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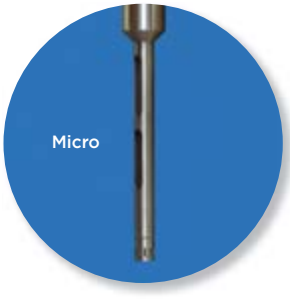

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Meagan Parrish
Senior Editor

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page 8

FEATURES

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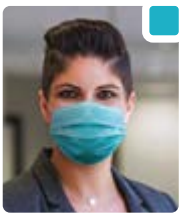
The fittest model

Is it time for pharma to evolve its drug development ways?



The species has been extinct for over 300 years, but the dodo bird continues to live on. Part anecdote about natural selection, part myth, part heartwarming tale about how humans snacked a species into extinction — the dodo bird has gotten a lot of press.

But the part that doesn't get enough attention is how the dodo bird was actually pretty adept at evolving. Facing no known predators on the tropical island of Mauritius, the birds grew larger than their pigeon relatives. They began nesting on the lush forest ground and gradually became flightless. Their beaks adapted to available food sources and became big and curved. They developed robust legs to support their weight and help them maneuver through the brush.

In short, dodos had evolved to be quite well-suited to the small island's ecosystem. All was well in dodoland until ships of sailors with a hankering for bird-BBQ arrived, bringing with them rats, pigs and other predators. As an added extinction whammy, humans turned the island into an agricultural plantation, destroying the birds' habitat and leaving them vulnerable.

And just like that, the dodos' once-helpful survival adaptations weren't working in their favor.

While on the topic of things that aren't really working, let's talk about pharma's drug development models. The industry itself acknowledges that there are flaws in its methods — specifically, the use of animal models in preclinical testing. It's commonly understood that biological differences between animals and humans make animal testing an inefficient way of modeling drug effects.

But acknowledging inefficiencies doesn't mean drug discovery and development hasn't evolved. Research has come a long way since ancient Greeks were learning about human anatomy by performing vivisections on live animals. The passing of the 1938 Food, Drug, and Cosmetic Act marked the start of mandated safety testing of drugs on animals and since then, pharma has continuously evolved its methods.

For example, with the advent of genetically engineered models in the latter part of the 20th century, mice and other species were modified to better reflect the specific disease pathways that were being studied. When combined with later advances in genome sequencing, animal models became even more efficient and targeted.

And yet, even with technological and scientific advancements, close to 90% of drugs still fail in human trials despite showing positive responses in animal trials. Most of these drugs flop for reasons that were not detected in animals.

Has the industry stagnated in terms of evolving its drug development models? Not quite. Emerging technologies including computational modeling, organ-on-a-chip and advanced cell culture assays offer alternatives to animal testing.

Of course, when it comes to these emerging technologies, there are still limitations and barriers to adoption. And while it is unlikely that alternative models will ever entirely replace animals in pharma, many estimate that technology is five to 10 years away from being developed enough to replace "most" animal models.

I'd argue any day that drug discovery and development are among the most crucial scientific activities when it comes to human health. As such, failure to improve the industry's methods is a risk to the future well-being of humanity. And while evolution by definition involves gradual developments, you never know when a party boat of sailors will pull up and force your hand — and in that scenario, it's good to have a better plan because without it, you risk extinction.

FDA decisions to watch

The U.S. regulator will have to make the call on a handful of highly anticipated treatments in upcoming months

Oxford-AstraZeneca's COVID-19 vaccine

After missing its April target for filing for emergency use authorization with the U.S. FDA, AstraZeneca says it is still expecting to submit its COVID-19 vaccine — developed jointly with University of Oxford — to the agency in mid-May.

Overseas, the vaccine, known as Vaxzevria, has been stalled by safety concerns over rare blood clots, and the drugmaker is facing a pending EU lawsuit over supply commitments. The vaccine's reputation also took a hit in the U.S. in late March when the National Institute of Allergy and Infectious Diseases raised concerns about the data shared from AstraZeneca's interim analysis of a phase 3 trial. According to NIAID, the data and safety monitoring board auditing the trial said the results "provided an incomplete view of the efficacy data." AstraZeneca later issued updated phase 3 trial data, lowering the efficacy from 79 percent to 76 percent.

While an FDA nod could help boost the damaged reputation of the shot overseas — especially in lower income countries where it is sorely needed — with three FDA-authorized vaccines already available in the U.S., a fourth isn't critically needed domestically. The Biden administration has said that if the vaccine gets the green light from the FDA, the U.S. will share up to 60 million doses with other countries.

Biogen's controversial Alzheimer's treatment

After years of speculation, anticipation and heated debate, the FDA is set to finally render a verdict on Biogen's Alzheimer's drug, aducanumab, this June.

In March 2019, Biogen pulled the plug on its phase 3 aducanumab studies after a futility analysis concluded that the treatment was unlikely to provide benefit. A few months later, Biogen then pulled a surprise about-face, saying that its analysis was wrong, and that aducanumab was moderately effective. The company then filed for approval.

In November 2020, an FDA advisory committee issued a resounding "No" vote against the drug's approval. The agency then pushed back its decision deadline from March 2021 to June, giving itself more time to review the data. The implications for the FDA's decision couldn't be bigger. Because no other disease-modifying drug for Alzheimer's has ever been approved, some analysts have speculated that aducanumab could become the best-selling drug of all time. And Biogen reported on an earnings call in April that it is preparing for an immediate launch of aducanumab if is given the go-ahead.

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The editors of *Pharma Manufacturing* will host several editorial-driven webinars on pressing industry topics throughout the year. The webinars will feature brief presentations from industry experts and leaders, focused on topics that matter most to readers.

These live presentations will be done in an interactive format where the audience can ask questions of the presenters. The discussions will be recorded and made available on-demand following the event.

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The push to reshore — Reimagining domestic drug production
June 23, 2021, 2:00 ET

The U.S. essential medicines supply chain is complex, dependent on foreign suppliers and in many cases, broken.

Join editors of *Pharma Manufacturing* magazine as we sit down with Phlow Corp. — the company now synonymous with the reshoring of drugs — to discuss their vision for reimagining the domestic production of key starting materials, active pharmaceutical ingredients and finished drug products. Expert speakers will discuss how continuous flow technology and green chemistry will help the company reduce costs and waste, improve quality and yield, and offer a more environmentally friendly alternative to batch manufacturing.

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Setting up a pharma cleanroom
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Visit pharmamanufacturing.com to register.

Novavax's COVID-19 vaccine

In the swirl of vaccines being approved and rolled out around the world, it's almost easy to forget that Novavax has also been plodding along developing its candidate with the backing of the U.S. government. After several setbacks related to manufacturing scale-up issues, the company launched its late stage trials months after its rivals.

Novavax has yet to report its phase 3 U.S. trial data, so it remains to be seen if the FDA will requires the inclusion of that data or if the UK trial data will suffice. Despite this, the company's CEO said in March that the drugmaker is finally hoping to get clearance for its vaccine from the FDA in May — which means it could beat the AstraZeneca vaccine to market in the U.S.

So far, Novavax has never brought a product to market, but it is on the hook to supply the U.S. with 100 million doses of its candidate. And given the reputational and supply challenges facing the J&J and AstraZeneca vaccines, the Novavax shot could be in demand domestically as well as abroad. In January, the company reported that its candidate was almost as effective as the approved mRNA vaccines at preventing COVID-19 complications.

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— Jay Bernsley

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The **next phase** of drug creation

Why animal models are on the brink of extinction

The team at Pfizer was deep into preclinical research of a new drug when something strange began to happen that soon became the talk of the lab. The novel molecule in development had passed rodent testing and was now being trialed in beagles. At first, the dogs seemed to tolerate the drug. Then, while sitting in their cages, their jaws suddenly started to click together at random intervals.

Called "canine jaw snapping," the unexplained side effect spelled doom for the treatment. The development team couldn't figure out why it was happening and thus, wouldn't have a sufficient explanation for the U.S. Food and Drug Administration — the gatekeepers for further trials. Ultimately, the molecule was scrapped.

"In truth, this might have been a good compound. It was a franchise I had hoped to continue working on at Pfizer," explains David Gortler, a former FDA senior executive official who launched his career at Pfizer about 20 years ago as an investigational medicine research scientist. "But, this is what can go wrong when you use animal studies to predict drug safety and efficacy."

Animal testing has been an integral phase of preclinical trials for every major drug on the market today. The FDA in fact requires that drugs pass through various animal tests before moving into human trials. But as the Pfizer story illustrates, a lot can go wrong with this approach. Aside from the ethical concerns related to animal testing, biological differences can make it an inefficient way of modeling the effect of drugs in humans.

"It's a heart-wrenching and outdated technology," Gortler says. "And it's rarely — if ever — predictive in humans."

Meagan Parrish
Senior Editor

To put it another way: Common estimates show that close to 90 percent of drugs fail in human trials despite showing positive responses in animal tests.

However, the use of animal testing in pharma has persisted — partly because there is no widespread infrastructure for alternatives. But now, with a rise of disruptive technologies, a major shift is underway and new drug development tests are evolving to take their place.

According to analysis released by Research and Markets last year, the global market for animal testing was valued at close to $10.74 billion in 2019 and is expected to grow at a compound annual growth rate (CAGR) of 4.27 percent between now and 2025 — but that growth will slow to 2.46 percent between 2025-2035.

And although the global market for animal testing alternatives was valued at just $1.11 billion in 2019, it is expected to swell by 10.4 percent over the next four years, with a CAGR of nearly 12 percent in the U.S. alone.

Within the field of animal testing alternatives in pharma is a swath of emerging technologies including computational modeling, organ-on-a-chip and advanced cell culture assays. And in addition to adding cost-savings and efficiency to early drug development, these technologies could shake up manufacturing processes in the coming years as well.

Have we reached a point where pharma can finally put an end to animal testing?

The dark side of development

Animals have long been behind the scenes of major breakthroughs in science.

In 1957, a dog named Laika helped pave the way to human space travel after becoming the first living creature to orbit the earth in a Soviet rocket called Sputnik 2.* And in 1996, a sheep named Dolly advanced our understanding of genetics and stem cell biology by becoming the first mammal cloned from another adult sheep's cell.

The use of animals in medical research dates back to the ancient Greeks, who pioneered animal dissections for anatomical studies. And in pharma, the roots of documented animal testing traces back to the late 19th century when the practice helped pave the way to the creation of critical medicines such as vaccines, anesthetics and antibiotics.

But animal testing didn't become mandatory until the early 20th century after a series of tragic drug and cosmetic launches. In 1937, a U.S. company released a new cough syrup called Elixir Sulfanilamide, which was dissolved with diethylene glycol — a human toxin. The product, which was not tested in animals before being commercialized, killed over 100 people.

A year later, Congress passed the Food, Drug, and Cosmetic Act, which sought to strengthen the FDA's grip on the safety of many consumer products and mandated animal testing in new drugs.

