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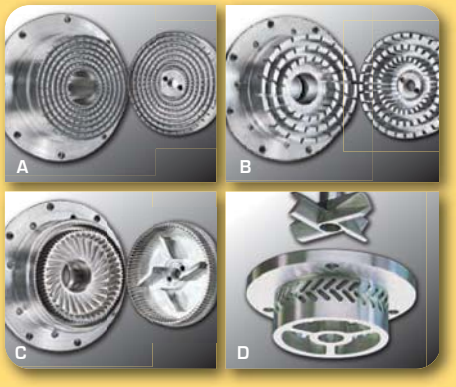

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1501 E. Woodfield Road, Suite 400N,
Schaumburg, IL 60173
Phone: (630) 467-1300 ▪ Fax: (630) 467-1179

Subscriptions/Customer Service
(800) 553-8878 ext. 5020 or
putman@stamats.com

EDITORIAL TEAM

karen langhauser
Chief Content Director
klanghauser@putman.net

meagan parrish
Senior Editor
mparrish@putman.net

christopher palafox
Digital Managing Editor
cpalafox@putman.net

keith larson
VP, Content and Group Publisher
klarson@putman.net

jim baker
Publisher
jbaker@putman.net

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DESIGN & PRODUCTION TEAM

stephen c. herner
V.P., Creative and Production
sherner@putman.net

michael annino
Associate Art Director
mannino@putman.net

rita fitzgerald
Production Manager
rfitzgerald@putman.net

ADMINISTRATIVE TEAM

john m. cappelletti
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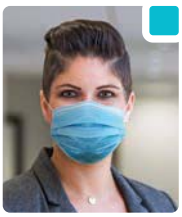
Karen Langhauser
Chief Content Director

Smooth transitions

Technology advances are music to pharma's ears



My first memories of music came from vinyl. I recall being entranced by the spinning records and how, like magic, lowering the arm of the Victrola brought musicians to life in the corner of my parents' living room. I can't tell you how many 33s probably met their demise because I insisted on awkwardly carrying them around everywhere I went. My parents eventually wised up and made me the proud owner of a plastic cassette player, which they likely quickly regretted, as I insisted that I needed to duplicate my coveted record collection with state-of-the-art cassette tapes.

But my time spent relishing in high-tech audiophile land was short-lived, because before I could even complete my Michael Jackson collection, cassette tapes were out and CDs were in. Convinced that CDs were the pinnacle of digital recording technology, I dropped a hard-earned $300 on the appropriate player, and filled my Sam Goody basket with the cardboard-intensive 12-inch long CD packages.

With each advancement in technology came an even bigger capital (read: allowance) investment and the need to start from scratch. And if I wanted to retrofit existing technologies — say, enable the tape deck in the car to play CDs — I needed to buy adapter equipment and cobble together a tenuous, overly-sensitive-to-potholes connection between old and new technology.

Such was the case, for years, with digital transformation in pharma manufacturing. Building a foundation for digital involved putting expensive, complex infrastructures in place. And those investments came with the high likelihood that newer technology would be both better and incompatible.

But today's pharma manufacturers have access to advanced toolsets that can be applied quickly and unilaterally to whatever data stream is needed. This improved technology has undoubtedly played a large role in increasing the digital optimism that was evident in this year's Smart Pharma Survey.

While integration challenges have not disappeared (integration, along with regulatory hurdles, remain top concerns) our survey found increased comfort levels with basic automation and a prioritization of digital when designing or upgrading facilities.

As you will read in our cover story, data has become the new manufacturing currency. Prior to the advent of audio files and streaming services, musical "data" was massive — bookshelves lined with records, cassettes exploding from the glove box, towers stuffed with CDs — and organizing it all was an ongoing project. Inevitably, a good portion of collections were never utilized. Similarly, pharma found that much of its quickly accumulating data was dusty and unused. But now, rather than onerously stockpiling historic data that rarely brings value, pharma manufacturers have the tools to collect data in real time and then run performance analytics that yield immediate payouts.

While music aficionados may argue that today's streaming music platforms lack the familiar charm of past musical formats and many, like myself, have nostalgically held onto collections, one can't help but notice that technology itself has made transitioning to new formats easier and more affordable than ever before. For pharma, modern technology's flexibility has the industry singing a new digital tune.

industry dose

Unlocking the story

Senior editor, Meagan Parrish, wins prestigious journalism award

At *Pharma Manufacturing*, we frequently repeat the phrase "trade publications don't have to be boring," as we push one another to think outside of the traditional box when it comes to content selection and bringing our readers impactful stories about topics that they care about.

To that end, we are thrilled to share that senior editor, Meagan Parrish, has received the American Society of Business Publication Editors' 2020 Stephen Barr Award for her December 2019 article, "The recall effect."

This coveted, "best in show" award honors one of ASBPE's most decorated journalists, Stephen Barr, who was sadly lost to cancer in 2002. Barr was the senior contributing editor of CFO magazine during a pivotal time in history characterized by billion-dollar companies navigating the transition to an internet-dominated business world. Barr was known for writing insightful articles that consistently demonstrated depth of investigation.

Barr left big shoes to fill in the world of trade journalism. This year, Meagan became the 17th journalist to join the prestigious ranks of Steven Barr Award winners.

Meagan's winning article, "The recall effect," was initially planned to be a simple rundown of the year's most important FDA regulations. But, after an eye-opening interview with a former FDA official, the story evolved into a powerful discussion of widespread impurities contained in APIs imported from overseas and our country's failure to keep these contaminants out of the drug supply.

The article told a story that has major ongoing implications for American drug manufacturers and patients. At the time, the industry was facing a massive recall of blood pressure medications contaminated by ingredients from China. Now, as the pandemic rages on, the issue of global supply chains and drug imports from China has become more important than ever before.

Please join us in congratulating Meagan on this well-deserved honor and visit pharmamanufacturing.com to read the winning article.

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> All of the elements needed for solid journalism — stories begging to be told, sources with intimate knowledge and readers clamoring for facts — are in place for trade publishers. The only missing piece? Just more editors and writers willing and able to turn the key.
>
> —Tom Zind, 2010 Stephen Barr Award recipient

Karen Langhauser
Chief Content Director

Making hydroxychloroquine great again

How a 65-year old drug became the center of partisan divide

One hour and 38 minutes into what started as a roundtable discussion with restaurant executives about the Paycheck Protection Program in mid-May, President Trump dropped the hydroxychloroquine bomb.

"I happen to be taking it," he slid in at the end of what began as a rant about whistleblowers.

He was referring to the prescription drug hydroxychloroquine sulfate (HCQ), approved in the U.S. for the prevention and treatment of malaria, and to treat lupus and rheumatoid arthritis. At the time of Trump's declaration, the drug had also been granted emergency use authorization by the FDA for patients hospitalized with COVID-19.

Members of the press exploded with questions. Why was Trump taking this drug? Had he been exposed to the virus? Did the White House doctor tell him to take hydroxychloroquine? Could hydroxychloroquine be used as a preventative medicine?

This was seemingly the response Trump was looking for. "I was just waiting to see your eyes light up when I said this, when I announced this," he said.

But HCQ had already become a political hot button, far before Trump's announcement. Results of small scale, early research coming from China and France began picking up speed on social media platforms in early March — when there were fewer than 1,000 reported cases in the U.S. — suggesting that the drug could have potential as a COVID-19 treatment.

In the weeks to come, the virus escalated quickly in the U.S. and businesses and schools around the country began closing as state after state went into lockdown, frantically trying to control the spread. Fox News political talk show host, Laura Ingraham, known for her far-right opinions, took HCQ under her wing and touted the drug to her audience. But things took a partisan turn when Ingraham's own network hosted global pandemic expert Dr. William Haseltine, who had previously been vocal about the Trump administration's poor COVID-19 response. Dr. Haseltine referred to HCQ as a "quack cure" that would likely have "very little effect on treating coronavirus patients."

And just like that, HCQ, a 65-year old antimalarial made by a dozen generic drugmakers and costing less than $1 a pill, found itself smack in the middle of a political divide.

Science forged its own response, as hundreds of clinical trials were launched around the world testing the potential of HCQ. But by the time Trump made his mid-May announcement that he was taking the drug, U.S. hospitals were overflowing and cases had surged to 1.4 million, with over 80,000 reported deaths. Americans wanted more than just a drug being tested for its potential. They wanted a game-changer.

At present, data from large, randomized controlled trials — considered the gold standard for ascertaining the efficacy and safety of a treatment by the FDA — does not paint HCQ as an effective COVID-19 treatment. And yet, a few non-randomized studies, anecdotal evidence from a handful of doctors claiming HCQ works and even a couple of viral conspiracy videos, have managed to kept the flames of the HCQ debate burning.

Part of the confusion can be attributed to the public's lack of insight into how and why clinical trials are designed and how to interpret data from these trials. But even as the scientific community continues to struggle to provide clarity, it's becoming increasingly difficult to hear the voice of science over the political screaming match.

The politicizing of HCQ — just one of many issues caught up in what has become a pandemic divided on party lines — will no doubt prove to be a cautionary tale of how quickly bias can muddy the waters of scientific progress.

Visit pharmamanufacturing.com to read the full story.

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2020 ASBPE honors

The recall effect
Steven Barr Award; ASBPE Regional and National Gold awards for editorial

Pharma Manufacturing **redesign**
ASBPE Regional and National Silver awards for design

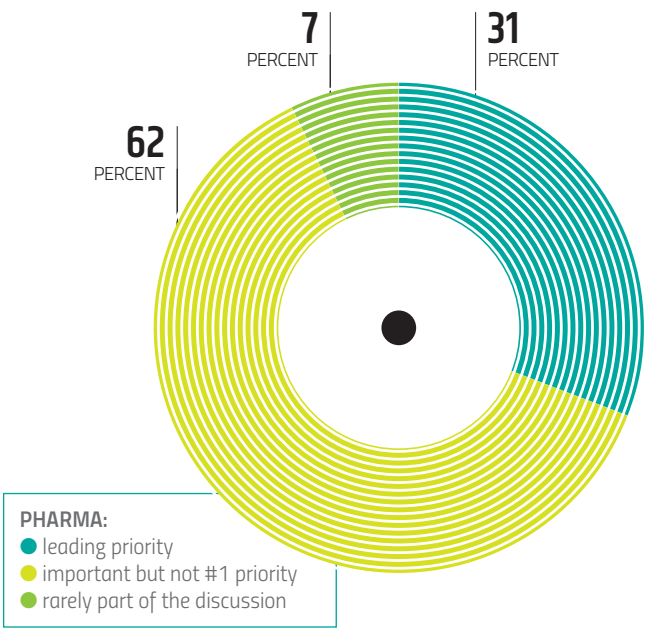
On the rise
ASBPE Regional Silver and National Bronze awards for design

Pharma Manufacturing **March front cover design**
ASBPE Regional Bronze for design

Karen Langhauser
Chief Content Director

EXHIBIT 1

How important is digitization to the discussion when designing/upgrading manufacturing facilities?



In a recent interview, Novartis CEO, Vas Narasimhan, told *Wired* magazine that when the pandemic hit, the pharma giant's digital investment areas that had "previously seemed like nice-to-have experimental areas that may transform us in five years" suddenly became "things that were fundamental."

It would seem that Novartis is not alone in this realization. Results from last year's *Pharma Manufacturing* Smart Pharma Survey generated concern that the industry's enthusiasm for the digital "revolution" was waning. But as we are all painfully aware, much has changed in pharma and the world since 2019. The pandemic put pharma's digital progress to the test and this year's optimistic survey results indicate that perhaps some of the industry's commonly mentioned roadblocks were based on antiquated concerns.

