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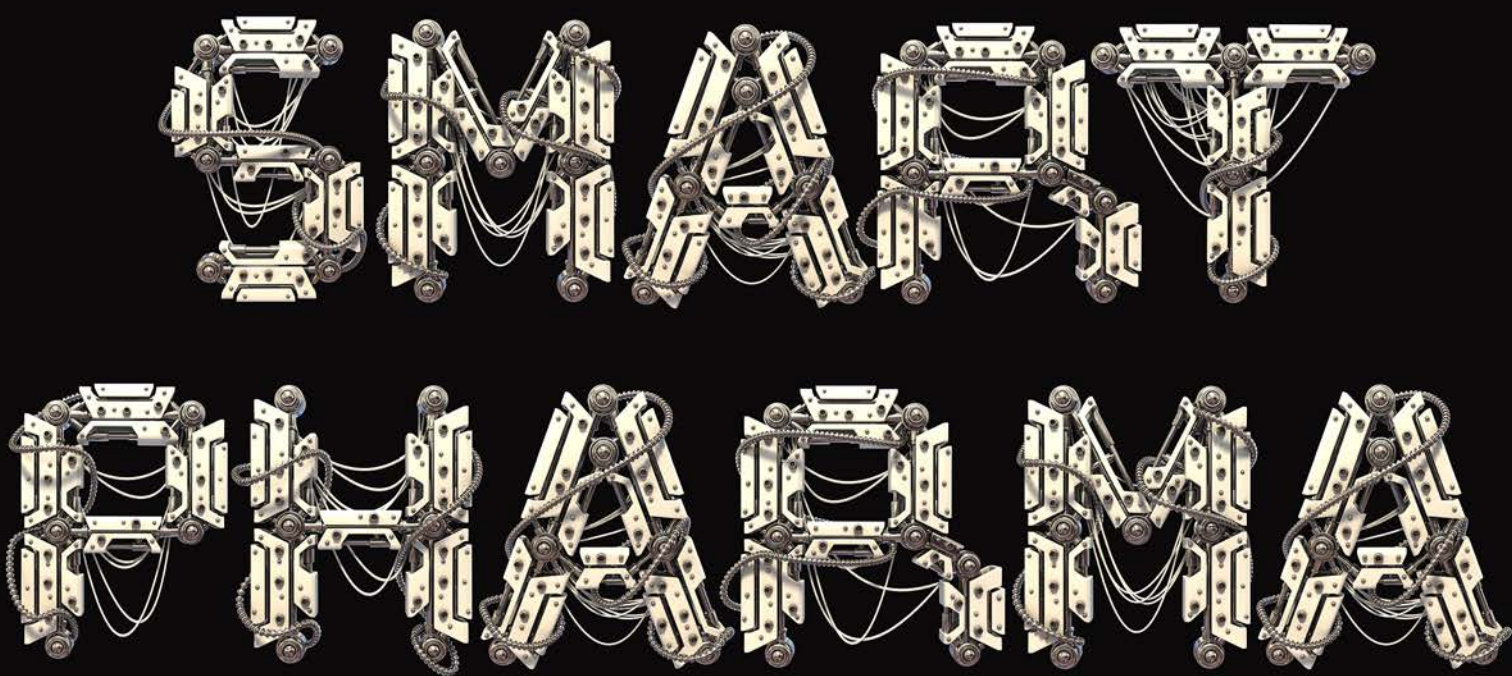

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Degrees of Digitalization

Armed with the education and motivation, pharma now needs a plan

By Karen Langhauser, Chief Content Director

It's not too late for the pharmaceutical industry to dodge its reputation for being woefully behind other industries in terms of adopting technology. Pharma, facing somewhat of a "digital crossroads," is still poised to capitalize on the vast benefits of digital transformation.

Digital transformation is best defined as the adoption of new manufacturing and business processes made possible by automation, communications and computing technologies represented by conceptual models such as data analytics, the Industrial Internet of Things (IIoT) and Industry 4.0.

The pharmaceutical industry has seen great advances in transformative technology, and it's becoming increasingly evident that many of these innovations can give manufacturers an edge.

A recent *Pharmaceutical Manufacturing* survey separately asked over 200 drug manufacturers and equipment and services suppliers(*) their thoughts on the industry's progress in terms of digital transformation. When asked which areas of pharma manufacturing they felt would see the most benefit from increased digitalization, both manufacturers and suppliers noted the

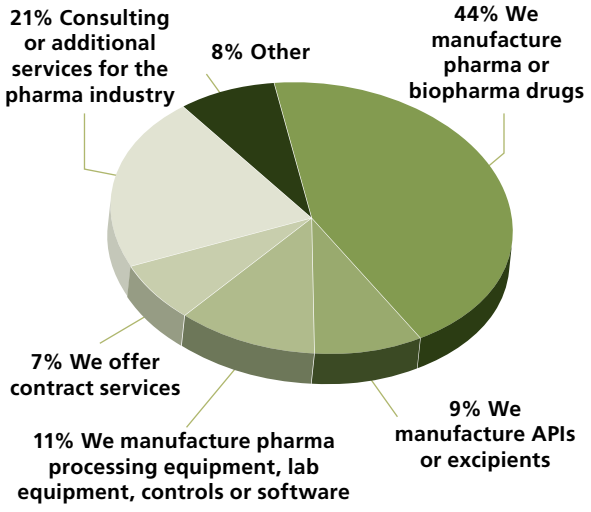
*** For the purposes of this survey, "vendors" are defined as companies who offer pharma processing equipment, lab equipment, controls or software, as well as consulting or related services. "Pharma manufacturers" are defined as those who manufacture pharma or biopharma drugs, make APIs or excipients or offer contract services.**

same top three target areas: plant-floor production, quality control and supply chain management.