Now, new medicines that survive lab testing must then graduate to a series of preclinical trials first focused on safety and dosing in rodents and small animals, then on safety and efficacy in larger mammals, such as primates.

But as the use of animals has grown throughout science, so has the backlash from animal rights activists. Today, animal testing has been phased out of most industries — yet, pharma is one of the last holdouts of required animal modeling. And although animal modeling has long been defended for its role in ushering safe new drugs onto the market, it's also a moral quandary of drug development that the industry would prefer to avoid.

During our interview, Mike Clements, vice president of marketing at Axion Biosystems, a company that develops microelectrode array (MEA)

Speaking of Research estimates that 10-25 million rodents are used each year in medical research at U.S. labs.

* Although the Soviets originally claimed that Laika orbited the Earth alive for several days, sensors showed that an extreme temperature rise inside her capsule likely killed her after a few orbits around Earth.

The global organ-on-a-chip market was valued at **$25 million** in 2020 and is expected to grow at a rate of about 30% each year to **$115 million** by 2026.

— Mordor Intelligence

assay systems, even side-stepped saying the words "animal testing" by referring to it as "traditional modeling" instead.

"I don't want to be critical. I used animal research as a PhD student," he admitted. "I think it's something that is unfortunately necessary, but people don't want to do it."

Going forward, the focus has shifted onto how drug developers can use a more reliable model — the human body.

Chipping away at animal testing

In a 2019 TEDx Talk entitled "Why our grandchildren won't know animal testing," Manfredi San Germano, a PhD candidate at Imperial College in London, showed the audience the tiny technology making major changes in drug development.

Holding up a chip about the size of a AA battery, San Germano said, "Biochips like these…may seem like pieces of plastic to you…[but] they actually contain entire communities of human cells living together, talking to each other, moving, changing shape, growing…and we can induce dynamic environments."

Packed with tubes less than a millimeter in diameter that are lined with human cells, organ-on-a-chip (OOC) technologies are able to model how organs function — a lung breathing in and out, or a heart contracting and relaxing — and then show the impact of a new variable, such as a compound.

Research that led to OOC started in the '90s, and the first successful model was presented in 2010 when Harvard's Wyss Institute produced a lung model of the technology. Many have been holding up OOC models as a potential savior from animal testing ever since.

Since then, market researchers have estimated that about 60 organ-on-a-chip companies have sprung up around the world — many focused on modeling single organs. TARA Biosystems, for example, has zeroed in on the heart, where Misti Ushio, the company's CEO, says safety flags in new molecules are most likely to be raised.

"One of the main reasons drugs fail is because of cardiac safety," she says.

After developing its heart-on-a-chip model, the company commercialized its tech and now performs safety and efficacy screening tests on molecules in-house for its clients. Along the way, TARA has formed partnerships with about 30 different companies in drug discovery, and has published scientific papers in collaboration with GlaxoSmithKline and Amgen.

Although companies are not currently able to completely replace animals with TARA's heart-on-a-chip tests, Ushio says the technology is "animal sparing." It also boasts a range of other benefits, including its ability to generate disease models of heart disease and pump out large quantities of human relevant data on a continuous basis.

"Organ-on-a-chip is not just one workflow point in time," Ushio says. "You can use it along an entire drug discovery and development continuum."

OOC technologies like TARA's can also be customized to model disease biology or different organ functions, offering users the ability to discover new medicines for heart disease, which remains the No. 1 cause of death worldwide.

"We're looking at the effect of compounds on safety and efficacy by measuring a variety of functional parameters that model the diverse functions of the heart," Ushio says.

Like others in the OOC game, an important part of TARA's work with pharma companies involves validating that their tech can produce data as reliable (or better) as data from animal models. For example, Ushio says that TARA has been able to

show that, if used instead of animal models, their model would have predicted safety concerns that would not have been apparent until human clinical trials. Having this information would have mitigated safety risks and saved pharma companies on development costs.

"We have seen drugs exhibit safety issues in clinical trials — an outcome our tech would have predicted," Ushio explains.

Ushio also notes that in the growing landscape of OOC technologies, there are some single-organ systems with minimal biology that can run more compounds at a lower cost per compound. TARA, however, has strived to engineer heart models with the most integrated human biology to offer more "richness" in content, increasing the likelihood of predicting clinical results.

"I think that's something to keep in mind," Ushio says of pharma companies looking to implement OOC options. "It is about matching the right technology to the challenge at hand, balancing throughput, costs and translational relevance."

For companies looking for even more integrated modeling options, multi-organ human-on-a-chip technologies have also emerged to offer assays that measure the impact of compounds on various systems in the body.

Dubbing itself "The Original Human-on-a-Chip Company," Florida-based Hesperos has sought to create ever-more complex models that can mimic the functions of two to more than five organs.

"Our thinking is that while a drug could show efficacy in a single-organ, isolated system, it is not going to predict side effects. So you could take that drug into clinical trials and it could fail due to off-target toxicity," Mike Shuler, CEO of Hesperos, says. "We want to offer a system that helps you make better decisions about which drugs will be both safe and effective in clinical trials."

Like TARA, Hesperos works like a contract research organization and runs its tests in-house on models that churn out continuous data on the effects of molecules on critical organs, such as the heart and lungs.

"We monitor the functional changes to each organ as treatment enters and metabolizes in the system," says Nate Post, director of business operations at Hesperos. "For example, we track the acute and chronic changes to key heart functions such as: beat frequency, contractile force, and conduction velocity. These types of changes to organ functions are indicators of a drug's toxicity — and we are tracking it in real time."

As the industry discovers more applications for OOC, Shuler says that the technology will be especially insightful for certain indications.

"There are diseases for which the current animal models are irrelevant or simply don't exist, such as rare diseases and the immune system," Shuler argues. "Chips will play a bigger role in that development."

So far, Shuler says that at least one company has submitted an approval application to the FDA using data from Hesperos. Although the company — Bioverativ, which was bought by Sanofi in 2018 — wasn't able to completely replace animal models in the development of its drug, it supplemented its testing with a Hesperos model that recreated a functional neuro-muscular junction, then damaged it and treated it with the new therapy.

These kinds of milestones in pharma and regulatory acceptance are going to be critical to wider adoption of the nascent OOC industry. Shuler argues that in many cases OOC offers more accurate data than animal trials, but acknowledges that the company is still "developing market trust in the technology" in pharma.

And although OOC tests can still take months to develop and complete, both TARA and Hesperos say that it is a cheaper option — especially if it helps pharma companies avoid ill-fated development investments.

"If you can have a higher success rate and it is now a 1 in 4 chance of success, versus 1 in 10 — that's potentially a multibillion-dollar improvement," Shuler says.

An example of organ-on-a-chip

PHOTO: WYSS INSTITUTE FOR BIOLOGICALLY INSPIRED ENGINEERING, HARVARD UNIVERSITY

Neither Hesperos nor TARA publicly disclose sales figures, but both said that sales have been at least doubling year over year — a clear indication that the shift to these new models is truly underway.

"It's the beginning of the next generation of what drug development and discovery is going to look like," Post says.

> **Animal testing in preclinical work is limiting the types of drugs that can be developed.**
>
> —David Harel

Advancing cell analysis

Multielectrode array (MEA) assays, which measure electrical signals from live cells, have been around for decades. But in recent years, MEA system companies such as Axion Biosystems have been innovating testing devices that allow companies to perform increasingly complex cell cultures for disease modeling and drug screening.

Rather than traditional systems, which use lights or dyes, Clements says that Axion embeds "microscopic electrodes that act like antennas that can sense changes in the cell." Axion's multiwell models are also high throughput systems that can track the real-time effects of more cell samples in less time. Importantly, Clements says that Axion's systems are also easier to learn and use.

"What makes us unique is that we have created a product where the end-user doesn't need to be an expert in electrophysiology," he explains.

Clements says that these kinds of assays, which can use human-induced pluripotent stem cells (iPSCs) with disease mutations to measure the impact of new molecules, are going to be fundamental models in the efforts to replace animal tests.

"[Our tests] have weeded out drugs that didn't need to go into animal testing," he says. "So if we can improve the success of the compounds that go into full animal models, that will ultimately mean fewer animals used in research."

After Axion commercialized its first multiwell system in 2011, most of its early adopters were in safety and pharmacology at agencies such as the FDA. Now, the company is seeing more use among academic labs and pharma companies. And critically for drug development, the design of the system gives users the flexibility to ask targeted questions.

"That's very important because a lot of pharmacology isn't just interested in seeing if a compound is going to destroy the brain tissue itself — they want to know if it's going to induce a seizure," Clements says. "Our users are coming up with ways to make our ever-more intricate systems answer more complex questions."

Upgraded humans

It was really just a matter of time before some company figured out how to conduct a clinical trial on a computer with just the click of a button. As it turns out, that company was Israel-based CytoReason.

Using the massive deluge of clinical trial data in the public domain, CytoReason has become a pioneer in the field of machine learning platforms that can simulate human systems on a cellular level with a computational model. Tissue by tissue, disease by disease, the company creates AI-driven discovery and development models that churn out biological data on illnesses in a matter of minutes.

According to David Harel, the company's co-founder and CEO, the platform helps overcome one of the most limiting factors of animal tests.

"Animal testing in preclinical work is limiting the types of drugs that can be developed," he says. "Our models are built on human data that can simulate clinical trials in significant and more accurate ways, and that opens up the ability to use and manufacture molecules that were considered too risky because they could not be validated in animals."

Harel says that typically, CytoReason's computational models, which have been implemented by several Big Pharma companies, are used in early discovery to better understand disease biology for targeted drug development.

Although the system is focused on predicting efficacy outcomes, Harel says it can provide some safety data. So far, the company's core platform includes models for over 180 diseases and it can be customized for specific use cases, accounting for patient stratification, indication selections or genetic variables.

The cost to implement CytoReason's platform varies widely and depends on factors such as how much of the body the company wants to model. But Harel says speed is a prime selling point.

"Every animal trial could cost $80-100,00 and take 18 months," he says. "If you do it with human data, once you have the computational disease model set up, the marginal cost will be zero and it'll take you 20 minutes."

While there are some limitations — because the system is based on available data from previous clinical trials, it works best when measuring outcomes observed in live patients — ultimately, Harel

says that platforms like CytoReason's are playing an increasingly important role in reshaping what the landscape of early discovery and development will look like in the future.

"All of these assays are important," Harel says. "They allow you to look at [drug development] from every angle and then you can aggregate all of it to get one full picture."

Manufacturing implications

Because the industry for many of the emerging drug development technologies is so new, their impact on manufacturing has yet to be realized. But companies in the space are envisioning a number of ways their tests could one day be used in downstream processes.

Precision medicine

One common prediction about the application of OOC technologies in manufacturing is the impact they could have on developing drugs for subpopulations.

"One of the main reasons drugs fail in clinical trials is because they work fine for 95 percent of the population but for 5 percent, they don't," Shuler says. "But you could build these chips to represent different parts of the population to test."