And it's possible that the pandemic will continue to drive digital change in the industry. Almost all pharma manufacturers surveyed agreed that the pandemic will alter the industry's perspective towards digitalization, with 65 percent specifically believing that the pandemic will increase the industry's use of technology to collect and analyze data in real time.

The sophistication of digital tools available to pharma manufacturers continues to grow. Digital transformation is the process of using these tools — smart sensors, artificial intelligence (AI), virtual reality and cloud-computing — to create new and better processes. Yet, digital transformation isn't just about the technology — it's a shift in mindset about how a company applies technology.

As pharma is finding out, today's technologies have the ability to create the efficiency and flexibility needed to navigate uncertainty. Combining this technology with the right mindset will enable the industry to move forward with renewed confidence in its ability to thrive in a digital world.

EDITOR'S NOTE

In 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/biopharma drugs, make APIs or excipients or offer contract manufacturing services. There were 263 total responses: 91 vendor responses, 140 manufacturer responses and 32 respondents who identified as "other" ("other" responses were included with manufacturer responses).

Tossing broken records

The pharma industry's aversion to risk, especially as it relates to implementing new technology, has endlessly played like a broken record in industry discussions. Yet when it comes to basic automation — the process of making tasks more efficient by using digital technology — recent evidence runs contrary to this widely held belief.

"It's not uncommon to see a pharma company with a good amount of automation in place, to the point where they are claiming they have more data than they know what to do with," says Rajiv Anand, CEO of Quartic.ai, which helps asset-intensive companies harness the data generated from their equipment and processes to create intelligence.

This exposure is reflected in the industry's growing level of comfort with automation on the plant floor and in labs. *Pharma Manufacturing's* Smart Pharma Survey, which separately polls drug manufacturers and equipment and services vendors about the pharma industry's digital maturity, has seen rising confidence levels. This year, 93 percent of manufacturers and 87 percent of vendors believed that pharma has become more comfortable with automation.

Pharma is not averse to breaking the status quo either. When manufacturers were asked if, given the option, their company would choose to automate a manual plant process that is seemingly effective, 85 percent (the highest in survey history) said "yes." Vendor optimism for pharma's conscious choice to automate, while still lagging behind that of manufacturers, also increased this year (from 63 percent to 75 percent).

Endress+Hauser, a global supplier of solutions and services for industrial process measurement and automation, is among the optimistic, and notes a more significant embrace of Pharma 4.0 technologies by the pharma industry.

EXHIBIT 2

Top concerns about smart equipment in plants

PHARMA:

1. **Integration**
2. **Regulatory hurdles**
3. **Education**
4. **Handling big data**

VENDOR PERCEPTION:

1. **Integration**
2. **Regulatory hurdles**
3. **Security**
4. **ROI**

"These survey results indicate this conservatism may be changing to a more aggressive approach, perhaps because pharma firms are realizing the risks of relying on manual processes outweigh the costs of upgrading from manual to automatic," says Bethany Silva, life science industry manager for Endress+Hauser USA.

Singing a new tune

There is an important distinction between automation and digitalization. While automation makes tasks more efficient through the use of technologies, digitalization goes a step beyond by collecting data and using it for advanced insight, thereby unlocking the benefits of true transformation.

This transformation requires a shift in mindset. To succeed, digitalization has to be prioritized, and pharma manufacturers appear to be doing just that. Over 93 percent of manufacturers surveyed said that when they are designing or upgrading facilities, digitalization is an important part of the discussion — and about a third of those respondents said digitalization is the lead priority. (Exhibit 1)

Vendors corroborated those numbers when asked the same question about their pharma customers — citing almost an identical breakdown.

Prioritizing digitalization and the collection of data is important, but it doesn't automatically yield new insight. Here, the quality of the data being collected is pivotal.

According to Anand, pharma companies have historically collected data just-in-case.

"And if they aren't using the data, it means they aren't actively monitoring the data's quality," he says. "Invariably that data has holes in it."

"Data is seen as the new currency in manufacturing," says Brian Vogel, global sales executive at Rockwell Automation, the world's largest company dedicated to industrial automation. "There is good currency and there is bad currency."

Modern tools don't offer much help if you are dealing with mountains of poor or incomplete data — a familiar scenario that can quickly dampen enthusiasm for digital initiatives.

"If quality data isn't there, there's no magic you can do with advanced analytics," says Anand.

Rather than stockpiling historic data, pharma manufacturers now have the tools to collect data in real time and then run performance analytics that yield immediate results.

According to survey results, pharma manufactures are recognizing the opportunity presented by these new tools. When asked to rank their top worries surrounding smart equipment in plants, pharma manufacturers ranked concerns about innovative technology (specifically the claim that technology being offered to the pharma industry isn't advanced enough) near the bottom of the list. (Exhibit 2)

According to vendors, newer pharma companies (≤5 years old) are twice as likely to be digitally advanced than established companies (20+ years old)

Digital tune ups

Looking at the big picture, more than 75 percent of pharma manufacturers surveyed believe that a more automated pharma industry will lead to improved productivity, quality and efficiency. This year, the number of respondents who also see the correlation between a more automated plant and reduced costs and increased innovation, has risen.

More specifically, both drug manufacturers and vendors agree that plant floor production would see the most benefit from increased digitalization — a belief that has stayed consistent throughout the history of this survey. This year, about a quarter of pharma manufacturers — more than ever before — point to supply chain management as the space that could potentially benefit most from a digital tune up. (Exhibit 3)

Anand points to another high-impact, measurable area that wasn't included as an option on the survey: Scale-up.

Tech transfer, which, at its most basic, involves transferring processes from R&D to the production floor, has long been marred by data silos and a lack of cohesive data management. At times, the digital systems used by researchers do not integrate with the systems used on the production floor. As a result, many companies turn to manual processes, such as spreadsheets and PDFs.

"Generally, pharma has good data in the process development stage, but the scale-up process involves a lot of manual data analysis," says Anand. "Having good initial data means modeling will be based off a solid foundation of data."

A foundation built from quality data creates the opportunity for digital transformation.

With many global pharmaceutical giants boasting robust drug pipelines, a more efficient tech transfer process will enable them to get products onto the market.

"In this space, digitalization directly hits the bottom line in terms of speed to market," says Anand.

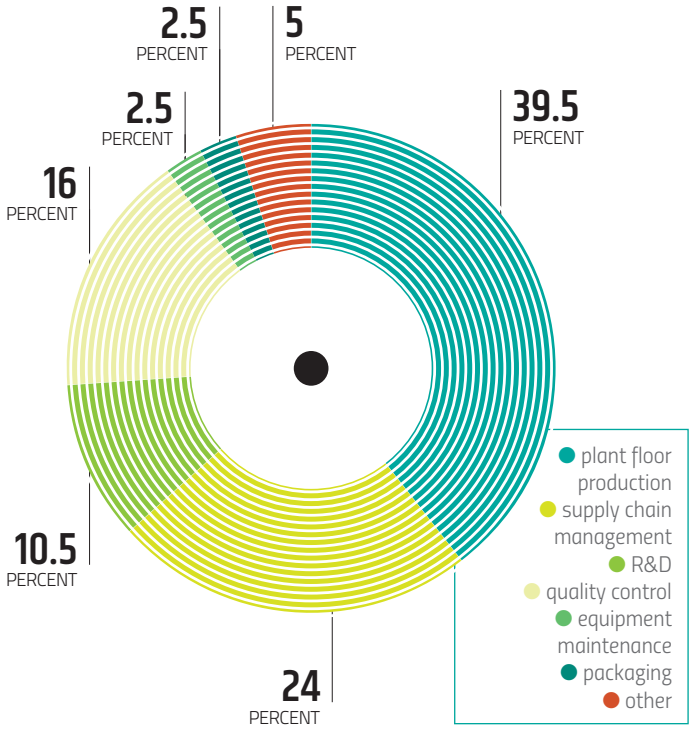
Pushing the needle

There is a lot of talk about digital transformation, but what about actual progress? When asked to evaluate their own company's progress on digital transformation/IIoT initiatives, a quarter of pharma manufacturers claim to be in the most advanced stage: They have identified applications and have made investments to match. But on the flipside, almost half admit their companies are still at the starting gate. (Exhibit 4)

Insight from vendors, many of which are selling digital technologies to pharma companies, is also relevant to the discussion. When asked to evaluate the pharma industry's collective progress, 41 percent of vendors think the industry is still at the starting gate and around 46 percent put pharma in the middle stage: identifying early applications to pilot. Only 13 percent believe the pharma industry has reached the investment stage.

EXHIBIT 3

What area of pharma manufacturing would benefit most from increased digitization?



The variability in survey answers can partially be attributed to the lack of a standard, unified method for evaluating a company's digital transformation progress. For vendors who sell digital solutions, sorting through this variability is crucial for success.

"As a vendor, you can't judge. You have to understand where organizations are at," says Vogel.

This assessment has to be thorough and consider more than just the end goal of digital transformation, explains Vogel. "It's great to focus on the outcome you want, but you need to look at this with a wider lens."

This wider lens is necessary because change in pharma doesn't happen in a vacuum.

Vogel uses the example of a Rockwell customer that wanted to focus solely on production management — with the specific goal of raising production output. Rockwell asked what changes they would be making to packaging and shipping, pointing out that an increase in production yield will have a ripple effect on other areas of the business.

"You have to look at the whole totality of your process to understand what the underlying problems might be and what is the appropriate starting point to fix them," says Vogel.

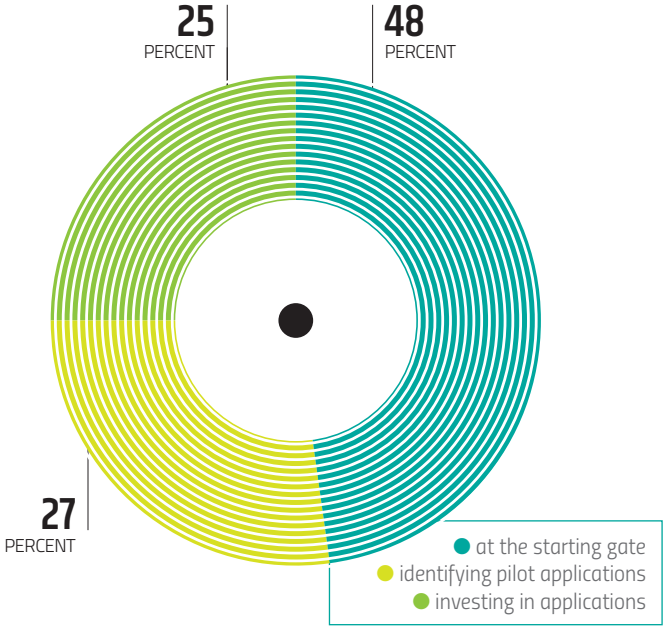
Silencing progress

Despite pharma's more open-minded attitude towards smart equipment on the plant floor, logistical concerns still linger. (Exhibit 2) For the past three years, the top concern associated with smart equipment, noted by both pharma manufacturers and vendors, has been difficulty integrating new technology with existing lines or equipment.

The No. 2 concern, also agreed upon by both manufacturers and vendors, is regulatory hurdles, specifically the lack of regulatory buy-in or understanding of new processes.

EXHIBIT 4

Which best describes your pharma company's progress on digital transformation/IIoT initiatives?



While these concerns are not without merit, especially in a highly regulated industry that operates a considerable amount of legacy facilities with aging infrastructures, Anand says it's important to dig deeper with pharma customers, making the distinction between perceived barriers and actual barriers to adoption.

"Have you actually tried or are you just making an assumption based on the status quo?" asks Anand.

On the regulatory end, the U.S. Food and Drug Administration has made strides towards shaking the agency's dated reputation as innovation blockers. In 2014, the FDA's Center for Drug Evaluation and Research's (CDER) Office of Pharmaceutical Quality created the Emerging Technology Program which enables pharma companies to meet with the agency to discuss, identify and resolve potential technical and regulatory issues regarding the development and implementation of a novel technology, prior to filing a regulatory submission.