Close analysis of the survey results against the backdrop of today's pharmaceutical industry landscape reveals that while the utopian picture of the benefits of digital transformation has been painted, in order to start realizing these benefits on the plant floor and throughout the supply chain, pharma needs a structured plan of action.

Exhibit 1

Breakdown of survey participants



CHALLENGES LINGER

Several commonly discussed stumbling points still need to be dealt with as pharma continues along its digital path. When asked to rank concerns surrounding smart equipment in the plant, both drug manufacturers and equipment vendors prioritized regulatory hurdles and integration.

It should come as no surprise that a lack of regulatory buy-in or understanding of new processes, whether real or perceived, remains a top-ranking concern. When vendors were asked what they felt to be the number one issue holding back their customers' digital progress, the leading answer (28 percent) was fear of regulatory backlash. Interestingly enough, this area that has traditionally caused the most hesitation in pharma's technological progress may stand to benefit most from digital transformation, as the smart factory's ability to automatically generate reliable audit trails, real-time reporting and electronic signatures promises to ease compliance burdens.

Integration concerns ran a close second among both survey groups. Respondents noted potential challenges surrounding the integration of new technology with existing lines or equipment. Despite the recent push toward automation, there are still many legacy systems in operation on the pharma plant floor that lack the capability needed to connect to high level automation systems or devices.

In fact, when vendors were asked if they felt that pharma companies were actively looking to replace outdated equipment with updated and improved robotics and automation, only 17 percent said that, overall, pharma manufacturers were actively updating. Just under 42 percent took a more

neutral stance, noting about a 50/50 mix of companies actively updating.

TECHNOLOGY AS AN ENABLER

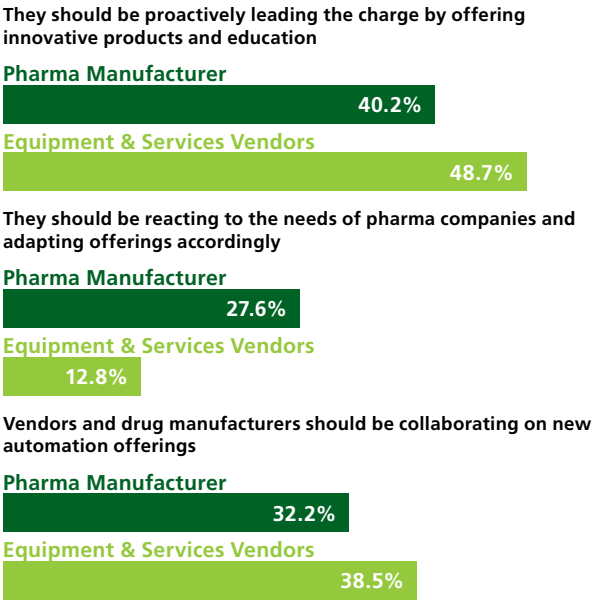
Survey answers support the assertion that the technological innovation needed for pharma to succeed on its digital transformation journey is available.

When ranking their concerns surrounding smart manufacturing plants, tech innovation was toward the bottom of the list according to pharma and dead-last according to vendors (a little tooting of their own horns there). But perhaps vendors are warranted in giving themselves a pat on the back, as it seems that overall, the industry is confident that the level of technology being offered is advanced enough to do the job.

These results are in consonance with the manufacturing sector in general, as well. At the recent Smart Industry 2017 conference — an annual event geared toward accelerating the ongoing digital transformation of manufacturing — Jose Rivera, CEO, Control System Integrators Association (CSIA), spoke about new opportunities and challenges for manufacturing's automation ecosystem. Commenting across all manufacturing industries, Rivera pointed out that previously, "technology was more a barrier than an enabler." The current technology revolution, however, says Rivera, "will allow manufacturers to get closer to their supply chains and plants."

Exhibit 2

What role should equipment manufacturers and software providers play in pushing the drug industry to automate?



