quality

Pharma 4.0: Building quality into pharma manufacturing from molecule to medicine

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This article discusses the current and potential future impacts of the application of Industry 4.0 concepts to the pharmaceutical manufacturing industry.

With the development of the global marketplace over the last dozen years, the pharmaceutical industry is at a tipping point in its evolution. The maturation of the BRIC nations—Brazil, Russia, India, and China—provides not only expanded market opportunity but also greater complexity in developing and marketing safe and efficacious drug products across the global supply chain. Macroeconomic trends driving global growth include reduced taxes, lower drug prices, and lower regulatory barriers for new drugs in the US; high GDP growth in China and India; and widespread population aging, high urban pollution levels, and sedentary lifestyles leading to an upsurge in chronic disease.

Healthcare expenditure per capita is expected to rise from its 2017 level of $1,137 to $1,427 by 2021 [1]. To many, this trend is unsustainable, and if industry does not set it sights on cost containment while managing business performance, there will be a severe reckoning in the marketplace.

Meanwhile, pharmaceutical companies are locked in a perpetual race against time to innovate and bring new drug therapies to market as quickly and

cost-effectively as possible even as they find their patent protection eroding. While a patent can provide a company intellectual property protection for twenty years or more, the company will spend more than half of that time turning the ideas embedded in an individual patent into a marketable product, leaving only a few years to recover the often billions of dollars spent in development. Combine this with a development engine in which only 13 percent of the drugs developed ever reach the market, and the need to improve the current model could not be more self-evident.

Evolution of industry

The German federal government coined the term Industry 4.0 in 2011 as part of a national strategy to promote computerized manufacturing. The 4.0 designation is a play on computer software version control and represents the fourth progression of the industrial revolution. The three previous progressions are shown in Figure 1 and can be described as follows:

- Industry 1.0 refers to the first industrial revolution, marked by a transition from hand production methods to machines, using steam and water power.
- Industry 2.0 is the second industrial revolution, better known as the technological revolution. It was made possible by the development of extensive railroad and telegraph networks that allowed for faster transfer of people, goods, and ideas. It is also marked by ever more present electricity, enabling factory electrification and the modern production line and is a period of great economic growth and increases in productivity.
- Industry 3.0 occurred in the late 20th century, after the end of the two world wars. It is also called the digital revolution, characterized by extensive use of computer and communication technologies in production processes.

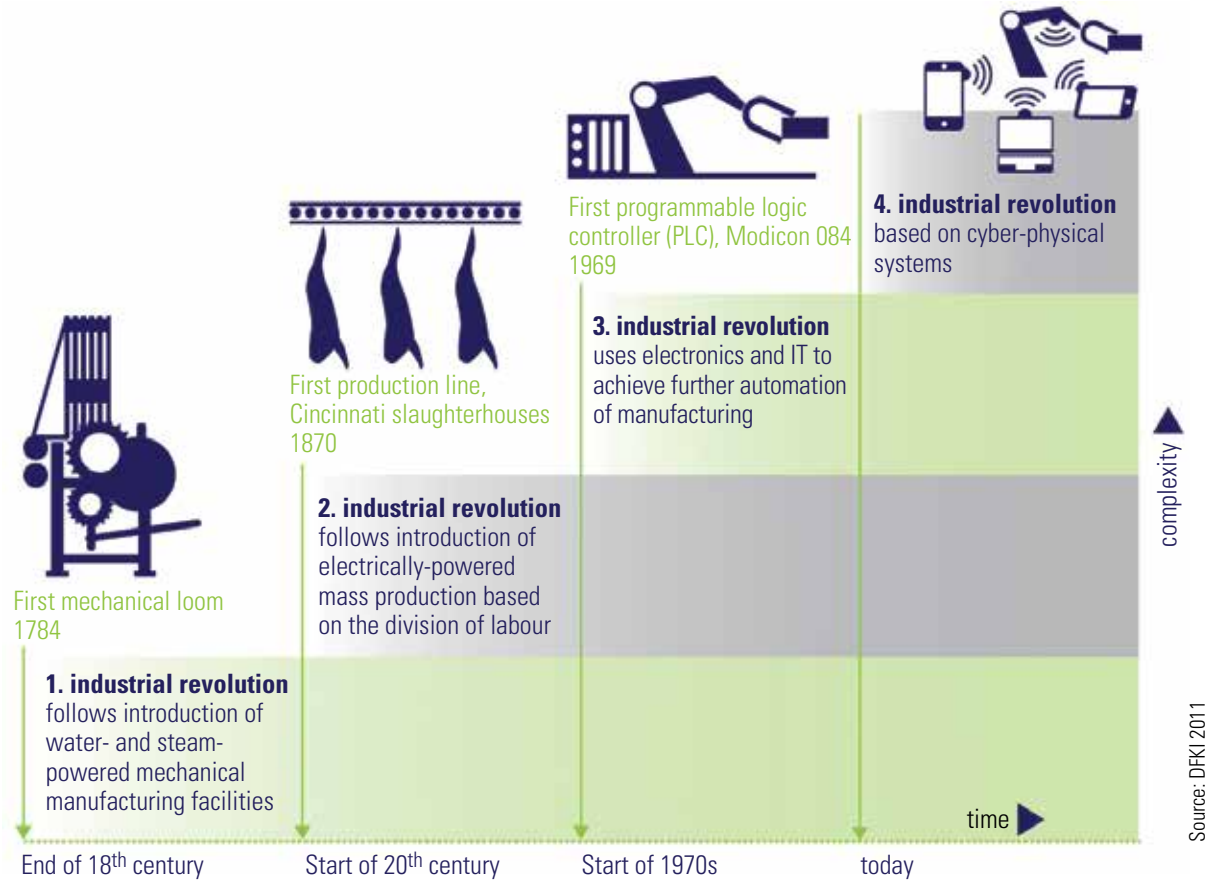
Industry 4.0 is based on the emergence of four technologies that are disrupting the manufacturing sector: the astonishing rise in data volumes, computational power, and connectivity, especially new low-power wide-area networks; the emergence of analytics and business-intelligence capabilities; new forms of human-machine interaction such as touch interfaces and augmented-reality systems; and improvements in transferring digital instructions to the physical world, such as advanced robotics and 3D printing.