According to Rockwell, technology improvements have also helped break down a lot of pharma's traditional barriers to digital adoption.

The foundational aspects of digital transformation that used to involve putting expensive, complex infrastructures in place have evolved, explains Vogel.

"Rather than putting excessive infrastructure in place, now we have a toolset that can be applied unilaterally — very quickly without a lot of heavy lifting — to whatever data stream deemed necessary," he says.

Quartic.ai notes an additional barrier to digital transformation that was not mentioned in the survey. The frequent movement of workers in the pharma industry — both internally to different positions and externally to different

companies — means technology vendors like Quartic.ai are constantly working with new customer teams.

"Any new technology requires dedication," says Anand. "In pharma, employees move around so much that we are constantly losing our digital champions."

Rockwell sees this employee turnover as a potential opportunity for vendors to step up and keep pharma on task, by propping up customers in the interim and assuming more ownership of the project.

"When people leave, vendors need to remind pharma of the importance of staying committed to the digital program," says Vogel.

Who are the champions?

The concept of "digital champions" warrants additional discussion. Does the push to transform pharma manufacturing always come from within? Surely equipment manufacturers and software providers — those providing pharma with the tools to progress — play a crucial role in championing the digital cause?

Just how crucial is up for debate. In survey results, neither pharma manufacturers nor vendors themselves could come to a consensus in terms of the extent to which vendors should push the industry. Should vendors be proactive, leading the charge by offering innovative products and education? Or should they take a more reactive role, by adapting products to the needs of manufacturers? For the slight majority of those surveyed, the answer lies in the middle. About 41 percent of pharma manufacturers and 38 percent of vendors think collaboration is key.

For Rockwell, strong, long-standing relationships with pharma customers, such as Pfizer, have been instrumental to advancing digital transformation within the industry.

When the pandemic hit, Pfizer was able to roll out remote collaboration tools in two weeks, which allowed employees to train with global subject matter experts through augmented reality via smart glasses and mobile phones. The drugmaker now is able to access shop floor data remotely, as they expanded their investment in security to ensure data protection during remote access — which became critical for continuing operations amid the pandemic.

11% of vendors surveyed think the pandemic will have no effect on pharma's perspective towards digitalization

Pfizer's digital preparedness was the result of a nearly two-decade working relationship with Rockwell that has evolved along with technology.

"Rockwell has been working with Pfizer before today's advanced toolsets were even available," says Vogel, who manages Rockwell's relationship with Pfizer. "Now we can connect systems in a single ubiquitous way that previously was not possible."

Today's technology vendors need to be more than just "data concentrators" if they want to win the trust of pharma customers.

"We [Rockwell and Pfizer] are partners. We got honest. We looked at what we were going to be good at, bad at, looked at what our challenges would be… we spent time figuring out how to meet those inflection points in a way that we could both mitigate and control," says Vogel.

As more third parties, such as systems integrators or industry consultants, become involved in pharma's digital transformation process, vendors are increasingly taking on the digital champion responsibilities. Vogel says in his experience, it is not uncommon for pharma manufacturers to hire consultants to evaluate manufacturing processes and inefficiencies. Armed with this important insight, the drugmakers then approach companies like Rockwell for help understanding and implementing the findings.

"Pharma wants to do this but often don't know how to start," says Vogel.

New processes, such as continuous manufacturing, are further driving pharma's need for outside support.

"We see pharma customers wanting support for automation related to managing the reality of the speed and magnitude of data associated with continuous manufacturing relative to batch," says Lisa Graham, vice president, Analytics Engineering, Seeq Corporation.

The backbone of new processes like continuous manufacturing is the real-time monitoring of massive amounts of data.

"For context, continuous manufacturing enables the collection of large data sets (~55,00 data points per campaign) and decisions must be made quickly," says Graham.

COVID and beyond

The lasting effects of the COVID-19 pandemic are still a story being written, but it's clear that the pandemic will put an asterisk next to all data and survey information collected in 2020. Of course, digital transformation in pharma is not a switch that was flipped as soon as the pandemic forced the world to turn to digital solutions. The infrastructure, both in mindset and technology, has been a

work in progress for years within the pharma industry.

But one can't help but wonder if the more positive digital outlook observed in this year's survey can be chalked up to pharma being put to the digital test — and performing better than anticipated.

In the same *Wired* interview mentioned previously, Novartis' Narasimhan commented, "We were better prepared than I expected. If you had asked me in January if we had taken 110,000 people and most of them turned virtual and our operations would still run, I wouldn't have believed it."

Pharma's altered perspective towards digitalization has widespread potential impact within the industry. According to survey results, 60 percent of pharma manufacturers and 46 percent of vendors believe the pandemic will trigger an increased interest in digitizing the pharma supply chain.

"COVID has highlighted the supply chain dependency risk across all industries, but more significantly in the pharma industry. This likely will provide a greater push in the direction of digitalizing the supply chain, again requiring more automation of previously manual processes," says Silva.

The role improved technology has played in increasing digital optimism should not be downplayed.

"It's simply not as hard as it used to be because technology has leap frogged a lot of traditional challenges," says Vogel.

But you don't have to take vendors' word for it — in this year's survey, pharma manufacturers ranked the concern that "technology being offered to the pharma industry is not advanced enough" at the bottom of the list of worries.

With almost half of pharma manufacturers and 55 percent of vendors surveyed believing the industry will have truly reaped the benefits of IIoT and smart factories within the next five years or less, pharma is edging closer to its digital transformation.

"These last couple of months have really enlightened both the vendors and the manufacturers that they need to be a lot more nimble and focused on solving immediate problems, while also keeping an eye on the prize of making sure they have tools that can grow with them," says Vogel.

Meagan Parrish
Senior Editor

Focus on: Brazil

Brazil's pharma industry has long been held down by high taxes and bureaucracy — but the weight could soon ease

As the behemoth of Latin America, Brazil has long been a sought-after market for pharma. Although most of the world associates Brazil with sprawling coastlines and tropical forests, the country is an attractive destination to pharma for another reason: its large population.

As the world's sixth most populous country, Brazil represents the biggest market opportunity in Latin America for multinational pharma companies. Valued at around $23 billion by EY, a global consulting agency, Brazil represented the seventh largest pharma market in the world in 2018.

Growth has also been steady. According to EY, the pharma industry has grown by about 7 percent year over year (in Brazilian Real terms) for the last five years, and withstood a recession that lasted from 2014 to 2017.

Nelson Mussolini, the executive president of Sindusfarma, a pharma industry trade association for Brazil's Sao Paulo region, says that the coronavirus pandemic is making estimates for future growth tricky, but that preliminary predictions indicate that commercial pharmaceutical sales will increase by about 5.5 percent in 2020 and grow to 8 percent next year.

"Pharma was isolated from the previous recession and there is potential to keep growing despite a COVID-related recession that could be coming," explains Fabio Schmitt, a Brazil strategy and transactions partner at EY.

Yet, significant barriers still remain when it comes to gaining access to this large pool of patients, for both global and local pharma companies. Despite its size, the industry has long had its wings clipped by high taxes, a burdensome bureaucracy, price controls and a high rate of API imports. And without sustained and significant investments in innovation, Brazil has been stuck in the grind of generics manufacturing, unable to produce notable advancements in R&D.

However, the industry could be approaching a turning point. With the coronavirus pandemic raging in Brazil, public and political will to bolster the country's access to health care resources is rising. And if regulatory changes roll pharma's way, the industry could shake off some of its chains and soar even higher.

At a glance

"The pharma market in Brazil is really divided between generics and patent," explains Schmitt.

According Sindusfarma, the Brazilian Ministry of Economy registered 418 pharma manufacturing plants in the country in 2018. EY estimates that nearly half of the industry's revenue is concentrated in its top 10 companies. Of those 10, six are Big Pharma companies and the other four are local. Generally speaking, Schmitt points out that while Big Pharma companies control the market for branded medicines in Brazil, almost all of the local companies stick with the generics market.

With access to free health care guaranteed by a program known as the Unified Health System (SUS), Brazil's government and hospitals gobble up a 30

percent chunk of the local low-cost drug market while the other 70 percent of drugs are sold through commercial pharmacies.

"Local companies have been successfully managing in this environment," Schmitt says. "But it's not a very easy market to play in."

The tax burden

Although Brazil's corporate tax rate is 15 percent, the country levies taxes on companies in many other ways including taxes on imports, exports, transactions, properties, services, income and more — adding up to a system that's far more burdensome than most other countries.

"This is a very complex system… maybe the most complex in the world," explains Eliane Kihara, a partner with PwC.

According to Mussolini, taxes correspond to nearly 32 percent of the amount paid by drug consumers.

"In the global context, the weight of drug taxes in the country remains an aberration," he says.

With such a high tax burden, Kihara says that pharma companies often have to invest a significant amount of money in human capital to support the tax system and avoid penalties.

"If Brazil did tax reform…that would be fantastic news and make the country more attractive for investments," she says.

Price controls

"Perhaps the greatest challenge [to the pharma industry] is the review of drug price controls," Mussolini says.

Every year, drug price increases are limited by CMED (Câmara de Regulação do Mercado de Medicamentos), an arm of Brazil's health regulatory body known as ANVISA. According to Mussolini, price controls were eased for some OTC drugs in Brazil, but discounts were largely maintained, which showed that the market is competitive enough to keep prices down.

"There is ample evidence that a series of drugs in Brazil can be freely priced, due to the excellent market competition. It is the case with generic drugs, which still have controlled prices despite having dozens of players in the various therapeutic classes," he says.

Mussolini also argues that price controls are denying pharma companies the ability to invest in innovation. Sindusfarma estimates that the country's entire private pharma market (excluding public sales to hospitals and the government), is worth about $17 billion, which, Mussolini says, means that "…the investment in R&D of a single large international laboratory is higher than that of the Brazilian private pharma industry as a whole."

API imports

It's a familiar story for many countries around the world. With Brazil relying on generic manufacturing to supply its demand for lower cost drugs, the industry has become wedded to API imports from India and China. EY and PwC both estimate that Brazil currently imports about 90 percent of its APIs, leaving the supply chain vulnerable to disruptions in the quantity and quality of its drug ingredients.

So far, Kihara says that Brazil has not experienced any supply disruptions during the coronavirus pandemic, but the situation has exacerbated concerns about shortages, and increased pressure on the industry and government to find solutions.

A coronavirus push

As a general rule, the pharma sector in Brazil has never been a major

Brazil's top 10 pharma companies by revenue

Pfizer
$1.28 BILLION

Sanofi
$1.22 BILLION

Roche
$936 MILLION

Hyper Pharma
$931 MILLION

Eurofarma
$925 MILLION

EMS
$906 MILLION

Novartis
$805 MILLION

Aché
$796 MILLION

Cristália
$469 MILLION

Abbott
$464 MILLION

—DATA COMPILED BY EY

PHOTO: KSENIA RAGOZINA / SHUTTERSTOCK.COM

contributor to the world's advancements in R&D, save for one exception — vaccines. While the world reels from the coronavirus pandemic, Brazil is poised to play a starring role in the quest to bring a vaccine to market.

Part of its importance in this epic push for a vaccine is apparent. Brazil is now the country with the second most confirmed cases of the coronavirus and the sixth most populous country, making it an easy market to find participants for large-scale studies. One late-stage trial of a vaccine candidate developed by University of Oxford and AstraZeneca is already underway in Brazil.

Its clinical research infrastructure is also primed for the task. Historically, Brazil has housed a number of major studies for vaccines including Zika and dengue fever, which has helped create the right environment for studying a vaccine. Several major institutions have partnered with Big Pharma companies in the past and have laid the groundwork for the next big shot with ample labs, testing clinics and professionals in place.