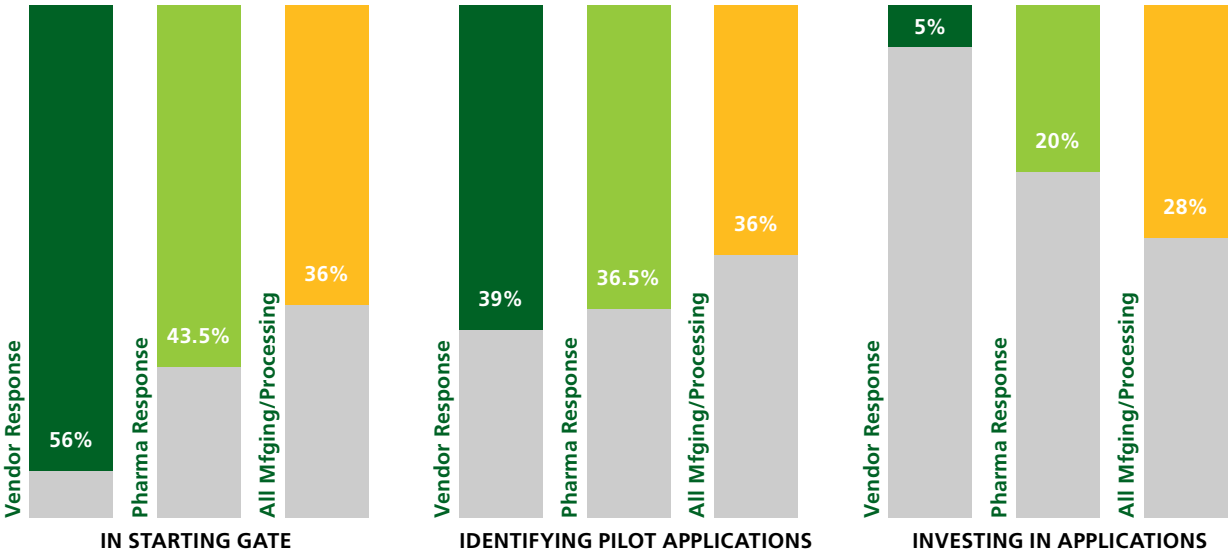
Much of the responsibility for advancing this technology in pharma has fallen on the shoulders of industry vendors. When asked what role equipment manufacturers and software providers should play in pushing the drug industry to automate, 43 percent of everyone surveyed felt that vendors should be proactively leading the charge. About 34 percent felt that there should be a collaboration between pharma and vendors (see exhibit 2).

MORE GOOD NEWS

It is clear that digital transformation is not an initiative that can be spearheaded by a single individual. But how does a traditionally conservative industry execute cultural buy-in? The top is not a bad place to start.

Exhibit 3

Digital Transformation/IIoT Initiatives Progress



"We are working with several different pharma companies and we are very impressed with how digitally savvy the leadership is — there seems to be a good deal of awareness of what's possible. There's a curiosity at a leadership level, as they look around their companies and decide what they should do where and how to best approach transformation," says Ryan Smith, Ph.D., VP of Engineering at Sight Machine (see Ryan's article on page 6 of this eBook). Sight Machine offers a state-of-the art analytics platform used by Global 500 companies to improve efficiency of manufacturing operations.

But while buy-in from the top is necessary, it's not enough. "Organizational readiness is the key component to success. There has to be a minimal threshold of organizational readiness, and that does not just mean support at the top. It means support at all levels, especially on the plant floor," continues Sudhir Arni, Sight Machine's lead for Digital Manufacturing.

According to *Pharmaceutical Manufacturing* survey results, however, employees on all levels are noting a rising comfort level with the new computing, control and communications technologies represented by the IIoT. Over 81 percent of pharma respondents noted an increase in automation-related comfort in the industry, while 68 percent of vendors agreed that the pharma workforce is becoming more comfortable.

Encouragingly, when it comes to designing or upgrading its manufacturing facilities, the majority (64 percent) of pharma respondents and vendors (55 percent) feel that

digitization is an important part of the discussion. Just under 28 percent of pharma respondents feel that digitization is leading the discussion, while 33 percent of vendors agree with that assessment.

EXECUTION VS. ASPIRATIONS

With the right tools available and a "big picture" view of IIoT benefits laid out before them, pharma's next steps are crucial. Throughout the survey, pharma manufacturers were consistently more optimistic about digital transformation progress than their vendors. When asked to describe the pharmaceutical industry's collective progress on digital transformation/IIot initiatives, 44 percent of pharma manufacturers felt the industry was at the starting gate, with a focus on learning and exploration. Just under 37 percent felt the industry was in the next stage, now identifying early applications to pilot. And 20 percent felt pharma was in the most advanced stage, having identified applications and made investments to match (see exhibit 3).

When vendors were asked the same question, however, the survey found 56 percent saying pharma was at the starting gate, and 39 percent claiming pharma was identifying early applications to pilot. Less than 5 percent of vendors noted actual investments being made.

The differing opinions of pharma manufacturers and vendors aside, the bulk of the industry appears to be stalled in the earlier stages of digital transformation. Here we see the true digital transformation crossroads: pharma understands the power of digital, but can't continue its journey without investing in a tactical plan.

"What it comes down to is that it's not really how you feel about it or how optimistic you are, but more so 'what do you have in place to make it happen?' Certain things need to be in place in order for an organization to be successful in digital transformation," says Ed Jimenez, VP of Marketing at Sight Machine.

In order to be truly ready to execute versus taking a more aspirational approach, pharma needs a structured digital transformation strategy.

Again, we see vendors stepping up to the plate. Sight Machine, for example, has developed a Digital Readiness Index (DRI). Started as an internal tool to help customers assess where they stand, the DRI quickly morphed into a more formal methodology for evaluating a manufacturer's readiness for digital transformation.

Manufacturers start by answering an online questionnaire and, based on the answers, the DRI uses a weighted scoring system to place organizations into one of five "Digital Readiness Zones." For each zone, Sight Machine has recommended quick

win projects and areas for investment to develop more advanced capabilities.

These "quick wins" are vitally important, as choosing initial applications that deliver value can stimulate company-wide buy-in and build much-needed momentum.