OOC could also aid in creating personalized drugs — a growing area of pharma investment.

"Patients could supply you with their cells and you could build a model off of them," Shuler says, noting that having a piece of liver tissue, for example, could show how fast an individual will metabolize a drug — something that varies widely across the population and has a direct effect on efficacy for that patient.

According to Clements, MEA assays could also be used to inform development for drugs based on genetic variables.

"For example, we've seen research on pediatric epilepsy…which is not caused by one gene," Clements explains. "So the researcher was looking at cells on a dish from different patients to study phenotypes and predict which compound could act as a potential therapeutic."

Shuler admits, however, that because of the time it would currently take to build personalized OOC models, its application would be limited to long-term care scenarios.

"The idea of personalized medicine is great but it is probably going to take a while to be effective because of the time between taking the cells and putting them into the device," he explains. "So it wouldn't work well for a drug you need in a few days."

Supply chain and scale-up considerations

According to Harel, companies are leveraging CytoReason's platform during critical decision-making points in phase 2 trials that could have ramifications for commercialization.

"A company may try a drug for certain types of cancer, for example, but then think about extending the label to other indications," Harel says. "Those decisions change the commercial dynamics."

In particular, Harel says that the platform helps companies make these decisions quickly so that they can assess supply chain considerations related to commercialization.

Shuler says that OOC testing could also have a major impact on product testing during scale-up when process changes could alter the drug.

"The product is defined by the process by which it's made," he argues. "In scale-up, there is always the danger that a product could become toxic because of side effects that were introduced along the way."

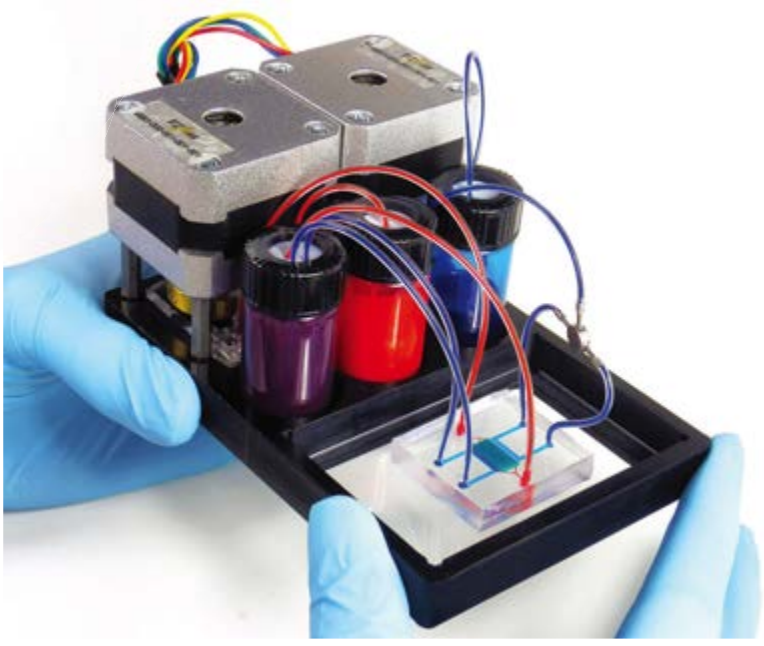

PHOTO: VANDERBILT UNIVERSITY

Blood-brain barrier on a chip
The blue dye shows where the brain cells would go, and the red dye shows the route for blood circulation.

By continually testing the product during scale-up, Shuler says that companies can ensure that the drug is still behaving the same way it did during clinical trials.

"I do see a way to combine these technologies with the manufacturing process to assess quality control and ensure that the product is still going to be effective and not cause toxicities," he says.

> "You could build these chips to represent different parts of the population to test.
>
> —Mike Shuler

Release criteria

In the burgeoning field of cell-based therapies, Clements says that cell testing could play a role in determining how well manufactured therapies might work.

"Companies are generating CAR-T cell therapies, for example, and they might want to test these cells to see if they've produced enough of them with the right viability…to make sure they are working before they're given to the patient," he explains.

Currently, Clements says that as far as he knows, regulators don't mandate this kind of release criteria. But as cell testing and manufacturing becomes more sophisticated, that could change.

"It makes sense that if you've made millions of cells in a bioreactor that you would want to know if you've made them with the properties you want," he says. "That is something the field is very interested in."

Waiting on regulators

While serving as a senior advisor to FDA Commissioner Stephen Hahn between 2019-2021, Gortler says he was spearheading an effort to pivot the agency towards the acceptance of non-animal models.

"Trump's whole thing was, 'Let's speed up drug development,'" Gortler explains. "And I thought, 'Let's do that and get rid of or reduce the torturing of animals.' It's a no-brainer."

With the White House's blessing, Gortler says he took the initiative to research alternative technologies, such as OOC, and was pushing the agency towards policies that would reward companies for using them. Then after the Biden administration took over in January, Gortler — a Trump appointee — was forced to resign, leaving his efforts to create incentives for non-animal models unfinished.

But there are signs the agency is opening its arms to alternatives. In October, the FDA signed a collaborative agreement with Emulate, a maker of OCC technologies, to test the safety, efficacy and mechanisms of drugs regulated by the agency on their models.

And in December, the FDA launched a pilot program called the Innovative Science and Technology Approaches for New Drugs (ISTAND), which lays out a three-step process for biotech companies to qualify new testing technologies.

Meanwhile, companies are continuing to submit data from new models alongside animal data to help validate them as equals.

"There is an enormous push to create and validate these models," Michael Graziano, chief scientific officer of TARA, says. "What it's going to take is drug companies bringing parallel data sets forward that show these technologies predict human outcomes as well or better than animal models. This is the path that will help replace one technology with another."

Are we there yet?

Although there is little debate that the process of drug discovery and development is undergoing a transformation that will make it look very different decades from now, there is still some disagreement over how much animals will factor into that future.

OOC technologies have been heralded by many as a replacement for animal models and to a certain extent, are already reducing that need. Yet, Shuler estimates that OOC technologies are still five to 10 years away from being developed enough to replace most animal models and being widely adopted by pharma.

"Animal models are going to be around for a little while," he says. "But today, nine out of 10 drugs are failing to translate from animals to humans. If we can improve that rate, as we expect using our models, we're better informing what's going to work at the end of the rainbow."

Will animals ever be completely eradicated from pharma drug testing? Unfortunately not, Shuler predicts.

"I think we get rid of 99.9 percent of animal testing," he says, "While this technology will eventually eliminate the need for animal testing in virtually every use case, there are certain complexities of a living being that won't fully translate to in vitro models."

For now, Ushio says that any reduction in animal tests is a step in the right direction.

"You don't have to go to animals to generate reliable data," Ushio says. "Having a human relevant model increases your probability of success. That's what matters at the end of the day."

Ron Ezsak
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Addressing the elephant in the supply chain

The pandemic era is a bad time — yet the perfect time — to talk about strengthening the pharma supply chain

How many years has the pharmaceutical industry been talking about supply chain fragility? Despite remarkable pharmacological and medical scientific advancements, the pharma supply chain's robustness has not advanced meaningfully.

But opportunities arise from crises. It has never been more apparent than it is in this pandemic era that there are ways pharma companies and the industry can strengthen long-discussed supply chain vulnerabilities.

Although the industry has enjoyed many triumphs throughout the COVID-19 pandemic, the supply chain's weaknesses have also been on full display. This is a challenging era for drug manufacturers to tackle supply challenges, and yet this work's importance can no longer be denied.

So what is meant by the desire for a "robust" pharmaceutical supply chain? For this discussion, a robust supply chain refers to manufacturers' ability to maintain target fill rates and service levels and reliably deliver therapeutics to their customers (the next link in a product's journey to patients) that are safe, efficacious, on-time and in the quantities demanded by the market.

Ongoing drug shortages

The formal tracking of drug shortages began in 2001. Over the last 20 years, the criticality of the drug shortage problem has ebbed and flowed, peaking in 2011 with 267 drugs in shortage. Despite lower numbers of drug shortages in recent years, unacceptably high shortage levels in key therapeutic areas, such as oncology, antivirals, antibiotics, pain relief, and numerous other areas, persist.

Drug shortages can and do occur for innovator drugs under patent protection; however, these shortages are less frequent than generic drug shortages. When innovator drug shortages do occur, they are typically caused by incidents such as natural disasters or other "black swan" events, severe and specific problems with raw material supply, or critical operational breaches within a manufacturing plant.

Generic drug shortages are more pervasive and occur for numerous less obvious reasons, including manufacturers' exits from specific markets due to low profit margins; quality problems among API, intermediate, and excipient suppliers; quality problems within manufacturers' operations; industry mergers; unforeseen disasters; and regulatory hurdles.

For years, the pharma industry and individual manufacturers alike have professed the need to improve the supply chain, and yet little transformative progress has been made. If the pandemic has not taught all of us the critical nature of pharma supply chain transformation, nothing will. But in order to get there, there are steps individual companies can take as well as considerations the industry as a whole must make together.

It's not all COVID's fault

The good news is that, despite shutdowns around the world, strained geopolitical relationships, and transportation challenges during the early months of the pandemic, some portions of the pharma supply chain held up better than many feared at the onset of the pandemic.

Although retrospective reviews will be required to assess the era accurately, the supply of starting materials, APIs, intermediates, and excipients for small molecule drugs seems to have held up reasonably well.

According to the American Society of Health-System Pharmacists (ASHP), shortages spiked in the first quarter of 2020[1] as the gravity of the pandemic's risk solidified and hospitals across the country stocked up in preparation. Drugs related to ventilating patients — analgesics, sedatives and paralytics — increased in demand sharply. Unquestionably, there were localized supply strains as the pandemic settled into different areas of the country at different times. There are lessons to be learned here, given that there were plenty of situations in which there was ample or even excessive product in one market, but exceptionally low supply levels in other markets.

Ultimately, the supply chain for the manufacture of small molecule drugs must improve; the drug shortage levels in any given year are much too high. These shortages risk patient health and cost the health care system hundreds of millions of dollars annually; yet the sector weathered the pandemic better than anticipated.

But as the COVID-19 pandemic surpasses the official one-year mark, a natural impulse might be to dismiss the supply chain pressures within the industry as solely COVID-related — or reactions to a once-in-a-lifetime event that must be endured.

However, while the small molecule drug sector seems to have fared well during the pandemic, quite a different scenario developed within the biopharma sector and, to a reasonable degree, small molecule aseptic products. The supply chain for cell culture media, buffers, single-use bioprocessing system components, aseptic fill-finish and related areas was pressured before the pandemic. Then, as Operation Warp Speed gained momentum and commercial vaccine production accelerated, points within the supply chain for many manufacturers became quite problematic.

While urgently working to manufacture vaccines for the largest vaccination effort the world has ever seen, the biopharma industry is struggling to manufacture a multitude of required therapeutics within the context of an already strained supply chain. Operation Warp Speed may prove to be quite successful, but what about all the biologics for other life-threatening conditions?

