marketing, customer services, and other departments need to access current, common, correct information about each product. A quick, flexible, and collaborative response to each customer-introduced design requirement will be required across all disciplines and departments. In some circumstances, biological, chemical, and materials formulation and simulation, may also enable product and manufacturing innovation and optimization.

R&D and engineering systems will need a diverse range of capabilities. These include 3D CAD, simulation, data management, bill of materials, product planning, manufacturing operations planning, program management, data management, and configuration and change management capabilities. In addition, the system should:

- Protect intellectual property without compromising a company's ability to collaborate internally and externally using cybersecurity technologies
- Extend compliance data to a broader audience to allow for more effective decision-making and awareness
- Translate quality and other customer needs into data-driven requirements for new complex products
- Provide robust support for strategic supplier relationships and ecosystems

### OT Systems: Modern MES Still Critical

Within the operational technology domain, the core production management and execution requirements for pharmaceutical manufacturers have been served by MES/MOM systems, spreadsheets, or paper systems. While some experts believe that new IoT platforms and analytics will replace MES/MOM

systems, integrated MES functions will still play a critical role in some IIoT environments.

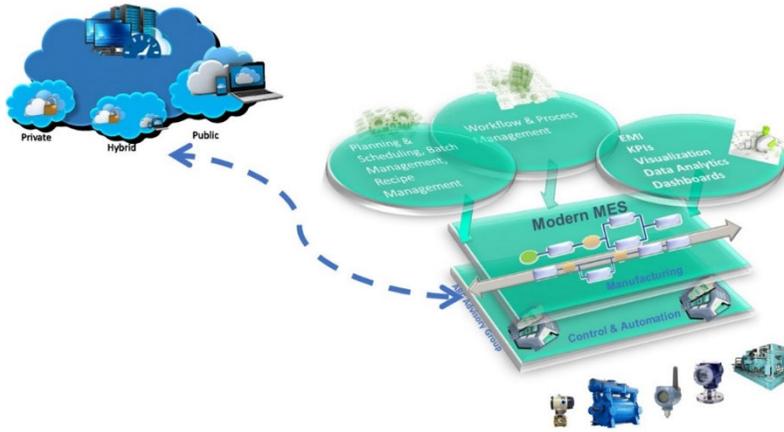
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*The modern MES dynamically executes processes and enables real-time intelligence for operations and enterprise decisions. It also provides middleware for ERP and automation systems and is able to integrate and aggregate both the transactional and real-time data.*

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In many pharma and biotech applications, modern MES solutions can enhance Industry 4.0 and IIoT. IoT platforms collect data from MES applications and historians because the manufacturing data is already standardized

and contextualized. MES will continue to enhance IIoT and edge analytics to optimize business performance by providing timely response for product, equipment changes, alerts, and intelligence to help optimize business outcomes by ensuring that the information is available to the right person or machine in the right context in real-time.



#### Modern MES Solutions Can Enhance IIoT and Analytics Through Timely Response

product changes. IIoT can also enhance MES capabilities, for example, by determining optimal workflows using analytics on historical data, but MES will continue to execute real-time production. For example, MES can ramp up processes rapidly when products change quickly as is required for batches of one, or the new generation of personalized or customized medicine production.

#### Services for Connected Products

Manufacturing technology suppliers, including suppliers of MES, ERP, quality management systems, traceability system, and validation solutions are actively contemplating new services and business models. Externally, the connected plant will have the greatest impact on the way suppliers deliver services to manufacturers. Some suppliers are leveraging IIoT to provide remote predictive maintenance, network monitoring, and other services that can improve performance. Ultimately, IIoT will create new business opportunities for technology suppliers. Rather than selling capital equipment, they will sell expertise and even production output.

## Recommendations

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ARC believes that many pharmaceutical, biopharmaceutical, and medical device manufacturers could realize significant benefits from digital transformation. But this will require implementing new business, manufacturing, and work processes; new digital solutions; and advanced automation technologies that interoperate effectively.

Processes should be reviewed for production innovation whether moving from batch to continuous manufacturing, to batches of one, or additive manufacturing. Data connectivity, interoperability, MES, digital twins, process simulation, augmented reality, advanced analytics, and AI (including ML) will be applied in ways that improve products, increase efficiencies, support delivery of new therapeutics and drugs, and provide other benefits.

If you have not already started investigating these types of manufacturing approaches and technology solutions, ARC recommends that you assess your current “as-is” state from both the technology and cultural perspectives, determine your digitally enabled “to-be” state, and then carefully develop and execute a strategic plan that reflects the need for continuous improvement.

### **An Invitation to Join the Digital Transformation Council**

Readers who belong to organizations that use software, hardware, or automation systems - such as chemical companies, food & beverage companies, municipalities, utilities, oil and gas companies, pharmaceutical, automotive companies, mining companies, metals companies, machine builders, and other similar organizations - may wish to join the Digital Transformation Council. The Council, created at the request of ARC’s end users, is a member-driven community for professionals who are interested in keeping abreast of the many emerging technologies and business trends, learning from others on similar journeys, and leveraging trends and technologies to achieve transformational growth. There is no fee to participate. Join at [DigitalTransformationCouncil.com](http://DigitalTransformationCouncil.com).

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### Acronym Reference:

<b>AGV</b>	Automated Guide Vehicle	<b>IT</b>	Information Technology
<b>AI</b>	Artificial Intelligence	<b>MES</b>	Manufacturing Execution System
<b>AM</b>	Additive Manufacturing	<b>MHRA</b>	Medicines and Healthcare Products Regulatory Agency
<b>API</b>	Application Programming Interface	<b>ML</b>	Machine Learning
<b>AR</b>	Augmented Reality	<b>NPD</b>	New Product Development
<b>CGMP</b>	Current Good Manufacturing Practices	<b>OEE</b>	Overall Equipment Effectiveness
<b>ERP</b>	Enterprise Resource Planning	<b>OEM</b>	Original Equipment Manufacturer
<b>ET</b>	Engineering Technology	<b>OQ</b>	Operational Qualification
<b>HRI</b>	Human-Robot Interaction	<b>OT</b>	Operational Technology
<b>IIoT</b>	Industrial Internet of Things	<b>PLM</b>	Product Lifecycle Management
<b>IoT</b>	Internet of Things	<b>PQ</b>	Performance Qualification
<b>IQ</b>	Installation Qualification	<b>SDK</b>	Software Development Kit
		<b>VR</b>	Virtual Reality

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