HOW PHARMA COMPARES

Perhaps the most important takeaway from the survey results is the message that pharma manufacturing is not yet — contrary to its reputation when it comes to initiating change — years behind other industries in terms of digital transformation.

Arni, who was the lead developer on Sight Machine's DRI project and has conducted much of the company's industry surveying, says the company is not seeing huge gaps in readiness from industry to industry. "In our experience, there is not much difference in terms of readiness between the pharma manufacturing industry and other manufacturing segments. The data from our Digital Readiness Index shows the pharma industry has the capabilities in place to move faster," notes Arni.

In a recent Digital Transformation: 2017 State of Initiative report, Smart Industry surveyed professionals from across manufacturing, processing and related industries. When asked about their company's progress on digital transformation initiatives, almost 72 percent reported not yet reaching the more advanced "identifying applications and making investments" stage. Additionally, more than half of those same respondents said they do not have a formal digital transformation strategy with timelines in place.

WHAT THE FUTURE COULD BE

The pharmaceutical industry understands the value of digital transformation. Survey results indicated that more than 70 percent of pharma manufacturers believe that a more automation-enabled pharma industry will lead to improvements in efficiency, productivity and quality.

With about 68 percent of those surveyed estimating that the pharma industry is somewhere between 5-10 years away from truly reaping all the benefits of IIoT and the "smart factory," pharma's next steps will determine its future.

What Sight Machine seeks to communicate with its Digital Readiness Index is a message that should be heard by all of pharma: "No matter where you are, there are always steps you can take today. Don't keep waiting — get started."

Proactive Digital Transformation

Motivated by technical advancements and marketplace pressures, pharma is finally beginning to recognize the power of data-driven decision making

By Ryan Smith, Ph.D., VP Engineering, Sight Machine

Few industries have as much to gain from data-driven decision making as pharmaceutical manufacturing. The disruptive forces impacting the industry — rising cost pressure, greater use of contract manufacturing, the introduction of personalized medicine, increasing packaging complexity, unrelenting quality control demands — cry out for the insights achievable through big data techniques.

Steering the industry through these disruptions will require not only rapid technical advancement, but also organizational and cultural adjustment. The industry's culture is marked by a widespread, if largely unstated, belief that more information can be dangerous, as it invites more regulatory scrutiny and increased cost of compliance. This cultural legacy has become counterproductive and must be shed by companies seeking to thrive in the era of big data.

Pharmaceutical and life science manufacturers have traditionally been more reactive than proactive in technology adoption largely due to regulations and domain complexities. Success in life sciences has historically depended far more heavily on research and product innovation than on manufacturing prowess. But challenging market conditions are now pushing companies to innovate in using data visibility and analytics to improve manufacturing.

Most large pharmaceutical and life sciences companies have undertaken digital manufacturing initiatives. The majority are in early stages, doing proof of concept projects, but a growing minority — after

Exhibit 1

Capability building: Skills need to be built across six key areas to ensure success with Digital Manufacturing

1	2	3	4	5	6
Sensing	**Connecting Machines & Data Acquisition**	**Data Modeling**	**Data Analysis**	**Last mile application developers**	**Change Management**
Control experts/IT/ machine builders who know how to ensure machine signals are available • Understand the sensors available • Identify which sensors have impact • Work with IT to enable sensor connectivity	IT/data engineers who connect sensors and understand machine data • Understand machine-to-IT network connectivity • Equip machines with right software • Acquire data from SQL, historians, IoT platforms	Data engineers who understand machine data and manufacturing processes • Understand process & part data, parameters • Define data relationships • Build manufacturing specific context	Data scientists who can mine for insights • Ability to run statistics: correlations, regressions • Comprehend insights from statistical process analysis • Build machine learning algorithms	Developers who create or identify apps that deliver operational value to the factory • Understand manufacturing metrics, KPIs and OT workflow • Understand the Digital Manufacturing software landscape	Consultants and operations experts who implement changes identified from analytics • Provide feedback loop on data / analytic needs to improve execution

demonstrating initial results — have begun rolling out those initiatives at scale.

WHAT IT TAKES TO SUCCEED IN A DIGITAL MANUFACTURING PROJECT

Pharma companies face similar challenges in digital transformation as their peers in other industries, and similar combinations of technical and organizational skills are needed for projects to succeed. Knowing what to look for in both sets of skills is important for selecting appropriate first-mover projects to gain proof points and momentum.

On the technical side, making the data available is the first step. At a foundational level, the key machines must be networked, and the data must be captured. Remote visualization of production data requires appropriate cloud and network technology, and companies need to be mindful of security while embracing new technology adoption. This provides a foundation of raw data to feed data models and sophisticated algorithms.

Companies also must navigate organizational challenges. If the top of a company is committed to digital transformation but plant leadership sees it as a threat, the project is unlikely to succeed. Similarly, an initiative at the plant level may struggle to reach full potential without the buy-in of corporate IT leadership. Also, an organization's ability to realize the benefits of new technology adoption relies on change

management, so there must be committed and engaged internal champions.

Sight Machine has made freely available a methodology for evaluating a manufacturer's readiness for digital transformation. The methodology, called the Digital Readiness Index, is available at sightmachine.com/digital-readiness.