Pharma 4.0

Pharma 4.0 is the application of Industry 4.0 concepts to pharmaceutical manufacturing. The goal of Pharma 4.0 is to create the intelligence needed for engineers and

Figure 1

The four progressions in industry's evolution



operators to make smarter decisions that increase operational efficiencies, improve yields and engineering productivity, and substantially drive business performance. Within modular smart factories, cyber-physical systems monitor physical processes, create a virtual copy of the physical world, and help make decentralized decisions. With the connected devices of the Internet of Things (IoT), cyber-physical systems communicate and interoperate with each other—and with humans—for real-time control and data collection, contributing usable information that's shared among participants of the overall pharma manufacturing value chain.

This enhanced business performance revolves around three basic elements:

- Broad deployment of IoT: Data are gathered from across the global supply chain via smart sensors and smart devices;
- Engineering systems: Data are integrated with intelligence to detect, analyze, and predict outcomes to everyday manufacturing challenges;
- Integrated intelligence: All data, including enterprise-level systems, are completely interconnected across the entire ecosystem, allowing for enterprise-wide intelligence.

The objectives of Pharma 4.0 are ambitious in that the intent is to make the leap from a reactive framework, historically achieved using automation strategies and technologies, to a predictive framework based on analytics, allowing companies to anticipate and address potential challenges in the overall supply chain. While the focus of Pharma 4.0 is the manufacturing supply chain, the principles are being applied in a much broader fashion across the entire drug development life cycle.

IoT across the supply chain

IoT is one area where we are seeing an expansion of the principles as early as drug discovery. Table 1 summarizes some of the key areas where IoT is deployed across the drug product development life cycle and supply chain extending from drug discovery all the way to post-commercial pharmacovigilance.

TABLE 1

Applications of IoT across the drug product development life cycle and supply chain

Drug discovery and development	Manufacturing and supply chain	Patient access
• Wearable devices for subjects to do real-time reporting • Monitoring and reporting of data from clinical sites, subject screening, and real-time reporting	• Serialization (AIDC) • Real-time logistics visibility • Smart warehousing and route management • Predictive maintenance • Yield optimization	• Wearable devices • Smart pills • Compliance and usage tracking

Supply chain visibility remains a very big challenge for pharma and biotech. The ability to anticipate failures or address excursions in real time has always been the end game. As with any process, the supply chain has its own unique sources of variability. Whether that is a result of human interaction or mechanical failure, the ability to monitor, measure, and ultimately predict excursions that are not part of the normal process control requires real-time or near real-time measurement capability.

Presently, IoT solutions include sensor network technology coupled with intelligent data analysis. Compliance with the FDA's Unique Device Identification (UDI) system and the Drug Supply Chain Security Act (DSCSA) is a significant driver for deploying IoT within the supply chain. Manufacturers, including both drug sponsors and contract manufacturing organizations (CMOs), needed to comply with the DSCSA by November 2018, a delay of one year from the original target. Compliance was defined as an implemented solution to create a unique Global Trades Item Number (GTIN), serial number, lot number, expiry date in human-readable format, and GS1-compliant data matrix code.

Looking only at the US market, this is a significant technical challenge, especially from a database management perspective. When you look at the global marketplace and supply chain, with more than 70 different serialization standards and regulations, it's easy to see how a patchwork solution architecture would not be viable in the long term.