According to Schmitt, the pandemic has also "fast-tracked" the push for modernizing the country's pharma industry as a whole.

"COVID-19 has exposed barriers we have in the country to develop and distribute drugs," he says. "It was already on the government's playbook to improve

Supreme Court watch

Brazil's highest court is currently deliberating on a case that could have major implications for the country's generics sector. In the case, the constitutionality of Brazil's 10-year minimum extension on 20-year patent terms is being challenged. Those in favor of the extra 10-year term argue that it protects property rights and encourages innovation, while those against the rule say that it violates free competition and hinders industry development. If the Supreme Court rules against the 10-year extension, Licks Attorneys estimates that 22,000 patents for pharmaceuticals in Brazil could be eliminated.

the country's pharma infrastructure and health care access. Now the demand for this is getting a boost, and I think the government will lean toward this."

Optimism for change

Since President Jair Bolsonaro took office in January 2019, Mussolini says that there have been promising talks between the pharma industry and the government, and that the industry's proposals have been "well received."

"The government's willingness to know and resolve issues related to health and the pharmaceutical industry is evident," he says.

Sindusfarma is pushing for several key changes including relaxed price controls, the elimination of taxes on the production of medicines and less red tape around drug approvals.

"It takes much longer to register a drug in Brazil than in the U.S. and the EU," he says. "Meeting the rigorous standards of a modern regulatory agency such as ANVISA is fundamental for developing the pharmaceutical industry. However, it is necessary to reduce the bureaucracy of processes and procedures to give more agility to companies and thus provide lower costs, more profit and investments in research."

Mussolini says that Sindusfarma is also pushing for a less restrictive environment for clinical trials.

"The current regulations create serious problems, which frequently make drug research unfeasible to the detriment of Brazilian patients and applied research in the country," he says.

When it comes to APIs, Kihara says that the government is expected to begin providing incentives to bolster local production by the end of this year. She says that the incentives could be tied to building new production facilities for APIs and are being discussed alongside the issue of lowering or streamlining taxes.

Given the current government's openness to considering changes and rethinking processes in the pharma industry, all of the experts interviewed for this article expressed optimism that although no new regulations have emerged yet, they are on the way.

"There is political will," Kihara says. "It is a now a matter of survival that there are changes within the next couple of years."

Meagan Parrish
Senior Editor

Under pressure

Can the glass packaging industry withstand the weight of COVID-19?

It was all smiles at the White House in 2017 when executives from Corning Incorporated visited President Trump's administration to unveil an innovative new pharmaceutical vial. As part of the White House's "Made in America" initiative, Corning brought a sample of its Valor Glass container, which was developed with Pfizer and Merck, and had become the first new pharma glass composition approved by the U.S. Food and Drug Administration in over 100 years.

To demonstrate Valor Glass' durability — one of its prime advantages over traditional borosilicate glass — Corning's CEO, Wendell Weeks, asked the president to break a conventional vial by pressing down on it with a lever. In one quick pop, the borosilicate vial was shattered.

"I'm pretty strong," the president quipped with a smile.

"You ain't seen strong yet, brother," Weeks responded to a room full of laughter.

When Trump pushed his weight onto the lever pressing down on the Valor Glass, the vial didn't budge.

At the time, it was touted as another example of ingenuity by an American company. Now, a few years later, glass vials — including Valor Glass — have become a critical linchpin in the White House's efforts to bring an end to the coronavirus outbreak. And the strength, not just of vials, but of the pharmaceutical glass industry as a whole, will be a determining factor in whether or not America — and the rest of the world — can finally bounce back from the pandemic.

In fact, it wasn't long after drug developers kicked off their mad dash to create a vaccine earlier this year that the world wised up to the additional concern of having enough vials. For the past few months, headlines have blared that there may be a vial shortage coming and the worries have thrust packaging — part of the pharma industry that's normally behind the scenes — into the public's glare.

Meanwhile, the glass packaging market has launched into a fervent sprint of its own to ensure that when a vaccine is approved, pharma companies will have a way to deliver it to patients. Like pharma companies developing a vaccine, the U.S. government has also been helping the packaging industry along, pumping millions of dollars into the efforts to quickly ramp up capacity for glass vials.

But as the industry races to produce the needed vials for SARS-CoV-2 vaccines, small- and mid-sized pharma companies looking to package other therapies could be left behind.

While some glass companies are optimistic that they will be able to meet the demand being generated by the coronavirus while keeping up with existing commitments, others admit that the market for glass vials could be in shortage for many months to come.

How can the glass industry keep its supply lines from cracking under the weight of COVID-19?

Stevanato Group estimates that global demand for vials will rise by 1-2 billion over the next two years.

Glass or no glass?

There's a kind of confidence your company can emit only when it's successfully been in business for over a century. In the tight-knit community of glass vial producers, that self-assuredness is well on display.

"Schott is one of the oldest companies in pharma history and is working closely with the top pharma companies globally," Stefan Marc Schmidt, vice president of global sales and marketing at Schott AG says. "Right from the start of this COVID crisis, we have been in close contact with customers and have been working on scenarios and different ways to be prepared. That's what we do."

When asked about whether or not Schott — one of the industry's leading glass manufacturers— would be able to produce enough vials to meet the surging demand for a coronavirus vaccine, Fabian Stöcker, Schotts' vice president of strategy and innovation, echoed Schmidt's sentiment that the company is poised and ready.

"We have been surprised that this is an issue in the press," Stöcker says.

The combined experience of the top titans in glass manufacturing should make the industry well suited to the task of meeting the unprecedented packaging demands for a SARS-CoV-2 vaccine.

Three companies — Schott, Corning and Nipro Pharma Corporation — control the lion's share of the market for pharmaceutical glass tubing, which is the primary component used to make containers such as vials and syringes. The top two glass tubing manufacturers have been in business for over 100 years each, and difficult barriers to entry, such as the high complexity and cost of manufacturing type 1 borosilicate glass (the most common type of glass on the pharma packaging market), have kept the tubing industry small. Underneath the glass behemoths, there is also a bustling market of converters — companies who turn glass tubing into vials or syringes.

"There are hundreds of converters who turn tubing into vials," explains Brendan Mosher, vice president and general manager at Corning. "So you have a very consolidated tubing market and then a very fractured converting industry."

Despite the combined experience of glass manufacturers, with so few of them, it also stands to reason that there could be concerns about the industry being nimble enough to handle a sudden surge in demand. Stevanato Group, an Italian manufacturer of vials, estimates that global demand for vials will rise by 1-2 billion over the next two years. Even before the coronavirus pandemic, the industry faced worries that there could be a type 1 borosilicate glass vial shortage. Part of the problem is that glass manufacturing facilities are expensive to build. Then, there can be challenges with obtaining the needed key raw material

— a particular kind of angular sand found in riverbeds and beaches that's in high demand around the world for a number of products.

Earlier this year, John Bell, a professor at University of Oxford (where one of the leading SARS-CoV-2 vaccine candidates is being developed) sounded the alarm over a potential glass shortage, claiming that there are just 200 million vials left in the world.

But Stöcker waves those concerns away. Based on Schott's internal auditing of the market, Stöcker says that the current capacity for glass containers for injectable drugs is 50 billion, including cartridges, syringes and other containers. Of that 50 billion, Stöcker says that the current global supply for vials alone is 16-18 billion.

The market was also already on the upswing. Due to rising demand for vials from developing countries, Schmidt says that the glass container market has been expanding 3-5 percent each year, and Schott had already planned a $1 billion investment in building out its existing capacity for both glass tubing production and converting.

"For the last few years…there have been drug shortages in the U.S.," Stöcker says. "But that has nothing to do with packaging."

Mosher, however, describes the market for glass tubing as "extremely tight."

"Corning is the second biggest borosilicate tubing producer behind Schott," Mosher says. "We make enough tubing for approximately six billion vials a year. But we have been in a sold-out condition for the past 18 months."

The hunt for glass

Lawrence Ganti, chief business officer at SiO2, a company that has innovated an alternative vial to borosilicate glass, agrees that some pharma companies are having a hard time securing glass packaging from the leading suppliers.

"We have been told by many customers that when they call asking for glass, they are turned away, or asked to pay ridiculous upfronts to obtain it," he says.

Given the challenging market conditions and the fact that glass manufacturers want to make sure they have enough supplies ready to fill orders for a coronavirus vaccine once one is approved, Ganti says that the top players in "Big Glass" are prioritizing who they can make commitments to — and it's often only Big Pharma companies.

Currently, Schott says it is not turning down orders or requests from customers.

"We openly discuss the business case, negotiate and make a competitive offer to our customers," Schmidt says.

But Mosher admits that Corning is sometimes "turning away customers because we have already committed capacity."

"Big Pharma companies that already have contracts in place should be fine," Mosher says. "I think for small- to mid-sized companies, it is going to be much more difficult [to secure vials] if they don't have existing supply agreements."

How can the glass industry juggle the sudden need for more vials and keep smaller pharma companies stocked up?

Borosilicate alternatives

When SiO2 launched, the goal was to develop a new pharma container that was as stable and safer than glass but as durable as plastic to reduce breakage during manufacturing. After about 10 years and $500 million in R&D, the company released a plastic vial containing a microscopic inner glass lining that's 50 times thinner than a human hair.

"What we've managed is to advance a new material which takes all the durability of plastic and marries that to all of the stability properties of glass so that you have none of the negatives of either but the positives of both," Ganti says.

Interest in the SiO2 vials has trickled in from pharma companies since the product was commercially released about a year ago — but many customers were reluctant to to take the leap.

"People said it was cool tech but they didn't want to change because they didn't want to be the first," Ganti says.

Now, since a number of Big Pharma companies have converted to the SiO2 platform and there's more focus on supplying vials for a coronavirus vaccine, Ganti says that the number of companies looking for an alternative vial has shot up.

"About 60 to 70 percent [of pharma companies] are coming to us now because of concerns with glass," Ganti says. "Before, the time between meetings with companies was months — now it's days."

Before 2019, Ganti says that there were seven drug products being tested in clinical trials with SiO2 containers — now there are 41. Given the sudden interest in securing vials, SiO2 has also doubled its sales forecast for this year, from a 200 percent increase over 2019 to a 400-500 percent jump.

Ganti admits that the SiO2 vials are still a bit more expensive (about 5-10 percent more) than traditional borosilicate containers, but stresses the many benefits, such as eliminating breakage, faster time to market and increased patient safety. And because the glass material is made by chemically applying the inner layer — made from SiO2 and vapor — by using plasma energy, there are no raw materials concerns.

Mosher says that Corning is also steering customers in the direction of Valor Glass if the company is unable to fulfill a request for borosilicate containers.

When developing Valor Glass, Corning's goal was to eliminate delamination from vials, which contributes to glass flaking and

subsequent recalls. After conducting a root-cause analysis, Corning discovered that boron — a mineral in borosilicate glass — can become unstable at high temperatures and contribute to delamination. Eventually Corning innovated a new composition that eliminates boron but keeps the glass' other needed elements: silica and alumina.

The aluminosilicate formulation in Valor Glass not only addresses delamination, it is also more mechanically resistant to temperature swings and is less prone to breaks and damage, which improves efficiency and speed on the filling line.

Mosher says Corning is working with customers every day on adopting Valor Glass for new drugs, but because of the investment associated with revalidating manufacturing lines for new containers, it's a tougher sell for existing drugs.

"It's a no-brainer for new drugs," Mosher says. "But there are time and conversion costs for existing drugs. For that reason, we are working closely with global regulatory authorities to streamline the adoption process for innovative technologies like Valor Glass."

Even with alternative packaging options on the market, the pharma glass industry is going to have to ramp up capacity for all vials if it's going avoid being pummeled by rising demand.