BUILD A PROPER DATA MODEL

Scaling digital manufacturing initiatives relies on a few critical areas of focus. From an IT perspective, handling the storage (Volume) and processing power (Velocity) needed for large amounts of information is typically front of mind. Of the three V's of big data, the Variety of that information is typically a distant afterthought, if considered at all during the planning phase.

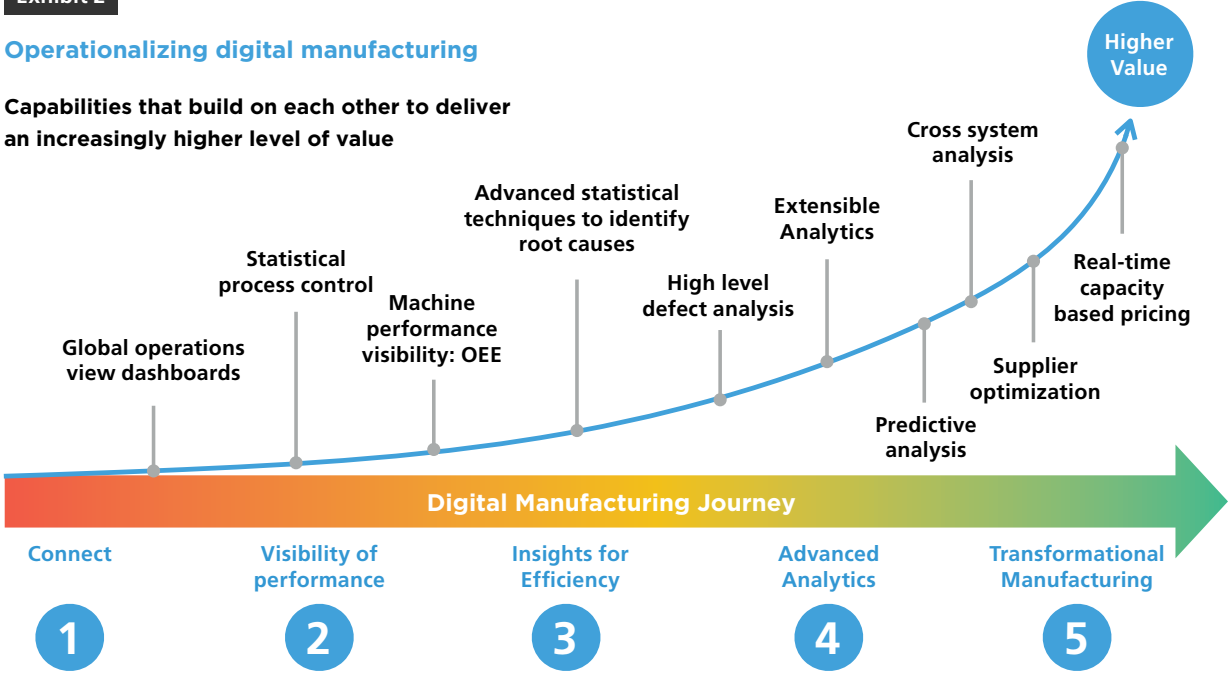
Forming a semantic model of a complex process such as a manufacturing line requires deep collaborative effort between those familiar with the technical tools for handling large amounts of data, as well as those well versed in the art and science of creating drug products. These are very different cross-functional skillsets, and many projects have failed due to the lack of alignment between Operations Technology and Information Technology.

Assuming OT/IT are aligned, enablement technologies can save appreciable cost and development time, as well as increase the likelihood of success in digital transformation. For instance, when looking at a number of manufacturing processes, it is challenging to ensure that a standard data model will apply to lines from dissimilar

Exhibit 2

Operationalizing digital manufacturing

Capabilities that build on each other to deliver an increasingly higher level of value



vendors, or those that produce dissimilar products. Interoperability of modeled data is critical for systems-level thinking. It is important not to fall into the project-based trap of doing one-off data projects, as this will curtail the upside from using digital technologies across the enterprise.

PHARMA/BIOTECH USE CASES

Data-driven decision-making is a powerful tool to address a wide variety of use cases in pharma and life sciences, including:

Cost Control

While there are still promising new R&D developments and the future of drug discovery is bright, there is a marked shift to cost control as the frequency of blockbuster drugs, and the associated margins, are decreasing.

Other industries, such as automotive, have been under significant cost pressure for some time. Lean thinking at each stage of the process is important for productivity gains, such as reduced scrap and increased throughput. Modern big-data techniques to model manufacturing facilities and apply statistical or machine learning methods can deliver profound increases to bottom line.

Technology Transfer

While a necessary step in scaleup, technology transfer can often be slow and cumbersome. A data-centric approach with real-time visibility can complement and accelerate such an effort. Instead of paying for employees to camp out at recipient facilities for extended time periods, companies can rely on data modeling to get real-time visibility into every remote parameter in order to complement an on-site team.

The real-time ability to track every process parameter in context, even if the source and recipient machinery are not identical, is a huge accelerant for tech transfer initiatives. An analytics approach allows for rapid correlation of machines within the process from the source and the receiving site. Dissimilar process parameters can be surfaced up for inspection, many of which are not available from the raw incoming data.

As an example, if there is an optimal time-pressure curve for every vial fill, a heuristic for the deviation from that optimal curve can be computed on a per-vial basis. Increased deviation at one site might correlate with increased scrap later in the process, perhaps due to bubbles affecting an automated visual inspection system. A modern data platform allows for rapid contextualization of the process, the ability to surface this correlation, and compare the process parameters between dissimilar sites, rapidly and in real-time.