How pharma can strengthen supply chains

De-risk the forecasts used to run manufacturing operations — Forecasts are always wrong

Today, nearly all pharma manufacturers run their organization's operations on materials requirement planning–based systems. Enterprise resource planning systems use materials requirement planning (MRP) to link all the other financial and operational aspects of the company's supply chain. The problem is that MRP-based systems require order volumes to function. Given that manufacturers lack concrete order knowledge, forecasts are used as the fuel to drive operations. Unfortunately, forecasts are always wrong, and MRP consumes them as if they were correct.

Stop focusing on investments in forecast improvement

Many pharma manufacturing supply chain professionals believe that the next technology step-change or more robust data will deliver needed forecast accuracy. They think that artificial intelligence and machine learning coupled with richer data will do the trick. Although these technologies are nice to have and are important, the most sophisticated assembly of forecasting technology and expertise in the world — the National Oceanic and Atmospheric Administration (NOAA) — tells a different story.

NOAA utilizes more than 100 years of historical data, supercomputers, AI, satellites — incredibly sophisticated technology tools and wildly talented analytical and scientific minds. Still, beyond 10 days, their forecasts are only 50 percent accurate.[2] If this is the best NOAA can do with all the resources at its disposal, how can a pharma manufacturer possibly run its operations effectively based on forecasts?

Forecasting certainly has its place — revenue, trend and longer-term operational forecasts, for example. But manufacturers will never be able to improve their supply chains by running day-to-day operations based on forecasts.

Embrace demand-driven material requirements planning

For organizations using MRP push-based planning (virtually all pharma manufacturers), there is no coherent tactical plan for running the supply chain. Planners know the forecast data driving replenishment is incorrect, and they intervene daily, but their systems put them in a chronically reactive posture. They manufacture more when they see they will run short and stop production until the stock sells down when there is an excess. The result is a perpetual state of imbalance, leading to holding way too much of some inventory in some markets while experiencing shortages in others.

Even worse, the lack of a stable plan hides real supply chain cost drivers, resulting in less-than-optimal decision-making. The only lever to reduce costs, especially for generic drugs, is the unit cost. Manufacturers pursue the reduction in unit costs, often outsourcing all or certain key aspects of production to low-cost global markets. As a result, pharma supply chains have become extremely global, longer and more rigid — and the problem is getting bigger, not smaller. Unit cost may have come down, but agility, competitive advantage and total cost have all affected it negatively. This is not even to mention the dire ramifications of disruptions at any point in the supply chain for any reason.

While the small molecule drug sector seems to have fared well during the pandemic, a different scenario developed in the biopharma sector.

Execute a demand-driven operational approach

Effective demand-driven material requirements planning (DDMRPII) execution requires the right technology tools — specifically, tools built on a market service strategy foundation accepting that operations must be linked to a pull-based supply chain methodology. In a properly designed system, variability in demand is both accepted and understood. Supply chain setup decisions are based on capacity and segmented market strategies, entirely rooted in the manufacturer's operational capabilities. It is quite simple: In a push-based approach, you are forced to match demand to your available supply, whereas in a pull-based approach, you match supply to your demand, which is fundamental for achieving target fill rates and service levels that ideally approach 100 percent.

DDMRPII approaches combine long-term strategic direction, market need and operational capacity. Marrying these factors with many tactical inputs such as product segmentation policies, material and plant capacity, resource planning, operational parameters, inventory buffer distribution and service-level policies generates a tactical plan tailored to accomplish defined business objectives.

Secure multiple sources of supply

Pharma manufacturers know that a lack of redundancy in the supply chain is problematic, but few have addressed the problem. Too often, pharma manufacturers continue to rely heavily on a limited number of suppliers — in many cases, a single source of supply.

Replenishment plans are driven by forecast, driving stocks up and resulting in continual re-work

Replenishment is driven by demand and inventory to buffer variability

Demand-driven planning resets the supply chain and addresses the root cause of planning failure by de-coupling the supply chain.

Although securing and validating multiple sources of materials and components supply is sometimes easier said than done, it must become a priority. Often, manufacturers will need to partner with global regulatory bodies to make this objective a reality. However, with a thorough understanding of both materials' and processes' critical quality attributes, manufacturers can determine and efficiently validate multiple supply sources in partnership with regulatory bodies.

Internally harmonize production

Even within their own operations, multi-plant companies often do not harmonize materials, equipment and processes. Take a biopharma manufacturer, for example. Suppose one facility is running low on single-use bioreactors. In that case, it often cannot tap excess supply at another facility within the company—many times, the same processes or similar processes are validated in different facilities, using different materials and processes. Even within the same company, facilities often cannot collaborate within their own network to manage supply. In many areas, a strong argument can be made for industry-wide harmonization; however, to start, biopharma organizations could implement consistent systems across their plants which would facilitate more efficient materials supply management within their organization.

Working together

Although individual companies can and must play significant roles to strengthen the pharma supply chain, there are areas where the industry as a whole, including equipment suppliers, international regulatory bodies and governments, must collaborate.

Materials of production harmonization

We can again use single-use bioprocessing systems as the example for this discussion, but there are many other materials of production in the industry with similar dynamics. In the case of single-use bioprocessing systems, various manufacturers' bags and components designed for the same purpose often cannot be used interchangeably because there are slight differences in port configurations and other characteristics.

Sometimes, differences within systems contribute to improved performance; other times, systems companies fabricate differences to lock in their customer base. It is easy to understand single-use suppliers' business strategies, but when biopharma manufacturers cannot tap other sources of supply, if individual manufacturers fall short, patients are ultimately put in an extremely vulnerable position. More consistency across the single-use market, and between systems companies in general, would enable pharma manufacturers to alter course if supply problems arise.

Regulatory harmonization

Heading into the pandemic, many pharma manufacturers had well-thought-out risk mitigation plans that included multiple sources of supply. However, in some cases, sources of supply that had been geographically distributed with considerable forethought were shut

down simultaneously. For instance, a primary supplier in India, coupled with a secondary supplier in Italy, might seem like a well-crafted plan. A "black swan" event that shuts down many markets at the same time cannot be predicted and explicitly planned for. But, during an emergency, regulatory harmonization would allow processes to be moved worldwide much more quickly.

Reconsider generic drug market constructs

Generic drugs are critically important for keeping health care system costs under control; however, all stakeholders (including patients) have an interest in making sure generic drug manufacturers can manufacture safe drugs profitably. Payer-originated downward pricing pressures can inspire innovation and greater efficiencies — to a point. But a system that causes manufacturers to exit the market and essentially encourages dependency on substandard materials and manufacturers must be reconsidered.

Effective public–private partnerships

The pandemic has reminded us of the critical roles both the government and industry have in contributing to patient health. While the precise contours of new approaches to public–private partnerships require ample discussion, the need for ongoing communication and revised approaches is apparent.

Getting to work

From a pharma industry supply chain perspective, the pandemic era has been stressful and has further revealed and exasperated known vulnerabilities. Many of the weaknesses discussed at industry conferences and in board rooms for years were on full display in a potentially catastrophic context. For the industry and the nation, the idea that the pharma supply chain has a realistic possibility of breaking, creating untold levels of devastation, moved from theory to a genuine possibility. Unfortunately, that possibility remains very real.

However, crisis breeds opportunity. Manufacturers might now be able to move away from their reliance on push-based MRP-driven operations and their costly and inefficient reliance on forecasts. Additional moves, including internal production harmonization efforts, could help considerably.

Work requiring cross-market collaboration and new public–private working relationships will take time but is equally important.

Despite these challenges, the great news is that many other industries have addressed and solved the challenges the pharma industry currently faces. Let us learn from successes in other markets and get to work.

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Karen Langhauser
Chief Content Director

Focus on: Sweden

Known for its R&D innovation, Sweden's pharma industry sets out to prove its manufacturing prowess to the world

Normally, a U.S president's "campaign rally for America" in a crowed Orlando airport hangar wouldn't make much of a blip on international radars. But about a month after Donald Trump took office in 2017, he delivered a speech in Florida that was oddly consequential to the country of Sweden.

As he was listing foreign countries recently plagued by terrorist attacks, the president's tone turned incredulous: "You look at what's happening last night in Sweden. Sweden! Who would believe this?"

As it turns out, no one in Sweden.

Responses to the now infamous "Last night in Sweden" speech ran the gamut from concern to outrage to social media mockery. While Trump later clarified that his remark was only a response to a Fox News segment he had watched "last night," and not commentary on a specific devasting event, the incident was not the first nor the last time Sweden would find itself battling misperceptions.

The birthplace of Volvo, IKEA, Skype and Spotify, Sweden seems to have a knack for growing forward-thinking companies. In fact, the capital city of Stockholm has been referred to as a "unicorn factory" — a nod to its ability to crank out start-up companies valued at more than $1 billion.

This entrepreneurial spirit entwined with scientific innovation extends to drug development as well, an area where Sweden has historically excelled — a point of pride that has been backed by long-standing government investments in R&D. A recent report from SwedenBio, the national industry organization for life sciences in Sweden, recorded close to 150 firms currently active in drug discovery, preclinical or clinical development — all in a country with a population the size of Los Angeles County.[1]

Having established a worldwide reputation for its groundbreaking research, the Swedish pharma industry's other strengths have flown somewhat under the radar, creating the impression that the industry lacks capability in other areas. Such is the case with advanced manufacturing in the pharma industry — so much so that many, including Helena Strigård, feel that it's a myth ripe for dispelling.

"Actually, the field of advanced manufacturing is where we have seen the largest growth in Swedish life sciences for many years now. So that seems to be a myth, that it would have been held back — [it's actually] quite the opposite," says Strigård, who serves as SwedenBio's director general.

Companies using the Testa Center have their own workspace and reserved access to a full range of the latest bioprocessing instrumentation.

Now, with industry investments accelerating and the government earmarking cash to support production, the Swedish pharma industry is looking to cast aside misperceptions and establish itself as an international hub for advanced manufacturing.

A competitive business environment

Much has been written, both positive and negative, about the Swedish economic model, specifically the famously high personal income tax burden placed on citizens. This has in many cases created misperceptions about the cost of doing business Sweden.

"First and foremost, we need to become better at promoting Sweden as a site for advanced life sciences manufacturing," says Strigård. "For instance, the overall investment climate for companies is competitive, taxes included, and highly educated labor is fairly cheap compared to other European countries."

The value of Sweden's medical and pharma exports in 2020 was $13.6 billion (SEK 115 billion).

