Technology Trends: THE TRANSITION TO DIGITALIZATION

By Scott Fotheringham, PhD

In the pharmaceutical industry, digitalization involves developing and implementing digital technologies at all levels of pharmaceutical operations. The aim is to transform the industry by capturing, analyzing, and using vast amounts of data collected from a wide range of sources to support research and development (R&D), clinical development, drug manufacturing, supply chain management, patient engagement, quality assurance (QA) and quality control (QC), product safety monitoring, and other objectives.

Despite the transformational potential of digitalization, the pharma industry has historically been slower than other sectors to adopt digital tools, such as cloud storage, artificial intelligence (AI), machine learning (ML), blockchain, and remote communication technologies, and make associated changes in workplace culture and strategic priorities. Now, however, the COVID-19 pandemic may be accelerating the pace of change.

What are the digitalization trends in the industry? What is the business case to develop and implement digital tools and digitalization strategies? And how can organizations introduce and use them? *Pharmaceutical Engineering*® spoke with industry experts with a wide range of experience in these areas to explore these questions and related topics.

DIGITAL MATURITY

According to Christian Wölbeling, Senior Director, Global Accounts at Werum IT Solutions GmbH, when the Pharma 4.0™ Special Interest Group (SIG) surveyed industry representatives about digital maturity in late 2019, only 16% of respondents said that their organization was involved in systematic, ongoing action to digitalize operations. Another 28% of organizations were engaged in pilot projects. These data suggest that more than half of organizations had either not yet started or were just starting to digitalize operations. This aligns with findings from an earlier (2018) survey report from Deloitte Insights, which found that only 20% of companies consider that they are maturing digitally [1].

"The Pharma 4.0™ operating model is interconnected, meaning that the digital tools allow for a fully connected network to allow direct communication between all levels in an organization," said Wölbeling. When the operating model is deployed, digitalization provides connection and results in full transparency, with data used for improved decision-making.

Wölbeling noted that the digitalization adoption rate depends on the industry segment. Large pharmaceutical manufacturers tend to have greater digital maturity than companies in the generics sector because the larger operations (e.g., Merck, Pfizer, and Johnson & Johnson) have more financial resources, superior data storage and collection assets, and greater access to digitalization experts. In contrast, he explained, generics companies are lagging, in part because budget constraints limit their ability to adopt digital innovations.

Advanced therapy medicinal product and cell and gene therapy manufacturers are the frontrunners in digitalization, Wölbeling said. "They have been highly digitalized from the beginning with all their processes, including a holistic control strategy for the end-to-end process that collects a patient's blood, modifies cells, and reintroduces them to the patient. Everything is still done manually but uses high-tech equipment and, in the end, the data are captured and analyzed by highly sophisticated machinery. The technology guides the operator through the manufacturing process."

AI- AND ML-DRIVEN INNOVATIONS

"AI and machine learning are being used in two distinct ways by biopharma," said Eric Staib, Vice President, PVAI QA/Compliance, at Genpact. They can serve to automate heavily resource-burdened or repetitive activities and as decision-support systems to accelerate the handling of vast amounts of data.

Virtual clinical trials are a potential application of AI/ML to overcome some weaknesses of traditional clinical trials, which tend to be slow, costly, and inefficient. Virtual trials can harness the power of digital health technologies—such as mobile apps and remote health tracking devices—to collect patient data regardless of location, thus increasing the potential for wider recruitment and participation [2].

"AI and machine learning can help analyze data to determine the best, most effective and efficient ways to virtualize clinical trials for a given target population," said Staib. Such systems can help industry stakeholders understand the relevant data in a much more comprehensive and extensive way than was previously possible.

In addition, "many companies are using these technologies to enhance the efficiency of processing, analyzing, and reporting adverse events (AEs)," he said. "With the vast growth in AE case volumes, the expanding number of reporting sources, and the complexity of therapies, such pharmacovigilance systems are sure to be game-changers—and a necessity—within the industry over the next few years."

FACILITY DESIGN

"Digitalization will change how facilities are designed and built," said Robert Guenard, Senior Director, Product and Technology Development, at Biogen. "There is a movement toward building digital twins to virtually model how the operation will function even before plant construction begins." (A digital twin is a digital replica of physical object/entity that can be used to run scenarios and simulate or predict outcomes [3].)

"In the digital world, we'll have a better understanding of what the need is and the likelihood of the need," Guenard said. "Often, we're building plants based on some level of risk and we don't know exactly what's going to happen with them, which leads to costly retrofits. The ability to predict the actual need using simulation will be better and will help inform the design specifications of the plant."

Successful facility design thoroughly anticipates needs related to automation levels and optimal data flow across the product life cycle, including how data from plants, labs, products, and supply chains fit together. "We have to think about how this [the facility and its network] meshes with vertical and horizontal integration using standards such as ISA-88 [4] and ISA-95 [5]," Guenard said.

This focus on increased digital integration should stretch "from the physical layer of the plant to how the sensing, controls, and automation work, all the way up to enterprise management and the supply chain," he emphasized.