Equipment Utilization

Data analytics can help manufacturers get more from their machines. Although

pharmaceutical manufacturers have invested heavily in advanced machinery, equipment utilization in pharma is far lower than in other industries. An advanced visual inspection machine might analyze 600 vials a minute, but only runs infrequently throughout the day.

Across industries, an Overall Equipment Effectiveness (OEE) score of 85% is world class. In pharma, where traditionally costs have been centered in R&D and product development as opposed to manufacturing, it is not uncommon to have lines operate with OEE in the teens.

Guided by the data, there is large opportunity to improve productivity. Increasing the productivity of an existing line reduces unit costs of production, both from operation costs such as the people and energy required to run the machine for a given time period, as well as capital expenditures, as output from existing machinery is increased.

Supply Chain Complexity and Offshore Manufacturing

Life science supply chains are becoming more complex. Firms are increasingly leveraging contract manufacturers, as well as deploying their own distributed operations in emerging international markets — often smaller, flexible, multi-product facilities designed to meet the dynamic needs of today's marketplace. All of this is dramatically increasing the data visibility and integration requirements of these complex supply chains.

The need to reduce costs has increased the number of pharmaceuticals and active ingredients manufactured in developing countries is increasing. Maintaining effective quality control is compelling pharma makers to increase their level of visibility and monitoring of offshore manufacturing facilities. Additionally, real-time exchange of information from primary component and raw material suppliers can reduce incoming quality inspection costs and allow proactive decision making for routing upstream components to the most appropriate receiving site based on

Exhibit 3

Using data to solve perennial challenges: Life Science manufacturing use cases

Quality	Productivity	Visibility
Measure and trend quality performance	Drive continuous process improvement	Access critical plant and CMO information at any time
CAPA avoidance and resolution	Determine root causes of product variability	Record production activity: serialization, track, & trace
Batch & in-line continuous release analytics	Predict out-of-control/spec processes and failures	Maintenance and CIP/SIP scheduling metrics
Increase first-pass yield	Predict equipment failure and downtime	Accelerate tech transfer
Set up alerts to maintain consistency/uniformity	Increase capacity utilization	Compare metrics across enterprise

knowledge of batch-to-batch variation.

Precision Medicine

There is a shift away from one-size-fits-all to products aligned to the specific genetic makeup, health-related behavior, environment, and lifestyle factors for subpopulations or specific patients. This new tailored approach to medicine will require significant changes in manufacturing capabilities to enable custom products.

In other manufacturing verticals, the number of products produced can be large, with regular change-over. In high-mix verticals, it is not uncommon to see a million different products produced annually. In traditional pharma manufacturing, the number of SKUs is quite limited, and as a result, a line is set up to do the exact same thing for the life of the drug. With the introduction of medicine customized for individual patients, the complexity of the product mix and associated production process will increase. Dealing with the combinatorics challenges of customized medicine requires a data-focused approach.

Increased product mix will also have a profound impact on regulatory requirements, as many of the systems in place rely on rigidity in the process that will not be possible with highly variable outputs. Showing complete knowledge of the manufacturing process is required to ensure appropriate control in a varied environment.

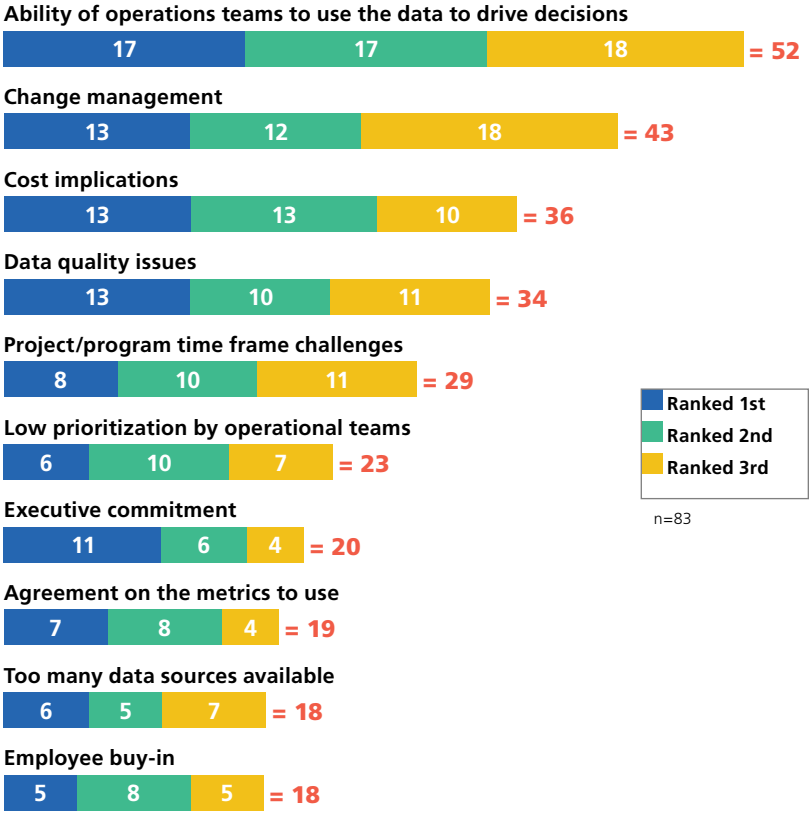
Continuous Manufacturing

For decades, most drugs have been manufactured using batch technology. Today, many manufacturers are converting their processes to continuous manufacturing where

Exhibit 4

Using Data: The #1 challenge to drive better operational decisions

What are the top three challenges your organization faces in the use of manufacturing performance metrics to drive operational decisions?