Source: Lif Service AB

The corporate tax rate in Sweden was reduced to 20.6 percent at the beginning of 2021 — which is lower than that of their German (29.8 percent) and French (26.5 percent) neighbors to the south.[2] This competitive economic environment, combined with a stable political and social climate, has created an ideal place for industry. This has worked in Sweden's favor when wooing overseas investors in the manufacturing sector. According to Business Sweden, the country's trade and investment council, overseas companies employ 40 percent of all workers in the Swedish manufacturing industry, and just under 70 percent of workers within the chemicals and pharma sector.[2]

One of the country's biggest pharma success stories is a hybrid in its origin — Sweden is responsible for bringing the "Astra" to the "Zeneca." Back in the 1920s, Astra AB had established its status as a leading Swedish pharma company, later introducing two important product families onto the local market: penicillin and anesthetics. Facing the pressure of increasing drug development costs in the '90s, Astra began searching for international partners, and in 1999 the company merged with British multinational pharma company Zeneca, establishing AstraZeneca's corporate headquarters in the UK.

Today, AstraZeneca's Södertälje site (near Stockholm) is the company's largest and also one of the largest sites in the world. The site manufactures approximately 40 percent of AstraZeneca's total global production volume. This is an impressive feat considering the company has 26 manufacturing plants around the world in 16 different countries, underscoring the tremendous importance of the Södertälje site.

The pharma industry also benefits from Sweden's skilled talent pool. According to Invest Stockholm, the pharma industry has the highest proportion of employees with postgraduate education.[2]

Still, Sweden is not immune to the global labor crunch facing the biopharma industry, an issue that will become more prominent as the industry continues to experience growth. "The entire life sciences sector is growing rapidly, with 80 percent of the companies within drug development reporting that they will hire in the upcoming year," says Strigård.

This means competition for skilled workers will be steeper than ever. But the country's reputation — Stockholm in particular — as both a green and tech-savvy place to live and work continues to attract young talent from around the world. In 2019, the three largest universities in Stockholm formed a strategic partnership, known as the

Stockholm Trio, with the aim of fostering new international collaborations that will help attract more international students and recruit top researchers.

Government cooperation

One key driver for pharma companies, both foreign and domestic, that choose to plant roots in Sweden is a long-term commitment from the government to protect the industry and continue to create an environment that facilitates global competitiveness.

"In parallel with increasing industry investments in life sciences manufacturing, the government has mirrored this through various efforts — for instance, by creating an infrastructure for scale-up of manufacturing of biologics, the Testa Center in Uppsala, and looking into how to support scale-up further within ATMP," says Strigård.

The Testa Center's 27,000 square-foot bioprocess pilot-scale facility was established in 2018 by the Swedish government and Cytiva. Cytiva (previously GE Healthcare Life Sciences) has been operating in Sweden for more than 60 years, and its products and technologies contribute to the production of around 75-80 percent of all approved biological drugs in the world. With a focus on biologics manufacturing, and a recent expansion to include cell and gene therapy, Testa Center provides education and a modern testbed for projects.

The pharma industry employs approximately 11,000 people in Sweden.

Source: Lif Service AB

AstraZeneca's Södertälje site is one of the largest pharma manufacturing facilities in the world and is currently undergoing a significant expansion.

On the research side, government-backed Vinnova, known as Sweden's innovation agency, promotes and funds research projects in a range of industries. The agency, which operates under the Ministry of Enterprise and Innovation, funds numerous pharma-related projects in the country.

One such initiative is the Competence Centre for Advanced BioProduction by Continuous Processing (AdBioPro) which is co-funded by Vinnova and pharma industry partners. AdBioPro aims to encourage the development of competitive technology for bioproduction — focusing on continuous processing and emerging therapeutics such as recombinant viral vectors and cell therapies.

Another important Vinnova-funded project is the Centre for Advanced Medical Products (CAMP). CAMP has zeroed in on the science and technology required to translate ATMPs from lab to clinic, including development, GMP-production and logistics. Utilizing $5.7 million worth of government funding from 2018-2023, the collaboration takes advantage of a public-private partnership between government, universities, health care and the pharma industry to accelerate new breakthrough ATMP therapies to patients.

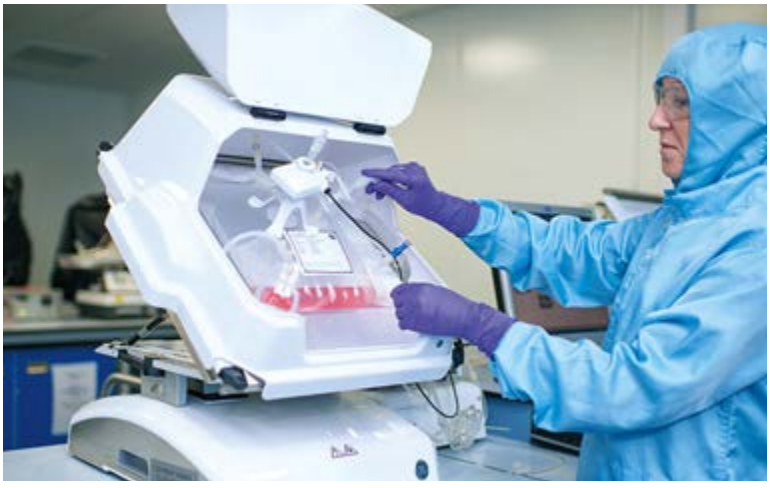
A hidden gem for ATMPs

There is no better target for a country looking to put itself on the map as a leader in drug manufacturing than advanced therapy medicinal products — the next frontier in pharma, offering new hope to patients with untreatable or incurable disease.

The foundation is certainly there, with 19 local and eight international pharma companies in Sweden active in the pre-clinical and clinical ATMP space — establishing Sweden as a leading country in Europe.[3]

"I would say that we already are an emerging hub within ATMP with companies such as Pfizer, Cobra Biologics, Sobi, AstraZeneca, Combigene, Valneva, Recipharm and a flourishing group of technology providers," says Strigård.

The pharma's industry's investment in the space is getting a boost from the government, whose vision is for "Sweden to become a world



Cytiva plans to further expand its Swedish facility, which is currently the world's largest facility for the production of chromatography resin.

leader in development and implementation of advanced therapies by 2030." The government has backed this with a $37.8 million commitment.

"The government is clearly focusing on this area and has already made important investments in facilitating this hub," says Strigård.

The advanced therapies field is one of five recipients of funding under the "Vision Driven Health" program recently launched by Vinnova.

Sweden of course is not alone in this quest to take ATMPs to the next level. Despite the clinical success of advanced therapies around the world, widespread adoption is hampered by the high cost of scale-up, manufacturing and distribution. In Sweden, the industry is banking on a strategy that involves continued investment in R&D combined with strategic partnerships and collaborations.

"Personally, I believe that what really will make us stand out as a hidden gem for ATMP is the holistic approach taken by the government and the industry alike, with a push for strong development within drug delivery and process formulation, key areas complementary to the manufacturing," says Strigård.

Sweden's pharma industry spends about $1.3 billion per year on research and development.

Source: Lif Service AB

Addressing the COVID in the room

At the start of the COVID-19 pandemic, Sweden gained international fame for its controversial strategy of handling the global health threat, which incited polarized responses around the world. Allegiance to specific political alignments, news media sources or even social media groups, further influenced the public's image of Sweden's pandemic response.

But while the public health agency response — which initially proposed the idea of herd immunity and did not advocate for mask mandates, widespread testing or enforced lockdowns — may have been contentious, Sweden's pharma industry's response fell in step with the rest of the world. The pharma sector, according to Strigård, reacted "quickly and diligently," developing new tests, vaccines and drugs as well as increasing production capacity and securing the supply of drugs needed for intensive care.

Recipharm, one of the largest CDMOs in the world and headquartered in Sweden, signed a deal with Moderna to support vaccine formulation and fill-finish from its plant in France, helping boost Moderna's vaccine efforts outside the U.S.

Several pharma industry groups worked together with Sweden's Municipalities and Regions (SKR) organization to facilitate greater collaboration between pharma companies and health care. Through this, pharma company employees with health and medical care training were able to contribute to a strained medical care situation during the peak of the crisis.

Debate about the successes and failures of the Swedish national approach to the pandemic still dominate the news, but shouldn't overshadow the country's vibrant pharma industry looking to reclaim its narrative and set itself apart as a leader in advanced therapeutics manufacturing.

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Consistent measurements from lab-to-process

Smooth scale-up requires using similar measurement technologies from the lab to full production

It is within the lab where various phases of drug development occur as new drugs and therapies are discovered and developed through extensive research. Labs are then used to provide quality control monitoring as promising drugs move through process development on a pilot scale, followed by non-GMP and then GMP manufacturing.

During the lab scale research phase, a significant amount of analytical development takes place. Once a promising new drug has progressed through development and shows efficacy, lab-scale process development begins. The next step is process development on a pilot scale, where actual manufacturing processes can be established, along with the establishment of standard operating procedures (SOPs).

In each step, the transfer of processes and procedures must be well aligned with the original lab protocols. Consistency of analytical measurements and technology helps ensure this transitional process progresses from the initial lab activities through to full scale production as planned.

This article will examine how process and analytical instruments are used to facilitate the progression of drugs from the lab to full scale production, primarily by replacing lab-based testing with online monitoring.

The role of lab testing

Throughout the production processes for drugs and therapies, labs serve the critical role of quality control, releasing product in each stage of the process to meet guidelines set by the U.S. Food and Drug Administration (FDA). Without lab sign-off, drugs cannot pass to the next phase of production. These signoffs require extensive lab analysis and process verification.

Pharma processes rely on pH, conductivity, dissolved oxygen, optical density, ultraviolet (UV) absorbance and other measurements. When these measurements are made in the lab via testing,

issues can arise. Inconsistency can occur due to sampling techniques, poor sample handling and variations between real-time measurements and lab analysis results. When a sample is extracted from the process, its properties — such as temperature, degree of mixing and other factors — may not match the process media. Further deviation can occur due to improper sample handling or simply inconsistencies among technicians, even when all are following SOPs.

Even if the sample perfectly matches the process media when it finally reaches the lab, there will be a time delay between sample extraction and test results. This delay often makes it impossible to apply closed-loop control to a production process, and it can also make it difficult to implement open-loop adjustments. In both cases, issues arise because the results of changes made to improve upon sample properties are not available for quite some time.

For many properties, the issues with lab testing can be effectively addressed by moving measurements online to create real-time readings.

With the application of PAT, pharma production is being streamlined as the analytical tools used in the lab become more available for use in production processes.

Lab-to-process digital liquid analysis

Today, with the application of process analytical technology (PAT), pharma production processes are being streamlined as the analytical tools used in the lab become more available for use in production processes. These improvements are made possible by new instruments and analyzers able to make online measurements for properties formerly requiring lab testing (see Exhibit 1).

One aspect of PAT involves bringing lab measurements out in the process to speed release, improve time to market and cut costs — all while maintaining quality. This approach requires consistency between lab analytical methods and production measurements, which is critical to ensure PAT can be properly and safely implemented.

Implementation of lab-to-process PAT requires transfer of off-line measurements to the process using consistent technology in the lab and in the process.

Transfer of off-line measurement

When discussing the transfer of off-line measurements to the process, common terms are "off-line," "at-line" and "in-line" measurements.