Using Data for Predictive Drug Processing

Christian Wölbeling sees the opportunity to use a combination of methods to transition from continuous manufacturing to Pharma 4.0™ intelligent manufacturing.

"In continuous manufacturing, we have data capture, but now we can use it in the manufacturing process in a predictive way," he explained. "You're not just learning about the past and reacting to it, you're using it for decision-making and preventive actions in the present. This uses analytics and predictive algorithms. AI and machine learning can add on to this but aren't necessary.

"The huge data sets that used to be captured on paper and have been digitized over the past 5 to 10 years were stored but not leveraged to make predictions," Wölbeling continued. Those data are now accessible, and there are affordable tools to capture and distribute them. "You can dig into data pools, structure the data, distribute them, and use them to predict.

"An excellent business case for using digital tools during drug processing is the popular current application of these data to predict the optimal harvesting point of a bioreaction. We take data from batches, create algorithms that can use data from a running batch to predict how that batch will develop, and then predict the harvesting time that optimizes titer. Even a small improvement (1%) in harvesting point calculation can lead to a huge increase in profit—as much as $100,000. There's a huge amount of money sleeping there. An electronic system makes this accurate and repeatable."

—Scott Fotheringham

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BLOCKCHAIN

Blockchain can be used for data security—and more. "Decentralized ledger technologies such as blockchain record data in a time series (i.e., the order of transactions)," explained James Canterbury, Principal at Ernst & Young LLP.

"The combination of the transactions (the events) and the time between transactions creates a pattern that is prime training material for machine learning and predictive analytics. This in turn can be used by artificial intelligence algorithms to suggest optimized business decisions. For example, we can use a blockchain to track the movement of drugs through various distribution channels.

"We are moving from centralized systems that require trust to decentralized systems that generate proof," Canterbury continued. "At the same time, we are shifting from process-oriented data structures to product-oriented data structures. In a decentralized system, the data can follow the product as it moves through its life cycle without needing to integrate all of the systems that govern it along its way. Cryptography plays a really important role in all of this, being able to provide proof that you know something, without actually revealing what you know. It opens up a whole new realm of information exchange. This will change the way we rely on systems, which in turn will change the way we manufacture drugs and devices."

QA AND QC

"We have the opportunity to evolve from a culture of compliance to a culture of quality," said Georg Singewald, PhD, Vice President for Global Quality Control at Roche/Genentech. Improved QA and QC can be accelerated by the ability to analyze data made available from sensors and connected networks. This affords "a degree of freedom within the tightly regulated environment to allow good decision-making and can be used over time to change processes and control systems," he explained. "We can eventually to understand root causes and analyze them. Digitalization helps identify and even predict clusters that we might not be able to see today," and will help us be more accurate.

Another benefit of digitalization is the ability to make accurate predictions. "Before these technologies were available, the quality team was looking at historical deviations that happened in a batch," Singewald said. "What we want to achieve for QA and QC is to use data for predictive models. This allows us to have more in-line technologies on the floor to provide analytical readouts, faster methods that can pick up trends in real time, and having elements that identify those trends and feed them into the quality system to compare with previous experience. In this way, the quality team moves away from being focused on records of batches that have already been produced to becoming a business partner to improve processes, as is seen in other industries."

He added, "These technologies need not interfere with the regulatory compliance requirements for release testing. We can bring in these new methodologies running in parallel and learn to use them as preventive measures, even if they are not giving us the final readout of a lot release."

Singewald foresees additional changes from digital technologies. "Once a company has reached a certain level of automation, including computer system validation, then the need for oversight can be reduced. Then you have a culture of quality that truly builds quality into the process. This will enable an organization that makes informed and consistent decisions at the lowest level possible, further fostering accountability and quality culture."

WORKFORCE EFFECTS

"New product modalities and manufacturing technologies require the existing workforce to settle into a mode of lifelong learning," said John Balchunas, Workforce Director at the National Institute for Innovation in Manufacturing Biopharmaceuticals. Workers will need to constantly advance their subject matter expertise and awareness of technologies.

"This is critical because companies are going to be hiring an increasingly diverse workforce to meet needs and grow into new areas such as continuous manufacturing, digitization, big data, and automation, as well as new product modalities like gene and cell-based therapies," Balchunas said.

"Employees need to take professional development into their own hands and think creatively about where to find opportunities to continue their lifelong learning," he said, noting that there is tremendous capacity for online and hands-on training available through universities, community and technical colleges, professional societies, and specialized industry training centers. In addition, because technological innovation often starts with suppliers and vendors, pharmaceutical manufacturing employees should view them not just as not just transactional partners but also as knowledge resources.

"From senior leadership down to technicians and operators, the fundamental need will be the same," Balchunas said. Everyone will need to learn how to collaborate with colleagues across a complex multidisciplinary workforce. "While everyone does not need to become a subject matter expert, they will need foundational awareness of new technologies to communicate effectively."