Accessing data, unlocking information

One of the first challenges the pharmaceutical industry has faced in attempting to step into big data analytics is that, currently, disparate data are largely trapped in isolated silos of automation and databases. This dramatically complicates predictive analysis and severely restricts the potential for any analysis that is new and innovative. If the goal is to have a complete 360-degree view of all relevant data and their relationships to each other across your business, patients, supply chain, and development pipeline, then the industry needs an architecture that can easily handle all types of data. With data in silos, the problem has become worse instead of better, despite many attempts at solving it.

Data integration has proven to be the most challenging problem in IT, and existing data-integration products and strategies are not working. Most organizations have a similar-looking IT architecture—a bunch of operational "run the business" systems utilizing a suite of extract, transform, and load (ETL) tools to feed data to respective "observe the business" data warehouses. In recent years, new sources of data such as IoT feeds, message feeds, artificial intelligence (AI), and machine learning tools have made the problem more complicated.

Today, ontological databases have matured to a point where they can address the challenges of managing and analyzing siloed, disparate data. Technical solutions exist that let you bring in data from disparate sources "as is,"

curate them, apply security and governance, and make the data accessible for analysis as needed.

Such systems now provide pharma with the potential for a single portal and interface to all potential data across the entire business value chain. Most importantly, this doesn't require disassembling any of the solutions that have been put in place. The reluctance to migrate away from legacy systems is one of the biggest organizational hurdles faced by cross-functional data management initiatives. Look for big data initiatives within the industry to shift to these solutions in the next three to five years.

Artificial intelligence, real solutions

Few areas of innovation have as broad a potential impact as AI. If you think of IoT as connecting devices to gather data, then AI makes decisions based on that data. As such, the applicability of AI is not limited to the shop floor or the manufacturing supply chain. Figure 2 shows the broad applicability of AI across the entire pharma and biotech value chain.

Broadly speaking, the term AI applies to any technique that enables computers to mimic human intelligence. To fully understand the applicability of AI, it is important to look closer at its two subsets: machine learning and deep learning.

Machine learning. Machine learning is the application of targeted statistical techniques that enable machines to improve upon tasks with experience. Machine learning has been used in combination with well-established techniques such as "fuzzy logic" to build a set of rules that allows equipment to consistently improve its performance against a predefined set of objectives as it gathers data. Facial recognition is one example of this application.

Machine learning is not only being used on the shop floor to optimize performance, applications of machine learning are being applied in drug discovery to improve the success rates of new drug therapies and drug modalities as they move through the clinical pipeline.

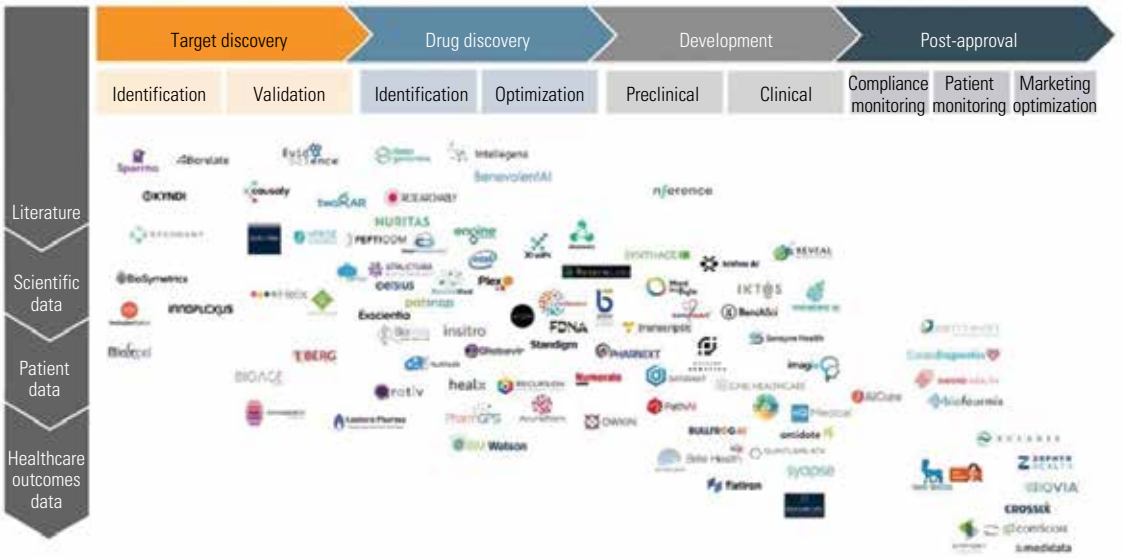
An MIT study published in April 2019 concluded, after analyzing more than 21,000 clinical trials between 2000 and 2015, that only 13.8 percent of drugs successfully pass clinical trials [2]. This success rate is not sustainable in the face of downward pricing pressures across the globe. One large pharma organization is using machine learning to improve its molecule selection process. The researchers are building large libraries of digital images of cells treated with different experimental compounds and then using machine-learning algorithms to screen potential compounds faster and with a higher rate of success than was previously possible.