A capacity cure?

Just as the Biomedical Advanced Research and Development Authority (BARDA) has been injecting the pharma industry will hundreds of millions of dollars to support the development of a vaccine, government agencies have also been throwing money at the vial problem.

In June, BARDA announced two major investments to expand vial manufacturing — one is a $143 million contract with SiO2 to scale its per-month capacity to 10 million containers (which can hold up to 10 doses of a vaccine each) by November. Ganti says the contract will add 200 employees to its manufacturing site in Alabama. In addition to supplying Moderna with vials for its vaccine candidate, the company is also working with six other coronavirus vaccine developers, who are testing their products in SiO2 containers.

> **There is a concern that once effective vaccines become available, lead times [for vials] may increase even further.**
>
> —David Enloe, president and CEO, Aji BioPharma Services

Corning also secured a $204 million grant from BARDA to increase capacity for its Valor Glass products at facilities in New York, New Jersey and North Carolina. Because Corning has agreed to grant priority access to drugmakers designated by BARDA who are developing a vaccine, Mosher says the company could sell out its capacity of Valor Glass to BARDA through 2021.

The Coalition for Epidemic Preparedness Innovations (CEPI) has also invested in securing a supply of vials across the Atlantic. In June, CEPI announced a supply agreement with Stevanato to procure 100 million containers that will be able to hold up to 2 billion doses of a vaccine.

Andrea Zambon, marketing and product management director at Stevanato says that the company has already secured an ample supply of glass containers and is fast-tracking access to four of its converting lines in Italy and Mexico.

"This preferred access [for CEPI] will remain in place through the end of 2021, by which time we will mostly like have a vaccine approved and distributed worldwide," Zambon says.

When asked if the CEPI deal could impact Stevanato's ability to keep up with other commitments, Zambon says "not at all."

"We've proactively increased our capacity worldwide, and are committed to maintaining exemplary service to our standing customer base as well as the approximately 30 additional programs in which we're involved pertaining to COVID-19," Zambon explains.

The widespread ramp-up mode of pharma is also trickling down to purchases for packaging equipment, according to the Association for Packaging and Process Technologies (PMMI).

"As researchers and scientists actively pursue development of a safe and effective vaccine for the coronavirus, PMMI's June 2020 Purchasing Index indicates that investments in packaging machinery for the pharmaceutical and medical device sector are vastly exceeding figures for other sectors such as food, beverage and personal care," says Jorge Izquierdo, vice president, Market Development, PMMI.

Despite the capacity increases, many companies are preparing for a rocky market in the short term.

David Enloe, president and CEO, Aji BioPharma Services, a global integrated drug product contract manufacturer, says his company is now experiencing extended lead times on glass vials that are up to 12 months in some cases — and the situation is likely to get worse before it gets better.

"There is a concern that once effective vaccines become available, lead times may increase even further, despite commitments from glass manufacturers to increase tubing and converting capacity. This

will be an added strain on CDMOs and their ability to meet clients' timelines for non-COVID-19 products," Enloe says.

To help mitigate the risks, Enloe says Aji BioPharma Services is working with its partners to select vials and stoppers that may be less impacted by the push for a coronavirus vaccine vial.

"For vaccines it appears that a 10mL vial and 20mm serum stopper are most popular, which would provide more than ten doses per vial. There is also interest in 20mL vials with a greater number of doses, which may help cut the vial demand by half," he says, adding: "It's important to remember that CDMOs, drug innovators and glass suppliers need to communicate and collaborate now more than ever to address these supply chain challenges in order to successfully address the upcoming COVID-19 vaccine demand as well as continue to support all of the other patient needs."

How long before the market levels out? The predictions vary.

"In late 2019, it had been predicted that the supply of glass tubing would stabilize by the end of 2020," says Kazunori Ashida, president of Namicos Corporation, a Japanese manufacturer of ampoule vials. "However, now due to the sudden increase in demand for vials in anticipation of a COVID-19 vaccine rollout, we expect the shortage to continue. For this reason, even though ampoule and vial makers are putting forth strong efforts to ramp up their production capacity, we anticipate that it will take several years to stabilize."

Mosher says that given the fact that all of the major suppliers have announced capacity expansions, the situation could start to resolve itself "in the next 12 to 18 months." Mosher adds that the increase in capacity could even eventually lead to an excess in the supply of vials.

One thing glass manufacturers all agree on is that — just like drugmakers — the industry is banding together to make sure there will be enough supply to effectively distribute a coronavirus vaccine around the world.

"The industry is putting aside the competitive spirit," Mosher says. "It feels like more than ever, that everyone is in this fight together."

Ram Krishnan,
Chief Marketing Officer, Aera Technology

Bringing lean up to speed

Blending lean with next-gen AI can radically improve supply chain decisions

The pharma industry's adoption of lean principles over the past decade has delivered mixed results. On the plus side, pharma companies have made substantial gains by applying lean to R&D and manufacturing processes — reducing waste, accelerating production, and improving quality control.

But on the downside, pharma companies haven't realized the same successes in extending lean across the organization, especially in the broader supply chain. In many cases, results have been underwhelming when introducing lean and Six Sigma models across procurement, demand planning, inventory, distribution and logistics.

Lean hasn't delivered the end-to-end visibility that's needed for supply chain optimization. In fact, supply chain visibility was the No.1 priority for life sciences executives surveyed by LogiPharma, a pharma supply chain community. End-to-end visibility is needed to contain costs, accurately forecast lead times, respond nimbly to changes in supply and demand, and ensure customer satisfaction.

The visibility goal remains elusive. Pharma companies face the stubborn roadblock of supply chain complexity, demand and channel volatility, a proliferation of underlying IT systems and rising volumes of data. Those challenges are only worsening in our hyperspeed digital world.

In addition, companies moving into biologics and biosimilars face additional challenges in the inherent complexity of sourcing materials and producing treatments based on living organisms. Lean and Six Sigma alone can't address the underlying issues that undermine pharma supply chain performance.

Instead, manufacturers should look to pair lean principles with next-generation technology designed to process large amounts of changing data.

Lean's limitations

The problem is that lean and Six Sigma, as process methodologies, do little to leverage the data that's essential to optimizing the pharma supply chain. Managers are still relegated to using imperfect data and conventional tools — ERP systems, planning applications and spreadsheets — to make critical supply chain decisions. That poses two issues:

1. Supply chain data isn't real time. It's static and often outdated by days, weeks or months. Result: Without definitive real-time data consolidated from multiple sources, the company can't intelligently respond to a disruption or a major shift in demand. It lacks the agility required to address both strategic and tactical threats and opportunities.

2. The extent of manual human work is extreme. Pharma supply chain teams spend untold hours manually piecing together information from disparate systems, and running analytics in a spreadsheet or business intelligence tool. This slow, imprecise and very costly process provides the basis for best-guess decisions that, unsurprisingly, often miss the mark.

A lean approach to pharma supply chain data management and decision making can certainly help pharma reach the goals of supply chain visibility and optimization.

Lean and Six Sigma are sound frameworks, proven in multiple industries since lean concepts were pioneered by Toyota as far back as the 1930s.

With an emphasis on waste elimination and efficiency, lean and Six Sigma are well suited to help pharma companies achieve multiple objectives across the supply chain:

- Cost reductions in procurement, manufacturing, inventory and distribution
- Faster production and order fulfillment
- Greater accuracy in data, processes and forecasting
- Improved ability to respond to changes and disruption

But for lean to truly succeed, it needs to be coupled with next-generation technology purpose-built to process vast volumes of fast-changing data and make intelligent recommendations. Together, a disciplined lean framework and digital transformation open new frontiers for pharma to radically improve the quality of supply chain decision making.

Coupling lean and AI

Today, top pharma companies looking for supply chain optimization are turning to a technology known as cognitive automation, which blends internet-scale compute power, a virtualized enterprise data store, and artificial intelligence/machine learning (AI/ML).

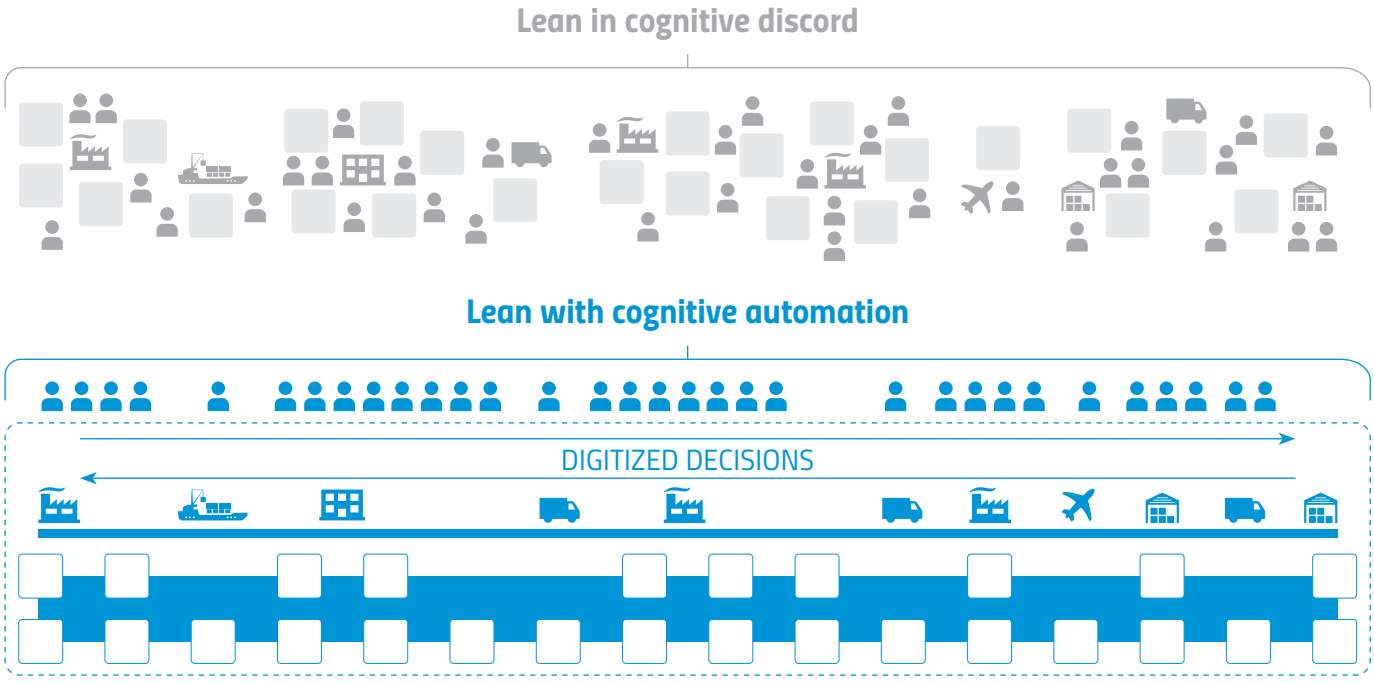
Deloitte is among the industry experts to believe that the pharma supply chain is ripe for transformation with AI.

In a recent biopharma report, Deloitte stated, "Biopharma manufacturing and supply chains produce vast amounts of real-time data that for years have been underutilized. However, AI technologies are poised to impact these processes through real-time data processing and decision making that can make supply chains truly data-driven."

Bringing together lean and cognitive automation accomplishes several things:

- Cognitive automation creates a near real-time cognitive data layer with thousands of Google-like data crawls each day across multiple internal and partner applications. That generates timely, accurate information with a high degree of granularity to respond to ever-changing conditions.
- AI and ML algorithms deliver exception management alerts and respond to queries. Cognitive automation delivers recommendations on optimal actions in various scenarios — addressing inventory shortage, responding to a regional demand spike, recalculating lead times, etc.
- Lean and Six Sigma processes can be embedded and digitized in the cognitive data layer to help ensure waste-reducing workflows and collaborations across stakeholders.