Source: Gartner, Inc.

ingredients are produced in compact, closed units, with a higher degree of automation and fewer manual interventions. In continuous manufacturing, real-time product release testing can now be completed on an ongoing basis rather than traditional batch release.

Continuous manufacturing processes will be reliant on analytical tools that are the next generation to Process Analytical Technologies (PAT) and Quality by Design (QbD). Correlation of process parameters with in-situ real-time measurements of critical product characteristics is now attainable, but rarely employed in practice in pharma manufacturing. For instance, downstream non-destructive tests such as weight or NIR particle measurements can provide closed-loop real-time feedback to the upstream blending stage to alter the process parameters in order achieve the optimal tablet consistency.

Regulatory Issues

The Drug Supply Chain Security Act requires that the industry implement end-to-end traceability by 2023. In addition to assuring compliance and continued product access for patients and customers, product-level serialization (unique tracking) can enable the investigation of counterfeit and diverted products, affording brand owners additional supply chain integrity and security. End-to-end visibility means that recalls, where necessary, can be executed more efficiently. All pharma companies are piloting efforts to improve product tracking and enhance visibility.

While simple traceability in an increasingly interconnected world is a good first step, is not the end state. Other verticals are becoming more proactive around data management. Auto manufacturers have had component level traceability for some time. More recently, they are not only tracing components throughout the supply chain, but are characterizing the production process parameters and relating them to each component at time of production. In the event of a quality issue or recall, the data has already been proactively organized for analysis instead of launching a retrospective effort to try and request and model the information in order to determine the root cause of a failure. Although not impossible in the past, this type of contextual modeling is far more approachable given recent technology advances and tools for working with information.

The analytical methods pioneered by consumer Internet companies like Google and Amazon are being applied across industries under the banner of digital transformation. Sectors including marketing and financial services have deeply embraced data-centric management practices. While organizational and technical challenges have slowed the embrace of big data in pharmaceutical and life sciences manufacturing, rapid technical advancements and marketplace pressures mean the digitization of life sciences manufacturing is now fully underway.

Pharma's Great Automation Migration

Companies should focus on the collection and curation of data because the variables selected could be the game changers when machine learning becomes standard

By David Torrone, Scientific Content Contributor, Nice Insight

For drug manufacturers, Industry 4.0 will look very much like Industry 3.0, just faster. The time saved in production will be a slow road ahead, and will mostly come at the very end of the transition when machine learning algorithms quickly make adjustments to the manufacturing line and production scheduling. The industry should be wary of over-fitting facilities with heavy machinery that may make them less agile and therefore less able to respond to changing markets. At this historic moment for the industry, companies should shift their focus to feature selection: the collection and curation of data. The variables selected today could be the game changers when AI models become industry standard.

FIFTY YEARS LATER, MORE OR LESS THE SAME

Although pharmaceutical firms have crossed galaxies discovering active pharmaceutical ingredients (APIs), the formulation of tablets hasn't changed much in the last 50 years. "If we used a time machine to transport a pharmaceutical scientist from the 1960s into a current pharmaceutical production plant of today," writes Lawrence Yu, FDA's deputy director of the Office of Pharmaceutical Quality, Center for Drug Evaluation and Research, "it might be surprising to learn that they would already be very familiar with most of the processes and production techniques being used."[1]

This is changing, however, and "what started with mortar and pestle has grown into more automated volume-controlled recipe processes that go through a quality check at each stage."[2] At first glance,

the crux of the transition might appear to be the industry migrating from batch to continuous manufacturing. And indeed, several successful examples of this transition have made headlines in the last two years. Current rockstar Vertex was the first pharmaceutical company to use continuous manufacturing with its Orkambi drug, and in April of last year the FDA approved the first transition from batch to continuous manufacturing with Janssen's HIV-1 treatment Prezista (darunavir).[1] But, ultimately, the switch from batch to continuous is only a small part to the story. What is actually happening in the industry is more profound. Watching Industry 4.0 take over the horizon, many businesses are beginning to gut the processes incompatible with this new era of manufacturing.

Taking the right steps today can help prepare a pharmaceutical company for the great migration that will begin in tableting with the change from batch to continuous manufacturing, and ending with the implementation of machine learning.

HUMANS TEACHING ROBOTS TEACHING HUMANS

Humans are still preferred to robots in many facets of manufacturing because they can quickly transition to meet ever-changing production demands.[3] "Agile means that the company is quick to adjust to changes in the market," says Joe Berish, senior manager for Oliver Wyman's Digital and Manufacturing Operations Practices. "In the sense of manufacturing, if you set up your system with all of these expensive robots that are very heavy, very hard to move and complicated to reprogram, then that's not agile. People are flexible."[4]

Over-outfitting, over-automation of a facility is an easy-to-make misstep for a company eager to meet the possibilities of Industry 4.0. Rather than buying-in, in regards to robots and automation, particularly in a manufacturing process as (arguably) rudimentary as tablet formulation, the first step a company should take is assessing and understanding the variables that will be fed into a machine learning model. "The biggest challenge companies will face in the implementation of machine learning to manufacturing is a lack of talent," says Berish. "Humans are still the conduit for teaching machines what to learn, so it takes a special kind of "tweener" who understands the business and the algorithms. Even the latest trend of 'machine learning for machine learning' to help scale up quickly, still needs a starting point."