Singewald agreed. "Competition for skilled IT and data specialists will be strong," he said. "We need to think about the mindset and skills that will build a robust operating model of continuous embedded change to processes within an organization."

COVID-19 IMPACT

The COVID-19 pandemic is shaping the industry's transition to digitalization in multiple ways. Notably, social distancing measures have prompted substantial changes to how and where work is done. "Companies are being forced to be more flexible and consider remote options, including having a qualified person working from home," Wölbeling said. "Having workers who are essential for business continuity unable to be onsite brings a business case to digitalization."

Speed to market for essential medicines is another driver of change. "Digital technologies will be 'must haves' for companies that want to bring new medicines to market quicker and safer," Staib said. "As a result of COVID-19, we can no longer rely on traditional means of conducting clinical trials and gathering pharmacovigilance data. We must know much quicker whether a given drug or therapy is a viable option. This can only be done through a mix of scientific disciplines, all of which involve, and rely heavily upon, technology, data, and best practices."

The pandemic is making it clear that "organizations can delay digitalization no longer," Canterbury declared. "Supply chains need to be more agile to account for better business continuity. Relevant data must be available—and trusted—so manufacturers can switch suppliers easily. In some cases, we cannot afford the time to do traditional, manually exhaustive, supplier qualifications. Even some of the most basic processes, like physically signing a document that requires people to be co-located, will need to change."

Singewald noted specific examples of digital technologies that have been key to effective operations during the pandemic, including digital signature systems and remote access to chromatograms or batch protocols; the latter allows offsite personnel to assess deviations and maintain supply and quality metrics. However, he said that "as long as we are in a hybrid state, where some parts of a process are electronic and some are not, or a whole workflow of a batch is not covered in an electronic way, you will have this challenge of needing to be onsite for some processes."

WHAT'S NEXT?

"The future is here now—it's just not evenly distributed or fully embedded in our industry," Guenard said. "Since I joined the pharma industry in 2003, I've wondered why this transformation

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[i.e., digitalization] is not happening more quickly. There are many reasons for this. Yes, this is a conservative industry in many ways, but we do incredible things in medical science, so innovation is really happening." Although he said innovative digitalization efforts in manufacturing are making progress, he also observed that companies often do not consider these efforts to have strategic value, which means they tend to be lower priorities than other work to run or improve the business.

Additional challenges, Guenard said, include perceived regulatory and quality barriers. However, "the regulators I've talked to want to see these digital innovations implemented because of the large opportunity to improve patient outcomes and ensure supply continuity."

Guenard noted that the pace of digitalization in the pharma industry relative to other industries may be slower because the incentives are not the same. "We don't talk about margins and cost of goods to the extent that it pushes us to innovate. In the chemical industry, a very small improvement in efficiency can determine whether you remain competitive. Contrast this to our industry, in which the competitive advantage is in efficacy, safety, product performance, and the experience of the customer, and generally not in manufacturing."

According to Guenard, the complexity of the pharma manufacturing industry also makes digitalization especially challenging. "We've seen studies about how other industries are more advanced, but some of our processes are highly complex and the way we manage those plants should be commensurate with the complexity of the process. There's a step change that we have to go through to be able to deliver products in a low-cost, reliable, highly agile manner. There's a significant opportunity here." Efficient digitalization, he emphasized, "is best done by designing it in and being strategic."

Wölbeling pointed out that AI and ML are not new to the industry. "The key trend is how to make a business case and apply them. The main challenges to implementing digitalization are having the right people choosing where and how to use it, developing the systems, analyzing the data, and, of course, the cost." Large pharmaceutical companies have large amounts of data, he said. "Now we have good data in a format that can be fed into AI, as well as interoperability of data sources across geographies and technologies."

However, Wölbeling believes that simply developing and implementing technology is insufficient. "You have to transform the culture," he said. A culture of digital maturity will encourage the mindset to accept, use, and benefit from these technologies and not see them as a burden.

"Decentralized systems are a team sport, and nearly all of the really good development work is being done on public, open-source networks," he said. It's important to play a role in those communities now, and to invest the time to understand the foundations of these technologies and how they will impact your business, he added. "For example, blockchains were originally intended as public utilities and if they're going to reach their full potential, they need to be thought of as such."

Canterbury suggested that industry stakeholders reach out to colleagues as they explore new options. "When you design an experiment or participate in a pilot, you need to consider the ecosystem and account for the right level of privacy versus transparency," he said. "The best way to get started is to talk about it with your business partners and industry groups, such as the ISPE GAMP® Blockchain or AI/ML Special Interest Groups."

Trust in data science is key to moving forward as an industry, Staib said. He also noted that stakeholders need trust in "the rigorous IT controls framework that ensures the quality of such technologies, and the integrity of data they rely upon." In addition, "the successful application of these digital innovations requires investment in the appropriate technology as well as collaboration with tech companies. The pharma and biotech industries need to invest heavily in the understanding and processing of data that are already available to them, both within their organizations and external to their companies, including publicly available information. They also need to embrace partnerships with large and small tech entities to create mutually rewarding codevelopment scenarios."

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