An example of off-line lab analysis is the use of a benchtop photometer for photometric sample analysis. With this off-line approach, a sample is manually delivered to the lab and analyzed using a benchtop instrument. The sample may

Process measurements must match lab test results

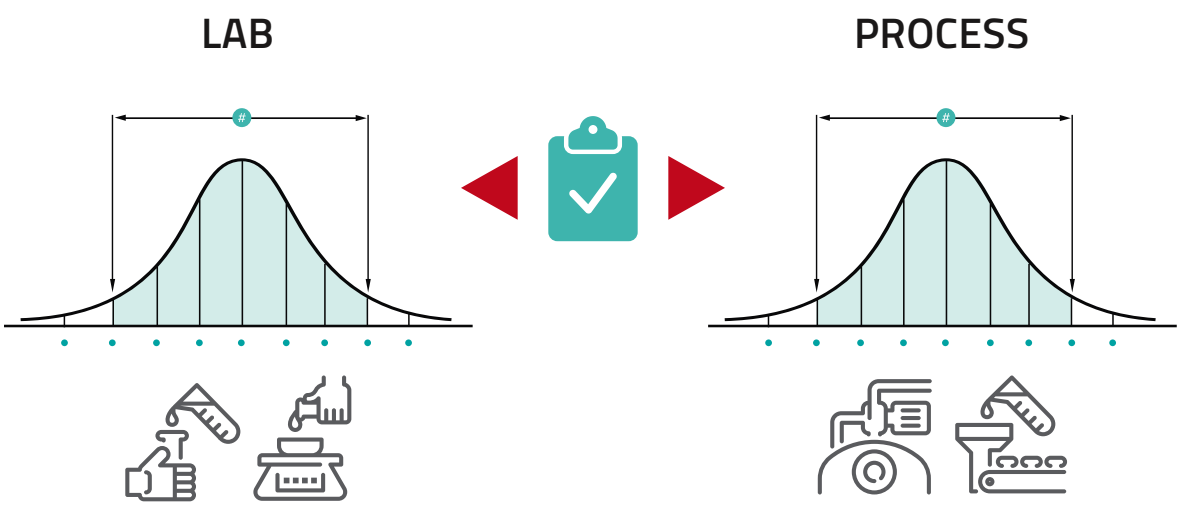
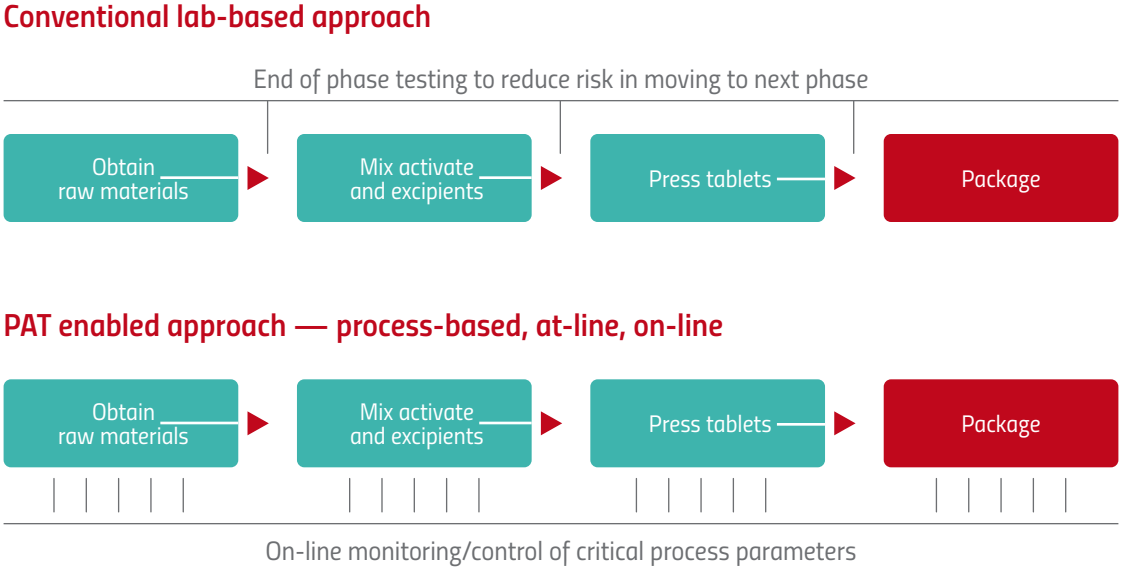


FIGURE COURTESY OF ENDRESS+HAUSER

EXHIBIT 1

Process approach comparison

A PAT-enabled approach requires replacement of lab-based offline testing of product quality and other parameters with on-line monitoring.



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or may not require preparation prior to analysis. This type of off-line testing can take hours to perform due to sampling time, sample delivery time to the lab and the schedule of activities occurring in the lab.

At-line (or on-line) analysis involves the use of a field-hardened analyzer, such as a gas chromatograph, to conduct an analysis by drawing a sample directly from the process. In this scenario, the analysis time improves from hours to minutes. Analysis time is the sum of time required to draw the sample into the analyzer and inherent analysis delay time. These types of instruments, such as field-hardened chromatographs, still require careful maintenance to maintain performance.

In-line analysis involves the use of an in-line sensor measuring a parameter directly in the process. This is typically a sensor inserted into the process, which sends a signal to a transmitter. The transmitter uses the sensor signal to create a real-time measurement, which is transmitted to the automation system. Examples of this are in-line Raman and tunable diode laser instruments, along with on-line sensors and transmitters using UV, visible or near infrared light technologies.

Consistent technology in the lab and process

With the advent of digital sensor technology for liquid analysis, industrial processes now have a greater opportunity to cross over from the lab to the process and back.

Digital sensor technology uses digital communications between the sensor and the transmitter. This improves measurement performance by removing interference effects commonly found with analog sensors — such as EMI/RFI interferences and ground loops — while also offering additional performance benefits. In addition, digital sensor technology includes sensor-to-cable connections and internal sensor memory to facilitate ease-of-use.

Originally implemented in process sensors, digital sensor technology can now be applied in the lab. For example, critical pH measurements can be made in the process using a sensor identical to the one used in the lab. Alternately, a

With sensors designed for the process as well as the lab, and electronics that can cross over between, consistency is provided from lab to process.

pH sensor with a protective plastic body can be used to make the same measurement in the lab, maintaining consistency with a more robust design for repeated handling.

As new drugs and therapeutics are developed in the lab, the same sensor technology can be used in the development lab as will be used later in production. And, with smaller,

> Lab measurements have been used for decades but can present problems.

more compact electronic devices to interface with the sensors, the lab can use the same device used by production to verify process measurement points.

Mobile handheld devices can be used in the lab as well as in the process for spot verifications, driving consistency across the process. These mobile handheld devices often employ Bluetooth technology and apps to interface with digital sensors, and measured values can be easily transferred to host automation systems using Bluetooth communications.

With sensors designed for the process as well as the lab, and electronics that can cross over, consistency is provided from lab to process.

Lab-based computer interface and sensor management

In addition to compact mobile handheld devices for sensor interface in the lab, more sophisticated systems are also available. For example, PC-based sensor management software is available to interface with a variety of sensors for benchtop operation in the lab. This type of software will typically provide sample measurement, sensor calibration and sensor lifecycle management.

Sensor management software provides direct interface to digital sensors in the lab. The software auto-detects a sensor and immediately stores actions in the system database associated with the sensor serial number. Sample measurements and sensor calibrations are stored for immediate retrieval from the system, even after the sensor has been disconnected from the system, and reports provide key regulatory documentation.

Some types of sensor management software can be licensed with 21 CFR Part 11 compliance to include data security, user management and a complete audit trail.

Labs serve as product development facilities and as quality checks on production processes. In its role of quality assurance, a lab will be used to make many of the same measurements made in the production process. To ensure consistency between process and lab measurements, it is increasingly important to use measurement technologies that are as identical as possible from lab-to-process.

Thermo Fisher Scientific

Felisha Pierre-Louis
Senior Product Manager

Konrad Knauss
Product Manager

Taking it to the extreme

The importance of temperature, humidity and light testing for drug stability

When it comes to preparing drugs and therapeutic treatments for market, assessing drug safety and efficacy is a complex and multi-layered process. Drug substances and products can be subjected to many environmental influences as they begin their journeys from the laboratory to the patient. Factors such as temperature, humidity, light and pH can have significant impacts on drug safety, efficacy and quality.

For this reason, testing is required to obtain a "stability profile," providing proof that a drug will maintain its desired characteristics through manufacture, transport and supply, until consumption. Since climate zones can vary greatly and manual testing in each area takes considerable time and effort, more manufacturers are choosing to emulate multiple climate zones by completing stress tests in accelerated and extreme conditions.

Knowing how and when to complete forced degradation assessments to stress test drugs will help create comprehensive stability profiles.

What is drug stability testing?

Drug stability testing is a critical stage in drug production. It must take place before a drug reaches the market, and the process must comply with the International Council for the Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) sections Q1A-Q1F. Sections Q1A and Q1B refer specifically to stability and photostability. And, it is through these regulations that manufacturers can help to assure regulatory bodies and prescribers that drugs are safe and efficacious, and will perform in the way in which they are intended. In fact, key regulatory bodies, including the U.S. Food and Drug Administration (FDA), the European Commission (EC) and Health Canada, all recognize ICH requirements as part of their approval processes.

By exposing the drug to extreme conditions, the intrinsic stability of the drug can be assessed. Degradation pathways can generate byproducts that destabilize products and alter their performance, but the stability profile can help set parameters around shelf life and storage conditions to ensure safety and efficacy within these buffers. In turn, packaging solutions can be designed to protect the potency and purity of the product, while extending the storage time in which the product can be safely used.

Four main environmental conditions have the greatest effect on a drug's stability: temperature, humidity, light and pH. Temperature is one of the most critical conditions as physiochemical stability is only ideal within a narrow range of temperatures and an increase

of 10°C can accelerate hydrolytic degradation by up to 500 percent.

The second condition, humidity, is a key factor in assessing both the degradants and active chemicals in a finished product. For this reason, the ICH recommends stress testing drugs at 90 percent humidity for a one-week period.

The third condition, light, can have a large impact on the chemical stability of a photosensitive drug, resulting in phototoxicity, photoallergy and photosensitization. Carefully controlling light in stability testing helps define these parameters and the necessary packaging required to protect the drug product and patient.

The fourth and final condition, pH, affects the stability of drugs that are prone to hydrolytic degradation, much like temperature.

All of these important parameters can now be tested in carefully controlled environments with precise programming used to replicate different climate zones in accelerated, extreme conditions.

Testing to the limits with forced degradation

Many manufacturers are now using environmental or light chamber technology to control forced degradation and accurately define drug stability profiles. By using these self-contained testing environments, researchers can achieve extreme conditions quickly and replicate multiple climate zones in one location. Various stress conditions can be generated, depending on the type of drug substance or product (see Exhibit 1), and workflows can be established to set the parameters under which a drug can be defined as photostable (see Exhibit 2).