One potential blockbuster application of AI and machine learning is the treatment of complex diseases that have multiple modes and mechanisms of action, such as autoimmune diseases like multiple sclerosis (MS) or ALS. Currently, research typically targets one gene anomaly or defect. Using AI, researchers may be able to identify multiple genes that influence the disease and devise drug therapies against multiple targets.

Another interesting application of AI is happening in clinical treatment. Some cancer treatments are toxic, requiring a complex dosing regimen called dynamic dosing, in which the dose is gradually adjusted to maximal delivery as the patient's treatment progresses. Using AI, doctors can continuously identify each individual

Figure 2

Application of AI across the pharma and biotech value chain



Note: Many companies span multiple drug lifecycle stages and data types, therefore relative positioning is indicative
Source: L.E.K. research

patient's optimal dose for each drug to achieve a durable response, allowing patients to live free and healthy lives during treatment.

Deep learning. Deep learning, the other subset of AI, is composed of algorithms that permit software to train itself to perform tasks, such as speech and image recognition, by exposing multilayered neural networks to vast amounts of data. One area that is ideally suited to deep learning is the collection of natural language-derived data, such as evaluating patients against inclusion/exclusion criteria for clinical trials. Identifying patients who satisfy the inclusion/exclusion criteria is a key aspect of constructing a viable controlled clinical study, and for most clinical studies, any time recovered from the enrollment timeline can translate directly to a reduction in time-to-market.

Usually, when drug developers submit details of a new trial, most of the information gets entered as structured data in formats such as drop-down menus. These data are easy to record and analyze by computers. However, patients' eligibility criteria get entered into free text fields where they can write anything they like. Traditionally, these data were nearly impossible for a computer to "understand" and interpret. Deep learning algorithms can read unstructured data so the computer can assign appropriate clinical trials to offer the patient.

Extending this concept to the treatment of patients, AI is being applied to analyze structured and unstructured clinical data, including doctors' notes and other free-text documents. Clinical data are separated into key elements while also protecting sensitive health information. The AI application then extracts thousands of these clinical data points to create a multi-dimensional profile. Doctors and researchers can then use these profiles to find suitable candidates for a clinical trial.

Blockchain

Blockchain's lineage is in cryptocurrency, and the primary requirement for buying and selling cryptocurrency is security, not speed or efficiency. Blockchain creates a digital ledger of all transactions that may take place in the supply chain. The application of blockchain in pharma is still in the investigative phases.

One application of blockchain that is being adopted by the global supply chain is the concept of smart contracts. A smart contract is a computer protocol intended to digitally facilitate, verify, or enforce the negotiation or performance of a contract without third parties. In this format, contracts could be converted to computer code, stored and replicated on the system, and supervised by the network of computers that run the blockchain. This would also result in ledger feedback, such as transferring money and receiving the product or service. International organizations, including pharma, governments, and banks are turning to blockchain to ensure and enforce the terms of their contracts.

Putting the cart before the horse

One of pharma's greatest shortcomings as an industry has been its tendency to focus on the wrong things. We saw this with process analytical technology (PAT), where the industry focused on the design and implementation of the technology and ignored the impact of foundational material characterization and supplier control. We also saw it with lean and six sigma, where the emphasis on the tools and certifications, in the absence of the cultural leadership components, relegated these operational excellence philosophies to simply a suite of tools rather than a holistic approach to business performance. Pharma 4.0 has the potential to fall into the same trap. The focus on technology in the absence of understanding the basic question to be answered can derail a cross-functional initiative in the blink of an eye.

There is no doubt that society is becoming increasingly digitized, and this can be a good thing—improved efficiency, enhanced quality, and better company compliance with ever-increasing, data-related regulatory requirements. Choosing the technology that will have the greatest positive impact on your company, in the area you most need it, is obviously a crucial decision. With production data now available for the asking, executives rightly wonder how to begin. Which data would be most beneficial? Which technologies would deliver the biggest return on investment, given a company's unique circumstances? Which data-leakage threats are causing the most pain? This last question made headlines in 2017 with the high-profile ransomware attacks that affected Merck's operations worldwide.

The industry confronted this basic question of how to begin with its first foray into big data analytics. The first step to identifying a strategy and solution is to understand what success looks like. Is the resulting analysis intended to be predictive, descriptive, diagnostic, or prescriptive? The answer to that question will determine pharma's path forward and which solutions the industry should consider. *T&C*

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