FEATURE SELECTION

Many of the discussions about how to implement machine learning technologies to improve production — which at this stage should remain more on the philosophical end of the spectrum — too quickly devolve into the practical aspects

Over-outfitting, over-automation of a facility is an easy-to-make misstep for a company anxious to meet the possibilities of Industry 4.0.

of purchasing equipment, software packages, etc. Companies should understand that what might feel like a need to move from batch to continuous manufacturing, if done correctly, is actually a traditional business process reengineering (BPR), with a digital transformation of the company as the focal point. This is how tablet manufacturers will become part of a new industrial era. In the past, these BPRs took 10 to 15 years to rollout. However, becoming part of Industry 4.0 must be faster — much faster. By conservative estimates, it will take a quarter of this time. "If a company is 'all-in,'" says Berish, "a digital transformation can put them at the forefront of the industry in as little as two or three years' time." He continues to explain that a true digital transformation would first include everything except manufacturing. "I don't want someone to get the impression that if they do the manufacturing part, then they will be a leader."

As we will be the conduits for these software suites, now is the time for the collection and organization of big data, or in the language of algorithmic modeling: feature selection. Instead of retrofitting a manufacturing line with the latest sensors and robotics, a business that takes the time and effort to find the best variables to feed into the model will dictate the speed at which machine learning algorithms can make adjustments that instill lasting changes to the manufacturing process.

TRANSLATING THE ART OF TABLETING

Drugmakers have been working with units of operation to mix, grind, test and mill in different batches since the 19th century.[2] In this way, tablet formulation is akin to cooking and therefore must rely somewhat on the intuition of experts. But in Industry 4.0, the art of tablet formulation must be quantifiable. Furthermore, anecdotal and experiential knowledge must keep pace with technological advancements. For example, particle shapes and sizes of an API and its excipients, as known by formulation experts, might first have to be translated to new technological advancements in particle characterization before being considered

valid variables for the model — this transition is the time to exchange antiqued variables for more accurate descriptors.

Eventually, as is the theory behind machine learning algorithms, these translational differences will cease to matter as the algorithm slithers its way between industries. Algorithms installed will be able to make adjustments in production based on upstream attributes of particle characterization at a partnering facility. The speed that they will be able to achieve this final goal depends on the time and effort put into the selection of variables today. Therefore, looking for talent for this transition might not mean finding the engineer with the best production experience, but rather the engineer with the best ability for language.

Although the machine learning algorithms will transform the tablet production, optimally implemented, "manufacturing should be the very last piece of the puzzle," says Berish. "You can install all the sensors [on the manufacturing line] you want — and that's okay — but at the end of the day, these sensors still need to know what to 'sense.'" The abstraction here between sensors and what they sense is an important one. Recent attempts at drug formulation using machine learning algorithms implicate that it is not the number of variables added to the model, but which ones. Overfitting a model with many extraneous variables can lower the predictability of the model.[5]

THE PHILOSOPHICAL APPROACH: BLOCKCHAIN PRODUCTION

Respondents to the 2017 Nice Insight CRO Outsourcing Survey rated quality compliance, on-time delivery, and communication and transparency as three of the most important attributes that factor into post-CRO engagement.[6] One of the least obvious ways that machine learning will have a positive impact on tablet manufacturing is production scheduling and quality compliance.

"Blockchain applications in the supply chain could enable instant reconciliation and adjustment of production schedules between suppliers and end manufacturers without any middlemen, thus lowering efficiency losses," says Berish. Therefore, continuous drug manufacturing of the future will not only mean continuous manufacturing of one formulation using rapid feedback loops on the manufacturing line, but will extend the manufacturing line to encompass outsourcing partners across the globe. Much like how intercommunicating self-driving cars will be able to eradicate congestion in city centers, machine learning algorithms will decrease congestion and inactivity on tableting production lines by adjusting schedules based on the completion and quality of excipients at partnering facilities.

A total digital transformation of a company that requires similar compliance with

its outsourcing partners will revolutionize the tablet manufacturing industry. In the near future, this will likely take the form of an industry standard, much like the ISO or cGMP certifications. "If you're surprised when one day you're being asked to comply to certain digital standards," says Berish, "then you haven't been paying close enough attention."

Blockchaining of the industry will also aid in the selection of outsourcing partners based on machine learning algorithms. Imagine a "right-first-time" approach to formulation that has the potential to constantly improve as new excipients emerge.

INDUSTRY 4.0

As a rule-of-thumb, changes to more automation should be evolutionary, but lead to revolutionary results.[7] Industry 4.0 in pharmaceuticals looks very much like a faster version of Industry 3.0. Machine learning algorithms will be able to quickly make adjustments to the manufacturing line and production scheduling, but these changes will mostly come at the very end of the transition. Now is the time for the businesses to collect and curate data, all while pondering the possibilities that Industry 4.0 could create for the future of the company.

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