Environmental chamber technologies enable wet and dry testing to extremes, or incremental testing from excessively hot to very cold conditions. This is critical when testing thermolabile compounds, such as vitamins or peptides, where stricter parameters may need to be established to ensure stability.

Light chamber technologies take testing to the next level, combining temperature and humidity testing with additional light tests in the visible and ultraviolet spectrums. By assessing the physiochemical effect on a drug, processes such as oxidative photolysis, isomerization, dimerization, cyclization, rearrangements, decarboxylation and the hemolytic cleavage of various bonds can be understood in relation to active ingredients and degradation compounds.

Choosing your chamber

Environmental and light chamber technology can vary widely between manufacturers. Whether the technology will be used in research and development laboratories, or as part of quality control procedures, particular features will determine the usefulness and day-to-day practicalities of the system.

The temperature range offered by the chamber should ideally fall between 0°C and 60°C, with complete temperature uniformity delivered throughout the unit. When it comes to drugs that are thermolabile in nature, the chamber should be capable of allowing for thermal stress testing even more strenuous

EXHIBIT 1

Typical forced degradation conditions for the stress testing of drug substances and products

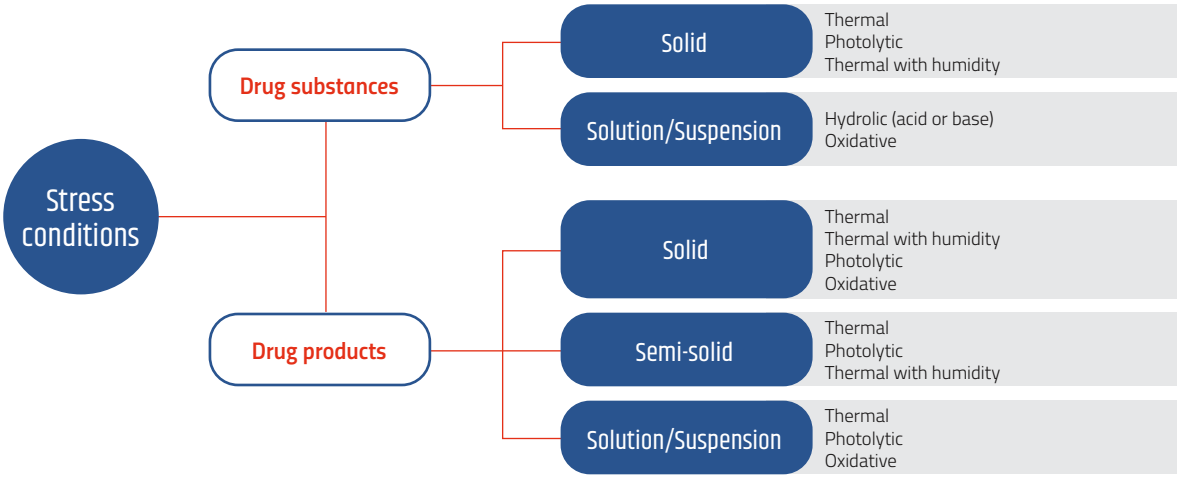
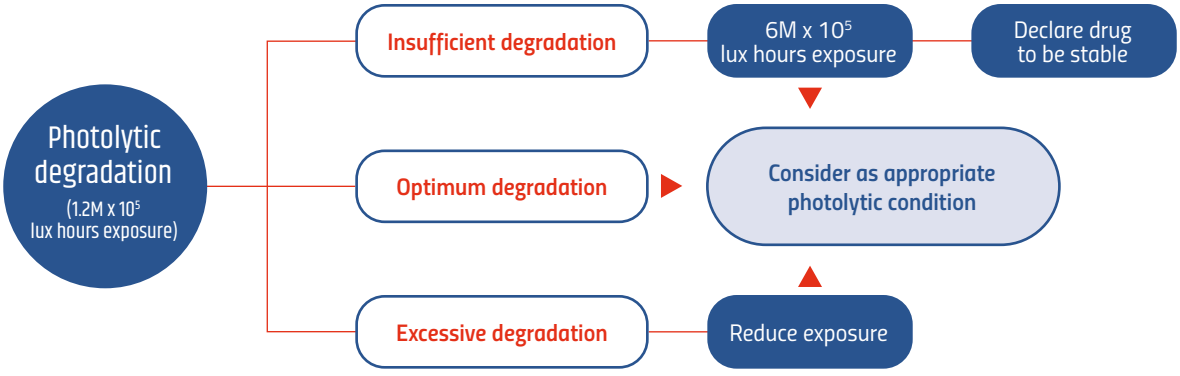


EXHIBIT 2

Standard workflow for photolytic degradation studies of drug substances and products



Creating a drug stability profile protects safety and efficacy once a drug is on the shelf but its creation requires the use of tightly controlled parameters.

than the recommended ICH Q1A accelerated testing conditions.

Features such as directed airflow systems can also help standardize the environment by minimizing product desiccation. Humidity control is a critical factor and although the ICH stipulates humidity testing at 90 percent, it is good practice to work in conditions from ambient to 95 percent, and environmental chambers should accommodate this. Versatile light sources are essential when considering light chambers, technologies that offer both visible and UV sources can expand capabilities and, of course, the system must be ICH Q1B compliant.

Versatility and flexibility must be key features of both environmental and light chambers. Depending on the sample size, shelves may need to be adjusted to fit larger samples or greater numbers, and the provision of perforated, solid and shaker support shelves deliver the widest coverage of testing scenarios. Automation drives speed and efficiency, but also helps to protect operators. Automated shut-offs, initiated when doors are open during UV cycles, and alarms that indicate quality control issues can all help to prevent accidents and ensure safety parameters are met. In addition to automation, intuitive operational features, such as simplified programming and one-touch settings, all help to streamline workflows and minimize operator training requirements. And finally, technology design plays an important role. Features such as a small footprint and durable construction can make all the difference in busy laboratories.

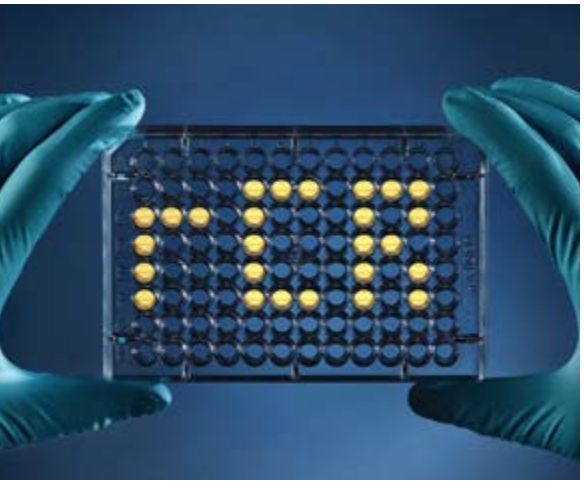
Going to extremes to make drugs safe

Drug stability testing is critical for both the research and development and quality control processes needed to take a drug to market.

Creating a drug stability profile protects safety and efficacy once a drug is on the shelf, but its creation requires the use of tightly controlled parameters. By using forced degradation testing in specially designed environmental and light chambers, manufacturers can now access a fast and fully compliant way to improve their processes and deliver consistent, high-performance drugs. By selecting the right chambers and ensuring ICH compliance, drug manufacturers can take important steps to protect brand integrity and ensure patient safety.

product focus

A ROUNDUP OF THE LATEST INNOVATIONS MAKING LIFE EASIER FOR PHARMA MANUFACTURERS



An animal-free alternative to BET testing

For decades, horseshoe crabs have been integral to the safe production of vaccines and injectables. In particular, injectable drugs must be tested for bacterial endotoxins using a Bacterial Endotoxins Test (BET) — also known as the Limulus Amebocyte Lysate (LAL) test. But the process, which involves the bleeding of live horseshoe crabs, is an unsustainable practice.

Now, to provide the industry with an alternative method, the Associates of Cape Cod, a Seikagaku Group Company, has launched a new, sustainable recombinant LAL reagent, PyroSmart NextGen for BET.

According to the company, lab analysts can maintain the same test method, sample preparation, and plate reader instrumentation used for traditional BET tests because the PyroSmart NextGen reagent is a recombinant cascade reagent (rCR) and follows the same enzymatic cascade pathway as traditional naturally sourced reagents. The new reagent is a direct replacement for naturally sourced reagents and eliminates the need to purchase new specialized instrumentation as required by first generation recombinant reagents.

As an added bonus, the PyroSmart NextGen can be used for a wide variety of endotoxin tests, ranging from standard water testing to samples requiring high sensitivity, such as intrathecal products and those requiring high dilutions to overcome interference.

Expediting packaging with automation

As pharma manufacturers worldwide push to produce billions of COVID-19 vaccines at an unprecedented pace, upgrades to operations, such as adding continuous labeling capabilities, will help expedite high-volume vial production.

Now, HERMA US, subsidiary of HERMA GmbH, a Germany-based provider of labeling machinery and self-adhesive labels and materials, has introduced continuous labeling capabilities for its 132M HC wrap-around labeler that add speed without sacrificing accuracy.

The company says that continuous operation is made possible by two new modules — EasySplicer and EasyCutter — that can be retrofitted onto existing machines. The new add-ons allow label and backing paper reels to be changed or disposed of without production interruptions. Because high speed labelers typically have to be stopped every 10 minutes to change the reels, this upgrade will result in a significant reduction in downtime.

The EasyCutter vacuums also improve sustainability efforts by collecting empty backing paper and chopping it into shreds that are collected automatically and can be recycled.

Speeding cell and gene therapy commercialization

The clinical manufacturing process of cell and gene therapies predominantly uses viruses as the vehicle to deliver the genetic information into the patients' cells. However, viral engineering processes are hampered by timelines that take months, cost millions of dollars and require significant infrastructure and downstream regulatory testing.

As an alternative, Kytopen's Flowfect technology is a flexible, complete technology solution for non-viral cell engineering that integrates the discovery, development, and manufacturing of cell and gene therapeutics. According to the company, the platform speeds therapies from the clinic to commercial use by enabling cell engineering without compromising functionality or viability. Ultimately, the non-viral process yields billions of high-quality engineered cells in minutes while maintaining cell health and function.

"Our Flowfect technology utilizes a novel combination of electrical energy and continuous fluid flow to engineer cells," Bethany Grant, head of research and development at Kytopen, said in a statement. "Our ability to engineer billions of cells in minutes with minimal disruption unlocks new opportunities to enable curative therapies in autologous or allogeneic therapeutic applications."

Standardizing content management

Legacy and other document management systems require companies to invest months defining requirements and customizing configurations. Even then, employees often find workarounds when it comes to sharing quality documents, which can increase compliance risks.

Recently, Veeva Systems announced the availability of the Veeva Quality Content Reference Model to advance quality transformation efforts and drive further standardization in quality management. For the first time, the company says that documented best practices from hundreds of successful implementations of Veeva Vault QualityDocs will be available to accelerate systems deployment, and drive consistent and compliant GxP content practices across the enterprise.