Lean and Six Sigma focus on local optimization which means teams meet with cognitive discord when trying to deal with end-to-end decisions. Cognitive automation can free teams from discord so they can focus on strategic, impactful decisions.



Decisions made are constantly monitored for outcomes based on self-learning capabilities in AI.

It's a breakthrough shift from status quo models involving homeostatic, monolithic systems. Supply chain managers no longer face the Sisyphean dilemma of trying to manually manage and analyze tremendous quantities of data. Machines take over that heavy lifting, liberating personnel to focus on higher-level strategic planning and anomalies that demand human consideration.

Reducing response time from months to days

The ultimate payback is in truly data-driven decisions. For example, consider lead time forecasting. There's invariably a sizable gap between planned and actual lead times due to the unavailability of real-time data, inordinate manual work, and changes in upstream and downstream signals that are difficult to track.

As it is, it can take a pharma company weeks or months to respond to variance in planned and actual lead times, and address unanticipated changes that triggered the gap. By then, opportunities to swiftly mitigate the root cause issue have disappeared.

Rooted in a lean framework with well-defined workflows, cognitive automation gives big pharma the real-time data and analytic depth that it's been missing all along. Lead time variances can be detected in days or hours, and alternative measures put into action in days. Cost savings and revenue preservation can amount to hundreds of millions of dollars.

It's not a pie in the sky vision. Pharma leaders such as Merck KGaA are using cognitive automation for supply chain optimization. Those innovators that capitalize on the opportunity will start small, experiment, and scale up under the leadership of a chief digital officer or team well positioned to drive adoption.

And they'll rethink lean strategies that have worked well in manufacturing by extending those proven principles across the broader supply chain in a next-generation technology framework.

EY Supply Chain & Operations, Ernst & Young LLP

Jay Welsh
Principal, Consulting

Srihari Rangarajan
Senior Manager, Consulting

Nicholas Zarling
Senior, Consulting

Steering through turbulence with IoT

How pharma can navigate disruptions by applying Internet of Things technology to supply chains

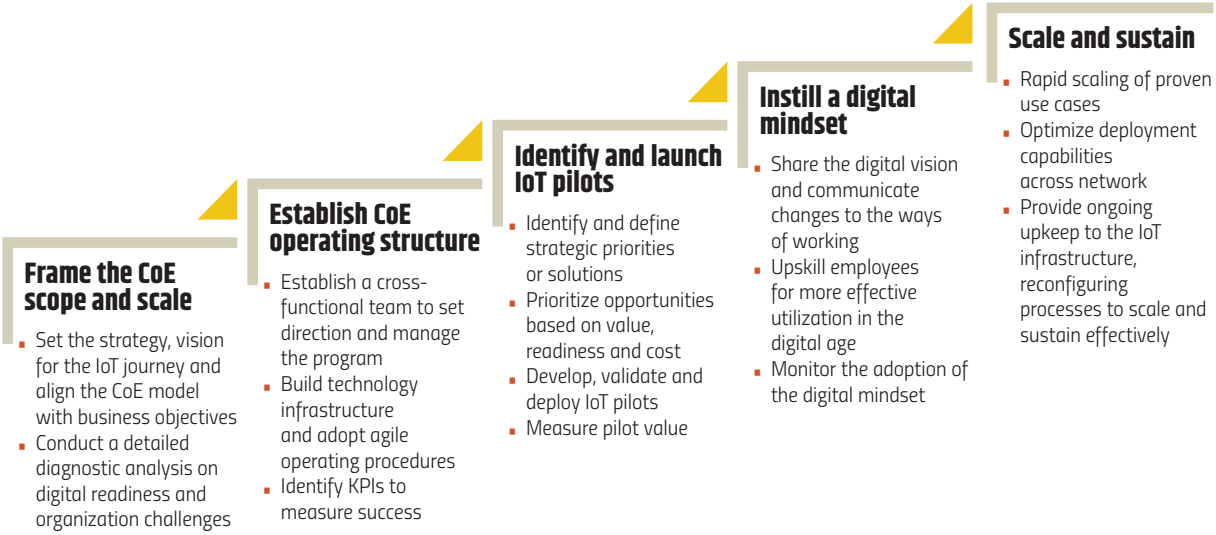
Uncertainty and changes to industry trends have created a difficult environment for the current pharmaceutical supply chain. But with challenge comes opportunity.

Pharmaceutical companies are facing challenges that stem from a rise in mergers and acquisitions, a shift to outsourcing of business functions, changes in patient trends and complications with operations.

The surge of mergers and acquisitions and increase in business function outsourcing has forced many underlying business functions to rely on incompatible, legacy data systems. This has led to fragmentation of data across manufacturers, distributors, pharmacies, hospitals/health systems and third-party logistics suppliers.

Additionally, the rise of personalized therapies has been a common trend within the industry. Therapies, such as individualized cell and gene therapies, increase supply chain complexity as future manufacturing is customized and made to order. This shift to customized treatments requires precise product temperature and location tracking to be viable. Within operations, a lack of visibility into manufacturing, aging assets and an underutilized

Pharma's IoT journey with a Center of Excellence model



workforce are impacting organizations' ability to produce and transport drugs efficiently. In fact, product losses due to issues such as temperature variations during transit are costing pharmaceutical companies over $15 billion a year.[1]

The current challenges within the supply chain have been further magnified through the disruptive force of the COVID-19 pandemic. The outbreak has directly impacted the logistics of supplying drugs to patients, disrupted the ability to plan and schedule production, and further complicated forecasting of demand and capacity.

Organizations can navigate industry disruptions by applying Internet of Things (IoT) technology to improve how drugs are produced and supplied to patients. The adoption of IoT will enable a more nimble supply chain that allows for rapid response during industry turbulence.

Embracing the disruption

We are entering an era where emerging technologies are reaching maturity. IoT has become far more than a futurist prediction — it's now the backbone of the connected world and a fundamental component of smart manufacturing and the modern supply chain.

IoT will allow data to flow seamlessly from operations and equipment into the hands of workers, management and executive leadership, providing end-to-end visibility and enabling real-time, evidence-based decision-making. The ability to connect, track and analyze processes from sourcing to storage and administration will provide an audit trail of compliance while improving control over inventory and delivery. Analytics will further advance the insights available from IoT data to promote drug product quality, reduce lead times, predict equipment failures, estimate downstream product needs and optimize capacity utilization.

Further, IoT will aid in the integration of supply chain data with other functions of the pharmaceutical value chain, including marketing, sales, finance and R&D. Capturing and analyzing supply chain data on shipments, usage, returns, claims and clinical outcomes will provide real-world evidence on drug efficacy. These insights can help pharma deliver the right product to the right patient at the right time.

In this pharma supply chain, changing stakeholder needs and industry trends are met effectively in real time. Leveraging IoT technology improves visibility across the supply chain and enables a more nimble approach to serving patients. The shift to a more intelligent, well-networked supply chain will help organizations cope with disruptions like the COVID-19 pandemic.

Addressing pain points

IoT has the potential to improve pharmaceutical supply chain visibility and productivity by connecting various data sources, enabling insights and providing optimization opportunities.

A combination of hard and soft sensors will enable organizations to capture data on often-overlooked variables, such as machine utilization, equipment health, process conditions, energy consumption and interplant logistics. Deploying sensors to the highly utilized equipment on a fill-finish line

allows manufacturers to monitor equipment uptime in an area where downtime directly impacts the quantity and timeliness of product reaching the patient. Unlocking new data points also allows for the monitoring of critical assets, such as autoclaves and centrifuges, while providing insight into process conditions, such as moisture content in a lyophilizer.

The improved data availability from IoT enables employees to monitor operations away from the production floor and even remotely. When used for reporting, this available production data enables a smart factory that is capable of monitoring operations in real time to improve the physical process control of drug production and material flow.

Outside of interplant operations, IoT enables organizations to integrate the flow of data from suppliers to customers by using cross-platform open source data frameworks. This will allow for individualized therapies, such as cancer treatments, to utilize a fully connected data infrastructure to efficiently transfer information between unaffiliated entities such as hospitals, laboratories and logistics centers. The ability to control the flow of data and bring different sources together also creates value within the organization's internal operations. Combining different data types unlocks insights not previously available. This new, connected digital ecosystem will enable delivery of treatments to patients in a faster and more secure way.

The use of analytics can further magnify the value unlocked by applying IoT to the pharma supply chain. Analytics, such as machine learning and artificial intelligence (AI), can predict equipment failures, forecast batch yields, sequence equipment efficiently and estimate downstream product needs. In fact, it is estimated that more than 50 percent of pharmaceutical and biotech manufacturers will employ prescriptive analytics and AI by 2021.[2] The availability of this forward-focused information enables smart manufacturing practices that improve overall equipment effectiveness (OEE), increase revenue and boost workforce productivity.

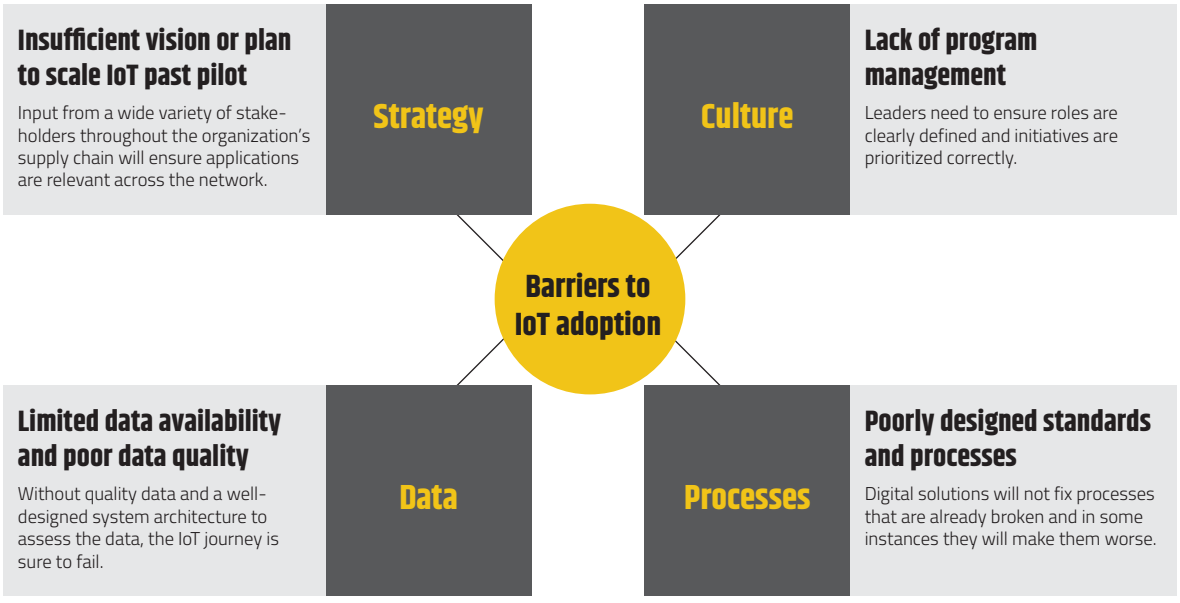
Augmented reality/virtual reality (AR/VR) further increase the value a supply chain will see from a digital IoT transformation. These technologies allow for improved data visibility in a hands-free environment, more effective trainings for operation employees and the ability to support and problem-solve operation critical employees remotely.

Embarking on the IoT journey will act as a supply chain accelerator by bringing the plan, source, make and deliver functions in closer alignment with the strategic imperatives of the organization as it becomes nimbler and more responsive.

