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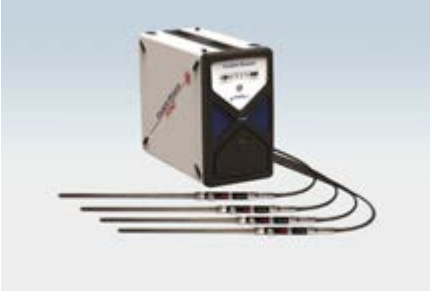

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Meagan Parrish
Senior Editor

Legal unea$e

How the generics industry is adjusting as the dust settles on price-fixing lawsuits

page 12

FEATURES

DEPARTMENTS

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Karen Langhauser
Chief Content Director

Drug deals

Casting the role of the 'bad guy'

Before America got desperate enough to binge watch "Tiger King," the TV industry went through a bit of a drug cartel phase. Specifically, a Latin American drug cartel phase.

From "Narcos" to "Breaking Bad" to "Sicario," the baddest of the bad guys were always streaming in from our southern borders with AK-47s blazing, leaving a trail of bikini-clad women, cocaine and the occasional severed head behind them.

Viewers seemingly had an insatiable appetite for this narrative, despite it being played out and riddled with stereotypes.

So naturally, when headlines began calling out the "largest cartel in the history of the United States," people kept reading.

Perhaps they were disappointed when the story was about khaki-clad pharma execs on the golf course, conspiring to fix the price of a generic Athlete's foot cream.

And yet, the scandal just kept getting worse. Just like a single shot fired in a cartel film often spirals into a street strewn with dead bodies, things got out of hand quickly and casualties were heavy.

As you will read in this month's cover story, what started as just a handful of antitrust allegations back in 2016 unfolded into a massive criminal price-fixing conspiracy involving close to 30 generic drugmakers and at least 300 generic drugs. Years later, numerous companies and individual executives have pled guilty, and some have even snitched on their peers in exchange for better deals. State and federal litigation is still ongoing and it's not uncommon to see news of another civil or criminal settlement in the headlines. Just this month, three more generic drug manufacturers agreed to shell out $447 million to settle federal allegations of pricing violations.

What's most shocking is that this is not the enemy we expected. Frequently referred to as the "underdogs" or "unsung heroes," of the pharma industry, generics have long been the counterweight to rising drug prices in the U.S.

In short, generics were helping America *win* the war on drug prices.

And they still are. An impressive 92% of generic prescriptions are filled at $20 or less and the average generic copay is under $7. In 2019, generic drugs saved America's patients $313 billion — including $96.1 billion in Medicare and $48.5 billion in Medicaid savings.

The TV industry has done a disservice to Latino characters by constantly portraying them as drug lords in the same tired trope. While the recent litigation in the generics space is compelling in its scandalous details, it would be unfortunate if it resulted in typecasting an entire industry based on the actions of some.

When all the legal dust settles, those who broke the law will likely pay the price to the tune of millions of dollars, as they should. Hopefully, next season will feature less drama, more compliance and star an industry more focused on doing what it does best: getting affordable, life-saving drugs into the hands of patients.

Karen Langhauser
Chief Content Director

What's trending in M&A?

A closer look at two hot sectors for 2021 deal-making

Although 2021 has thus far been a year almost entirely devoid of pharma mega deals, the space has certainly not been quiet.

Shaking off the pandemic-induced deal-making lows of 2020, the pharma M&A landscape is healthy. Even though only one deal to date has hit the magical $10 billion-plus mark, the year's top 10 M&As have all had values of $1 billion or more.

Some market analysts are predicting further uptick before the year's end — a much rosier outlook than anticipated earlier, given the promise of increased scrutiny from the U.S. Federal Trade Commission. Back in March, the FTC announced a new working group, comprised of antitrust enforcers from around the globe, focused on taking "an aggressive approach to tackling anticompetitive pharmaceutical mergers." The initiative vowed to more closely evaluate pharma mergers in light of concerns about anticompetitive behavior and drug pricing.

But pharma deals have largely gone unscathed and two sectors — mRNA and rare disease — are especially hot. Here's a look at some key M&As:

mRNA

MilliporeSigma buys AmpTec

MilliporeSigma, the life science arm of Merck KGaA, was fast out of the buying gates in 2021, snapping up German mRNA CDMO AmpTec in January. The plan? Combine AmpTec's PCR-based mRNA technology with Millipore's expertise in lipids manufacturing to truly beef up offerings across the mRNA value chain.

PCR technology is an important component of mRNA manufacturing — and AmpTec's technology has proven to yield significant advantages.

In addition to specializing in mRNA technology, AmpTec has a diagnostics business that focuses on producing customized long RNAs and DNAs for in vitro diagnostics.

MilliporeSigma is already providing lipids, the star delivery device for mRNA therapeutics, to Pfizer-BioNTech for their COVID vaccines. The AmpTec buy (its price tag was not disclosed) will help firm up MilliporeSigma's investment in mRNA, as the company continues to scale up.

Sanofi buys Tidal Therapeutics — $470M

Although not quite as large as other deals this year, Sanofi's April purchase of Massachusetts-based Tidal Therapeutics set the stage for the French drugmaker's deeper foray into mRNA.

Born out of a nonprofit launchpad called LabCentral, Tidal developed a novel mRNA-based approach for in vivo reprogramming of immune cells. The company has ongoing preclinical programs, including in vivo reprogramming of T-cells for cancer indications. Tidal's technology platform will expand Sanofi's research capabilities in both immuno-oncology and inflammatory diseases, and may prove applicable to other disease areas.

Following the Tidal deal, Sanofi launched a first-of-its kind mRNA Center of Excellence. Sanofi says the center will work to accelerate the development and delivery of next-generation mRNA vaccines.