In pharma, there are currently no widely accepted standards for managing quality content. Now, Veeva's reference model will streamline the process by providing a standard document hierarchy, taxonomy, and metadata for organizing and delivering quality content. It can also be used to streamline collaboration with contract partners.

The reference model is also free, and any company can apply the content management best practices to harmonize processes and improve collaboration with partners across the product life cycle.

Safer automation with robots

Robotics have transformed many areas of pharma's warehouse operations, adding speed and ease to packing and moving containers. But companies are often hampered by the high cost of installing fixed infrastructure for robotic operations.

To overcome this obstacle, Boston Dynamics has innovated Stretch — a small, box-moving robot with an omni-directional mobile base that allows it to navigate loading docks, maneuver in tight spaces and adapt to changing facility layouts.

The multi-purpose mobile robot can tackle a number of tasks where rapid box moving is required, first starting with truck unloading and later expanding into order building. Stretch is also equipped with a custom-designed lightweight arm and a smart-gripper with advanced sensing and controls that can handle a large variety of boxed and shrink wrapped cases.

Boston Dynamics is currently seeking customers to pilot test deployments of Stretch with truck unloading tasks ahead of its commercial deployment in 2022.

Richard Lockwood
Regional Director, Asia Pacific, Matcon

Material handling matters

Assembling a factory is not simply a question of "fitting it all in"

When it comes to designing a pharma facility, a complete understanding of the processes, equipment and space required to manufacture products is critical.

At the start of any new production line project, you'll need to know what steps are involved in the product's manufacture. For an oral solid dose manufacturer, commonly the focus of attention is on the processing stages of granulation, compression, coating and packing. But careful consideration must also be given to the ways in which powders, granules, tablets and capsules are handled and moved from each stage of the production process. Often overlooked, or not considered early enough in the facility design process, are the questions: "How are the materials moved from one process step to another?" "What is the best way to do this?"

Without fully considering these fundamental questions when designing a facility, the manufacturer not only risks compromising the productivity of a given product line, but also limiting future potential for expanding capability and capacity.

While the actual processes involved in OSD product manufacture are of course crucial, the materials handling methods required to move between these processes are often overlooked during the design phase, and these can introduce time, energy and profit-sapping inefficiencies.

Of course, there is not a "one size fits all" solution to materials handling. Not only do different product lines with different ingredients and formulations have different materials handling requirements, factors such as building space constraints, containment requirements, material characteristics, regulations and budget must also be considered to arrive at the optimum facility design.

> "Ignoring the materials handling element can have a detrimental effect on production efficiency and capability in the longer term.

A compression phase example

Ignoring the materials handling element of the project can have a detrimental effect on the production efficiency and capability in the longer term.

Take, for example, the compression stage: The space needed to operate within is considered and designed accordingly, and thought must be given as to how the powder or granular ingredients will be delivered to the inlet of the machine, and how the compressed tablets will be collected. The ways in which input and output materials are handled and moved can affect the optimal production set-up more than the compression process itself.

If you plan to tip material into the tablet press by hand, or use a vacuum system then a single floor facility with a low ceiling height would suffice.

However, if drums or intermediate bulk containers (IBCs) are to be used to feed materials in to the tablet press, a taller room height would be needed to accommodate a gravity feed system. At this point, it is worth considering using a dedicated materials handling floor above the compression room, creating a two-floor facility, or using a mezzanine level.

This example considers only one stage of the process, and for only one type of product, yet there are many more decisions that are taken concerning materials handling further down the line.

Consideration also needs to be taken on how pressed tablets will move to the coating machine or to the bottling area. Should the tablet press outlet be coupled directly to the next stage of the pipeline, or are tubs, boxes or drums more efficient in moving tablets from one area to another?

Achieving optimal materials handling efficiency should be a key driver in facility design. Whether starting from scratch, or adapting an existing building, getting it right from the outset and creating the "leanest" environment possible will undoubtedly pay dividends.

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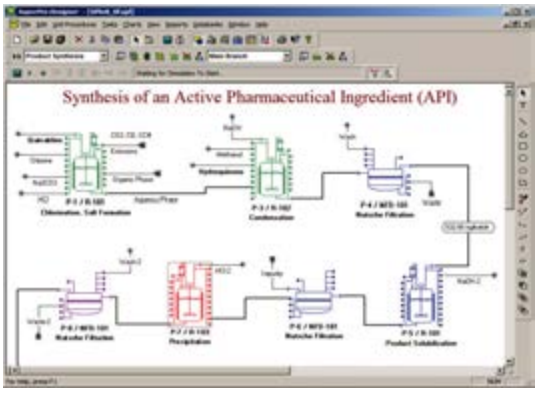

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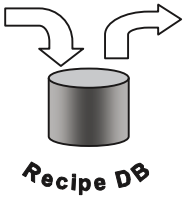

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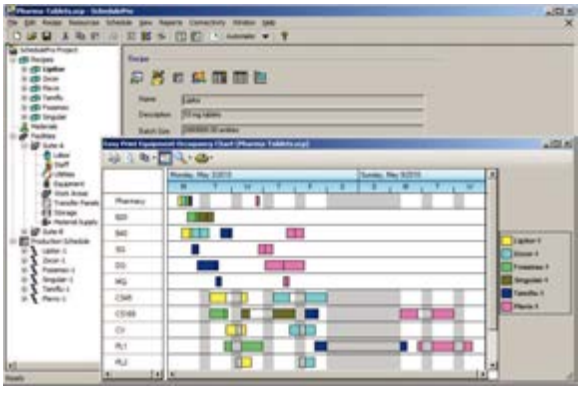

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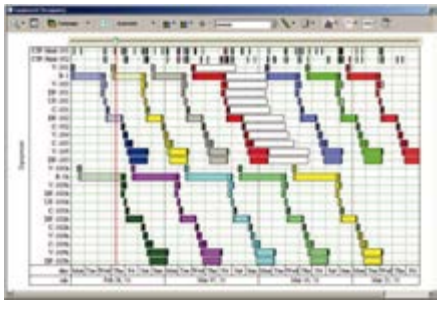

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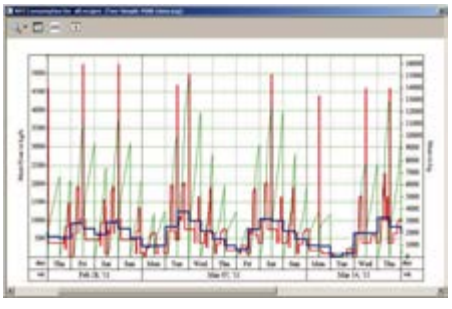
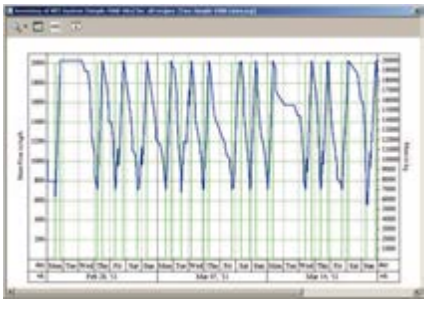


Tracking demand for resources (e.g., labor, materials, utilities, etc.)



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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Nir Kossovsky
CEO, Steel City Re

The temporary halo effect

Pharma's reputational luster could be short-lived

The pharmaceutical industry would be gravely mistaken if it expects the momentary investor enthusiasm and popular adoration spawned by its speedy development of life-saving COVID-19 vaccines to diminish reputational headwinds on the horizon.

If companies fail to exploit this window of opportunity with a substantive reputation resilience strategy, this short-lived halo will succumb to the gravity of historical grievances. Spoiler alert: This does not mean more corporate social responsibility or feel-good marketing.

In fact, once pharma companies' remarkable success with COVID vaccines is in the rearview mirror, stakeholders could well begin to question why pharma is not having similar successes in combatting other diseases.

The fact that pharma's biggest companies have spent more on marketing and sales than on drug R&D indicates a fundamental flaw in their reputation risk management strategy. Pharma companies need to take the time to understand who their stakeholders are and what they expect — and how those expectations may have shifted.

Pharmaceutical companies can't leave their reputations entirely to marketing. They need to build more expansive reputational risk management and governance processes that address the interests of both shareholders and stakeholders, using a framework that is sensitive to expectations, behaviors and economics.

Filling the gaps

The risk management process requires intelligence gathering among all the disparate corporate functions, identifying where gaps exist between stakeholder expectations and the company's ability to meet them. And companies need to take meaningful steps to manage those expectations, operate to meet those expectations, or mitigate the reputational damage from persisting gaps. The act of balancing the costs and benefits of triage for each of the stakeholder groups to yield a coherent enterprise reputation risk strategy, usually under the supervision of general counsel and with oversight from the board, comprise the underpinnings of an effective reputation resilience solution.

Here's some additional color to how a reputation resilience solution can be delivered by a firm's enterprise risk management apparatus. Clear metrics and quantitative rigor are essential in demonstrating a company's credibility and authenticity, and metrics measuring one's reputational value should be built on a track record of performance. Consider, for example, the metrics used over nearly 20 years by stock indexes, which predict what companies will outperform their peers based on their reputation.

Pharma's risk management process going forward needs to engage its board while also enabling it to focus on strategic issues and avoid a constant stream of piecemeal issues and potential threats. A reputation risk solution framework should be a coherent, seamless business process packaged for oversight.

Reputational resilience is also something bond raters and investors are currently rewarding, especially when it is authenticated. Bringing in third parties, whether outside corporate counsel, consultants, or underwriters, can help both authenticate the framework and protect the enterprise if reputational crises do occur through insurances and financial risk transfer through captives.

Pharma's reputational risk headwinds have implications for every company in the industry. And it's not just proxy advisers, bond raters, institutional investors and the courts of public opinion that they need to be worried about.

Reputational stakes

Courts of law are increasingly holding corporate boards accountable for financial setbacks related to reputational damage. They are upholding pleadings that argue reputation is mission critical and, therefore, falls under a director's duty of loyalty. Federal lawsuits mentioning reputation saw a nearly 60 percent increase last year from the year before, according to *Agenda*, a publication used by public board directors and company executives.

If Big Pharma doesn't create systems and oversight processes to manage their reputational risks and build in reputational resilience, their COVID vaccine sheen will quickly wear off, opening the industry to public ire once more. Companies that build a robust reputation risk management infrastructure, however, will have a compelling and credible story to tell.

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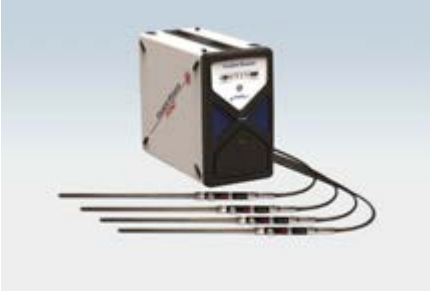

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