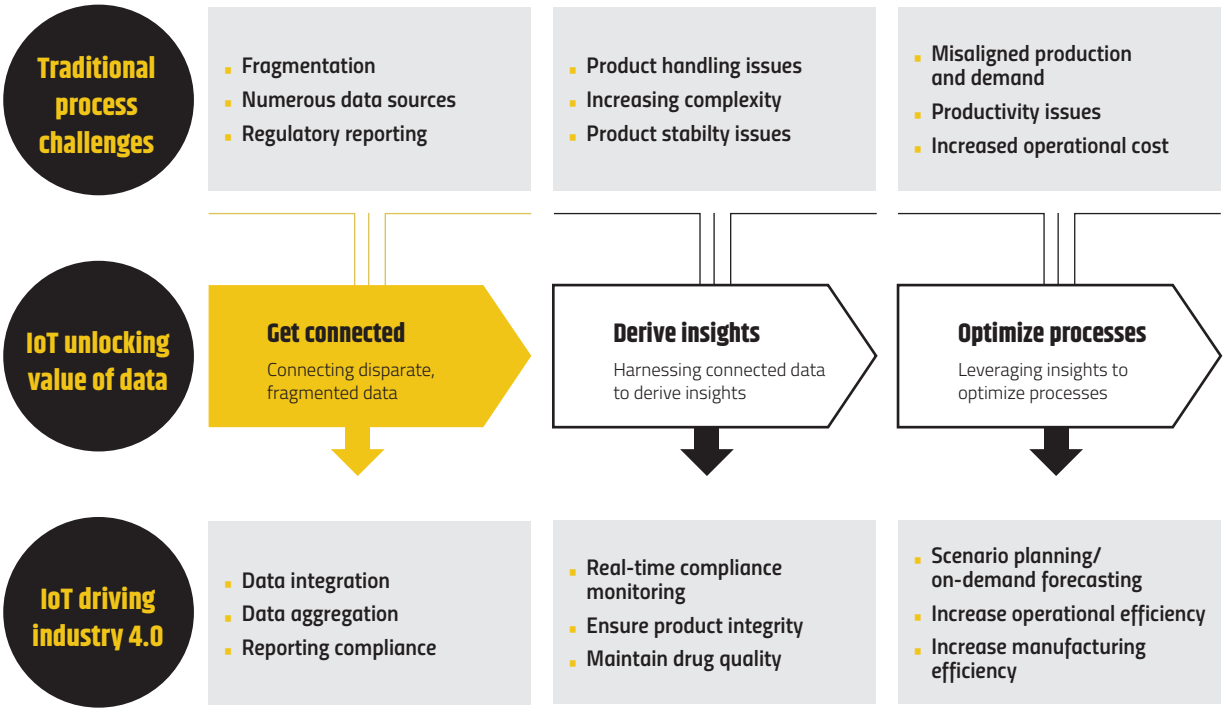
There are no shortcuts

Thirty percent of IoT projects fail in the proof-of-concept stage. This isn't

Barriers to adoption



IoT addressing critical pain points



a reflection of the technology; there are many successful deployments. However, too many businesses try to begin the journey despite badly implemented processes, unclear roles and responsibilities, poorly designed organizational setup and other issues. These problems need to be resolved before the push to digital can begin.

Embarking on an IoT journey is a significant, company-wide responsibility demanding the dedication of substantial resources and investment across multiple departments. Because the groups of stakeholders come from fundamentally different worlds, it is critical to establish a common ground from the beginning. Creating an IoT Center of Excellence (CoE) will align strategy with execution by ensuring shop floor stakeholders are able to provide thought leadership and direction to the team executing on the IoT journey. Enabling team members to work in parallel with end users fosters an environment of continuous learning and communication.

Adoption is equally as important as execution. The organization is only able to extract the full value from IoT technology if it is effectively used throughout the supply chain. To adopt the technology in the most impactful way it is important to consider necessary changes to SOPs and ways of working. This concentration on adoption ensures the program maintains a forward focus on scalability and the realization of value.

The IoT journey

Frame the CoE scope and scale: Pharma organizations should first build a foundation by understanding the current context and future direction of the supply chain in which the CoE will operate. A detailed diagnostic analysis is conducted to understand digital readiness and identify where digital capabilities align with challenges facing the organization. This first step on the digital journey sets the expectation within the organization on what level of investment and type of infrastructure improvements will be required.

Establish the CoE operating structure: Now that expectations and direction have been set, the organization needs to design its operations to be able to execute. Within the CoE, reporting lines and team structures should be redrawn with digital in mind to create cross-functional teams that eliminate siloed work. Agile training will enable these cross-functional teams to efficiently deliver capabilities that empower employees throughout the supply chain. To

The shift to a more intelligent, well-networked supply chain will help organizations cope with disruptions like COVID-19.

enable CoE members, agile SOPs that align with the digital mindset and ensure transparency should be implemented. Measuring the success of the CoE is also important. Leadership needs to define and monitor key performance indicators (KPIs) to understand the team's achievements and identify improvement areas.

With the agile ways of working established, pharma organizations must prepare technological infrastructure by identifying a development platform, defining system architecture standards and building analytics capabilities. Cross-platform data frameworks should be implemented to enable the flow of data between different source systems and entities. To ensure the right decisions are made it is important to align the direction of the organization with its current digital maturity and technology needs. An assessment can help steer decisions that directly impact the development feasibility of IoT applications.

Identify and launch IoT pilots: With a solid operating structure established, the next step is to define strategic priorities for IoT initiatives. A top-down/bottom-up approach allows the steering committee and shop floor end users to set the direction, reducing the likelihood that a one-off solution is developed. Many organizations that are working to improve smart manufacturing capabilities will conduct an assessment of current operations and prioritize quality control, energy monitoring, predictive maintenance and materials management for IoT application development. When deciding on pilots it is important to consider criteria like ease of delivery, network applicability and business value.

After opportunities are identified and agreed upon, it is time to execute on developing the IoT applications as pilots or proofs-of-concept. The pilots are important for gathering stakeholder feedback and

should be measured to demonstrate business value before the solution is scaled throughout the organization.

Instill a digital mindset and conduct change management: Running a successful IoT transformation program is not just about tools and technology; it's also about the people. A digital mindset is crucial for building a performance culture that delivers and adopts digital solutions effectively. This digital mindset needs to be adopted at all layers of the organization to create ownership and ensure effective communication. For shop floor employees, digital working methods need to be implemented that maximize the effectiveness of IoT technologies while enabling workers to focus on higher value add activities. Conducting a current-state shop floor team capability assessment will allow the organization to understand where training is required. A training road map or plan should be devised that includes interactive exercises on how to use the new technology. Outside of IoT adoption, it is important to upskill employees to perform tasks outside of their current skill sets.

Scale and sustain: Without upkeep, a digital transformation is sure to fail. Deploying IoT solutions on a large scale will impact all functions, including finance, human resources, sales and R&D. It is important to work with these areas of the business to ensure all functions are pursuing the digital journey with a similar mindset and integration points are considered.

Scaling best practices and sustaining a digital transformation requires resources to maintain system architecture, monitor application usability, document business impact and follow application life cycle management processes. Scaling and rapidly deploying IoT capabilities across manufacturing and supply chain operations will directly impact the return on investment (ROI) for the CoE and IoT program.

Taking the first step toward the giant leap

The time is now for companies to make a move or risk spending years struggling to catch up later. To best understand the opportunities inherent in IoT adoption, companies should begin to assess which areas of their supply chain are best suited for the technology. A clear plan that ties into the company's overall strategy and creates buy-in from stakeholders can provide that first step.

Success will require a lot of experimentation. Setting reasonable expectations at the start, promoting frequent conversations between developers and users and providing competent training will facilitate the trust needed to achieve the vision of an intelligent, networked future supply chain. If all done correctly, IoT can help the supply chain adjust to shifts in industry trends and navigate unforeseen disruptive forces like COVID-19.

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Carmine Stropoli
Life Science Technologist, CRB

Are you ready for robotics?

A user-friendly guide to successful implementation

Even if there's no immediate need to add robotics to your operations, there likely will be soon. Developing a strategy to implement robotics and automation will allow you to introduce the technology smoothly and in a measured way.

The pharma industry is venturing further into new and improved methods of operating, such as planning for lean and linear workflows, employing flexible filling lines capable of processing multiple formats, continuous manufacturing, and increasing the use of highly potent compounds. Consequently, the need to maximize operational efficiency combined with ensuring worker safety is creating an ever-increasing demand for automation and robotics.

The applications in pharma manufacturing are vast, including aseptic roller bottle processing, multi-format aseptic filling, aseptic cytotoxic compounding, packaging, warehousing and distribution. These applications all have similar requirements for which robotics can offer an improvement over manual fulfillment.

There are four key elements for a successful implementation of this technology:

Recognize robotic and automation opportunities: In general, consider such things as redundant operations or high batch sizes, or areas demanding uniform, predictable presentation. Consider whether the technology can offer operator and product protection, and if it can improve operating and arrangement efficiency.

A particularly important measure of the applicability of robotics in your operation is how uniform your product output may be. The same is true for lot sizes. If you produce in high volumes, robotics makes more economic sense than if you make many different products in smaller quantities and lot sizes.

Prepare a game plan: The opportunity you've identified for introducing robotics into your operation will give you a good foundation from which to generate a User Requirement Specification (URS) in which you initiate a dialog with vendors and involve them in preparing responses to your inquiry.

Typical robotic system URS criteria will include process description, block flow diagrams and operating rates. You should be thorough in detailing how vendor product specifications are to be presented, as well as requesting any supportive sketches for implementation.

In pharma, HVAC considerations will always be essential. Be certain to obtain HVAC classification, with specifications for product and airflow protection.

You may find that the URS may be an iterative process as you continue to refine requirements based on further considerations. This part of the process can take six weeks or longer, depending on the scope of your specifications and the number of vendors participating.

Consider proof of concept studies: Rather than committing to an entire new installation from the start, it usually makes more sense to introduce robotic systems in smaller studies to ascertain the viability of the technology.

It's during the proof of concept phase that you may make important realizations — such as whether the payloads you're handling may be too heavy to reach the speeds at which you've specified systems to operate. Such realizations should lead to further refinement of the URS, or a modification of your approach to robotics overall, and can give you greater insight into the applicability of robotics in your operations.

Develop/manage design, trials, fabrication, testing and implementation: When conducting testing, it's best to break the process into sections. There's testing at the site of work (vendor factory), but there is also testing to be done once the system is installed. This requires a considerable review of qualifications. Has the system been installed properly? Does it perform its functions properly? Does the entire system as a whole operate properly?

You will need to group testing into different segments that follow each other logically. Take care to minimize or eliminate redundancies; testing done by the vendor may possibly be used as qualification testing on-site, which could reduce the total time required for this phase of strategy.

This portion of the process, because it is so application-dependent, can to take anywhere from six or eight months or up to two years.

There's little doubt that robotics will be an integral part of the pharma manufacturing process in the future. The only questions are: How soon will your operation implement the technology and how difficult will the transition be?

product focus

Meagan Parrish
Senior Editor

Continually improving

Pharma makes strides to optimize continuous processing

The benefits of continuous processing are numerous. Switching from batch manufacturing can reduce costs and increase efficiency throughout operations. Continuous processing can also address several issues that have become more prominent during the coronavirus pandemic. Yet, pharma has yet to fully jump on the continuous bandwagon.

"Continuous processing is one approach to cut processing costs common in many industries, but — due to regulatory concerns — pharma has been a relatively slow adopter," explains Florian Walter, product manager at Watson-Marlow Fluid Technology Group.

In addition to regulatory hurdles, manufacturers looking to transition to continuous face a number of other operational challenges. But pharma vendors are innovating solutions that can help manufacturers leverage the benefits of going continuous.

Improving safety

Before the coronavirus pandemic, David Sieglitz, president of Readco Kurimoto, says there was a lot of interest in switching from batch to continuous, mostly for improved product quality. Now, given the increased concerns with safety, that interest has grown.

"We're experiencing more interest in boosting production rates to meet increased demand," Sieglitz says.

The Readco continuous processors are available in nine standard paddle diameter sizes in custom configurations.

"At the same time, manufacturers are struggling with how to safely manage and support staff in the workplace. The ability to run 24/7 unattended has become much more valuable."

Readco's line of continuous mixing processors were developed to solve the quality and consistency challenges with batch and eliminate several processing steps to create a faster cycle time while yielding a high-quality, homogeneous product. The processors feature twin shaft, co-rotating screws set within a closed barrel to promote the contact among wet and dry materials needed to ensure the end product at discharge meets desired specifications for moisture, texture, color, uniformity, and other criteria.

"Additionally, the continuous processors can be controlled and monitored remotely online from a phone or tablet anywhere in the world," Sieglitz says. "The continuous processor limits human interaction and errors while keeping operators safe and healthy."

Confronting contamination

"The pharmaceutical industry is facing challenges to cut costs and produce medicines more efficiently, as the pressure of aging populations

Watson-Marlow's Certa Plus pumps offer lower shear, lower power consumption, full traceability and ultimate cleanability.

on health care systems is transferred onto pharma," Walter says.

Despite the benefits of continuous processing, Walter points out that companies have to be careful that quality is not sacrificed when transitioning from batch operations.

"Concerns lie in the ability to maintain product consistency and quality without risking contamination," Walter says. "It's therefore important for equipment providers to ensure sterility and product quality is maintained throughout the extended production cycles of continuous processing."

To that end, Watson-Marlow recently launched the Certa Plus series of sinusoidal pumps that Walter says provide sustainable, high quality, versatile fluid management. According to Walter, the Certa Plus line is capable of transferring and handling a wide range of challenging products — from syrups and sugar solutions to lozenge products.

"These pumps offer lower shear to protect the quality of high value medicinal products, lower power consumption to further reduce costs, full traceability for regulatory satisfaction and clean-in-place capabilities to ensure sterility and minimize cleaning time in continuous processes," Walter says.

Christian Ott, manager of R&D Biotech and Life Sciences at Schott, also cautions that with some biopharma processes, this risk of contamination with continuous processing can increase.

"As a direct consequence of continuous processing, the longer operating life of the cultivation compared to traditional manufacturing increases the risk of potential contamination," Ott says. "Further, when different operation units in upstream and downstream processing are not working at the same pace, buffers in between are needed."

To that end, Schott developed non-invasive process analytical technology (PAT) components, called ViewPort, that enable in-situ bioprocess monitoring without compromising the sterile boundary.

One key benefit of the ViewPort customizable components is that they enable the control of key process parameters — such as saccharides, peptides and cell growth — in real time, which can be measured through tightly-sealed optical windows. Ott says that not having to open the bioreactors for such measurements results in a significantly reduced risk of contamination.

Schott's ViewPort components further enable advanced process control for an optimized yield performance.

"Real-time monitoring means that the processing times can be adapted to bring the operation units into an equilibrium," Ott says.

Increasing independence

Digital technologies can also play a critical role in moving to continuous.

"Modernization of manufacturing, including continuous, can be enabled by technologies such as AI and machine learning," says Rajiv Anand, the CEO of Quartic.ai.

Earlier this year, Quartic.ai and Bright Path Labs partnered to develop an AI-powered continuous manufacturing platform for APIs and other small molecule drugs. According to the companies, the AI tool will combine Bright Path Labs' continuous flow Spinning Tube-in-Tube bioreactor with Quartic.ai's smart manufacturing technology, which will speed the design, validation and approval of molecules.

The companies say that the new solution will not only improve continuous processing, it will also make API production more attractive to American manufacturers. If more API production is moved to the U.S., it will decrease our reliance on imports.

"This new AI-powered joint solution will help strengthen America's drug manufacturing independence and ensure a critical supply of medicines to patients," Larry Taber, chief technical officer of Bright Path Labs, says.

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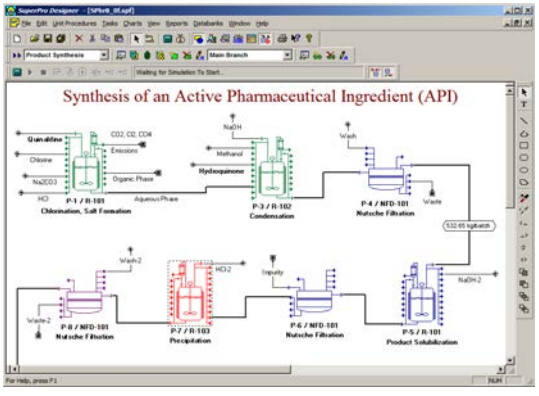
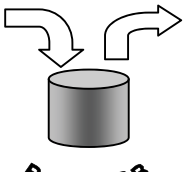


Use SuperPro Designer to model, evaluate, and optimize batch and continuous processes



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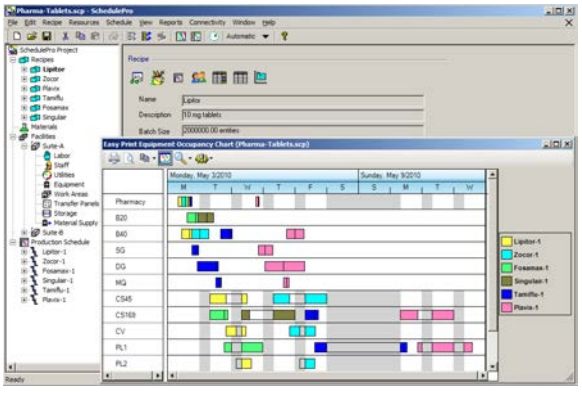

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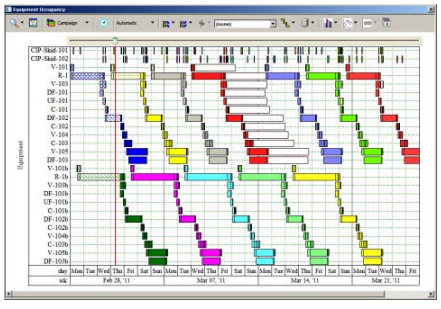
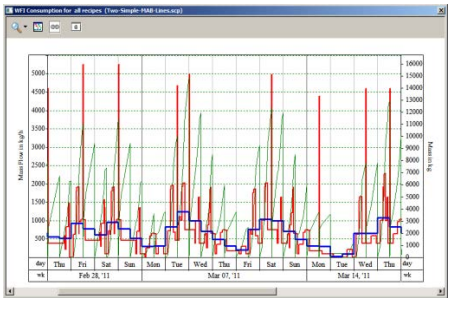
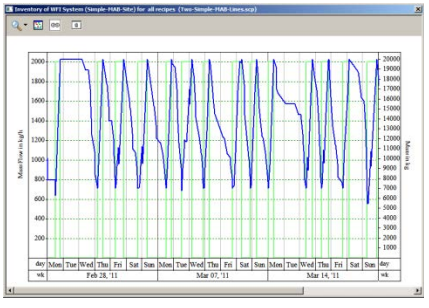


Easy production tracking, conflict resolution and rescheduling



Tracking demand for resources (e.g., labor, materials, utilities, etc.)



Managing inventories for input, intermediate, and output materials

SuperPro Designer is a comprehensive process simulator that facilitates modeling, cost analysis, debottlenecking, cycle time reduction, and environmental impact assessment of integrated biochemical, bio-fuel, fine chemical, pharmaceutical (bulk & fine), food, consumer product, mineral processing, water purification, wastewater treatment, and related processes. Its development was initiated at the Massachusetts Institute of Technology (MIT). SuperPro is already in use at more than 500 companies and 900 universities around the globe (including 18 of the top 20 pharmaceutical companies and 9 of the top 10 biopharmaceutical companies).

SchedulePro is a versatile production planning, scheduling, and resource management tool. It generates feasible production schedules for multi-product facilities that do not violate constraints related to the limited availability of equipment, labor, utilities, and inventories of materials. It can be used in conjunction with SuperPro (by importing its recipes) or independently (by creating recipes directly in SchedulePro). Any industry that manufactures multiple products by sharing production lines and resources can benefit from the use of SchedulePro. Engineering companies use it as a modeling tool to size shared utilities, determine equipment requirements, reduce cycle times, and debottleneck facilities.

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jill kaletha
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Mossberg & Company
jkaletha@mossbergco.com
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PRODUCTION

rita fitzgerald
Production Manager
rfitzgerald@putman.net

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Jamaica P. Szeliga
Partner, Seyfarth Shaw LLP

A post-pandemic FDA

The agency's regulations, oversight, collaborations and funding could change

The U.S. FDA has taken unprecedented actions during the COVID-19 crisis to bolster medical supplies, rush testing to market, and help develop potential treatments. The actions have had both positive and negative consequences, which are just beginning to emerge.

On a big picture level, the FDA's response during COVID-19 will provide a guide for what to expect when the next public health emergency occurs in the U.S. But from a day-to-day perspective, the pandemic could lead to major changes as well, and impact how the FDA regulates and polices products; how it develops treatments for broad distribution and experimental use; how it interacts with the public, private companies, charities, and other entities; and how it conducts and drives research.

On a big picture level, the FDA's response during COVID-19 will provide a guide for what to expect when the next public health emergency occurs in the U.S.

A few themes have emerged from the responses to COVID-19 that could become institutionalized. The FDA is historically notorious for its caution — for the extended vetting, testing, and inspecting it performs on medical products to make sure they are both safe and effective before they are allowed on the market. During the crisis, however, the agency stepped back from its gatekeeping role, allowing some products to be commercialized without FDA review or with much less evidence than traditionally required. We foresee that trend continuing, reflecting a shift away from prevention and towards enforcement, with the agency encouraging new products and treatments to reach the public as soon as possible.

COVID-19 has also changed how the FDA handles the monitoring of products and devices once they are on the market. For several FDA-authorized COVID-19 medical devices, the unique identifier requirements of the agency are not enforced. When issues arise related to such COVID-19 devices, the FDA can only take broad action rather than pinpoint and solely remove the noncompliant product. In addition, some products no longer require the manufacturer or distributor to monitor for adverse effects. The FDA instead has relied on the public, watchdog groups, and competitors to flag products as harmful or, more often, not effective.

The collaborative efforts seen during COVID-19 are another element likely to remain post-crisis. The FDA has entered into partnerships with established companies to speed up testing, treatments and product supply. The FDA is also collaborating with other government agencies; for example, it is working with the National Cancer Institute to test and validate products released on the market without screening. The FDA is working closely with nonprofits and universities, particularly with respect to the development of new treatments.

We also foresee that the FDA will continue to develop standards for products, innovation, testing and treatment. While FDA does not require compliance with these standards, they have been streamlining the development process. For example, the agency has made simplified guides to help new companies produce authorized medical devices like hand sanitizer and face masks. The agency has employed these protocols as part of its efforts to accelerate the development process.

While it is likely the FDA will continue to reduce certain requirements for products to enter the market, bad actors and current adverse events will shape how the agency implements such changes in a post-pandemic world. For example, the FDA has greatly reduced the requirements for producing alcohol for alcohol-based hand sanitizer, as well as for the production of hand sanitizer itself. Following these changes, the agency has been made aware of a steep increase in calls to the National Poison Data System related to hand sanitizer.

These adverse events — due, at least in part, to a failure of producers to properly follow reduced guidelines issued by the FDA — highlight the importance of the FDA's oversight and will also shape how the agency exercises its authority in the future.

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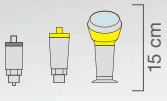

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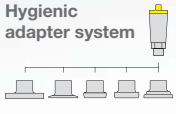

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