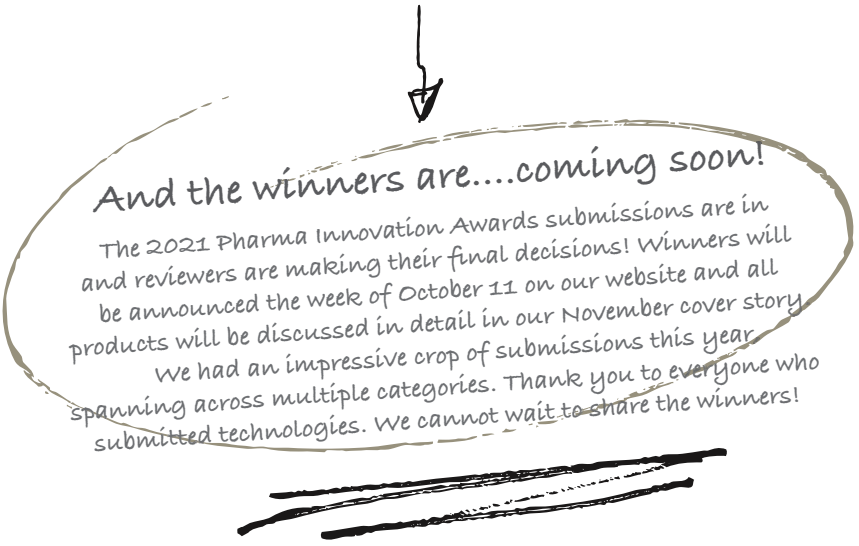
Sanofi buys Translate Bio — $3.2B

Not done yet, Sanofi landed a $3.2 billion deal to buy Massachusetts-based Translate Bio.

Announced in August and completed mid-September, the deal hinged on Translate's mRNA platform, which Sanofi hopes to use to develop transformative vaccines and therapies using mRNA technology. The companies had already teamed up to co-develop mRNA vaccines for infectious diseases in a partnership that started back in 2018.

Just recently, Sanofi announced that — despite positive data — it had pulled on the plug on the mRNA COVID shot acquired as part of its takeover of Translate Bio.

Given the already sufficient supply of authorized mRNA COVID vaccines, Sanofi said it plans to focus its mRNA resources on its newly



created Center of Excellence to address future pandemics and other infectious diseases and therapeutics where there is a strong unmet need.

Rare disease

Jazz Pharmaceuticals buys GW Pharmaceuticals — $7.2B

One of 2021's biggest value acquisitions happened in February when Jazz said it planned to buy GW Pharma for $7.2 billion, gaining GW's approved cannabidiol Epidiolex, indicated for seizures associated with rare forms of epilepsy.

The deal, which closed in May, helped Dublin-based Jazz — already active in the rare disease space — strengthen its robust pipeline, which now includes clinical-stage development programs addressing unmet patient needs across neuroscience and oncology, including in sleep, movement disorders, psychiatry, hematology and solid tumors.

Horizon Therapeutics buys Viela Bio — $3.05B

Announced in February and completed a month later, Dublin-based Horizon's $3.05 billion pipeline expanding play firmed up the company's already strong presence in in the rare, autoimmune and severe inflammatory disease arena.

With the purchase of Maryland-based Viela came its deep, mid-stage biologics pipeline as well as the commercial drug Uplizna, which is approved to treat neuromyelitis optica spectrum disorder, a rare, severe autoimmune disease.

AstraZeneca buys Caelum Biosciences — $500M

In late September, UK giant AstraZeneca announced its plan to acquire NJ-based Caelum Biosciences in a deal worth up to $500 million. The deal piggybacks off AstraZeneca's monster $39 billion buy of rare disease specialist Alexion Pharmaceutical, announced late last year.

Per the latest deal, Caelum will become part of AstraZeneca's Alexion division, giving AstraZeneca another potentially lucrative rare disease drug. Caelum's drug candidate is a potential first-in-class treatment targeting AL amyloidosis, a rare life-threatening disease that damages the heart and kidneys.

Merck buys Acceleron Pharma — $11.5B

Just when you thought it was safe to say 2021 lacked mega-deals, in crashes Merck, with a whopping $11.5 billion deal to buy Massachusetts-based Acceleron.

The deal, aimed at helping Merck grow its rare disease portfolio, comes with Acceleron's promising drug candidate, sotatercept, which targets pulmonary arterial hypertension, a rare condition caused by high pressure in blood vessels that impact the lungs. Merck thinks the candidate has the potential to hit multi-billion dollar peak sales. As part of the acquisition, Merck will also pick up Reblozyl, a first-in-class injectable approved to treat anemia in certain rare blood disorders.

For a deeper dive into these two buzzing sectors, visit our website to read:

mRNA takes off
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Estelle Beguin, Ph.D
Strategic Marketing Manager for SAFC® Synthetic Lipids portfolio, MilliporeSigma

Advancing drug delivery with lipid nanoparticles

Nucleic acid therapies could change the way pharma addresses disease — and LNPs help new treatments get there

RNA-based vaccines have played a starring role in the ongoing COVID-19 pandemic. There is also great potential for RNA to be applied to more indications, such as vaccines geared towards other infectious diseases or cancer.

As nucleic acids are highly negatively charged and fragile, the right delivery systems are needed to protect RNA from degradation. One technology — lipid nanoparticles (LNPs) — has proven to enable the drug delivery of RNA-based therapeutics.

Pharma Manufacturing recently spoke with Dr. Estelle Beguin, Strategic Marketing Manager for the SAFC® Synthetic Lipids portfolio, MilliporeSigma, to get a better understanding of lipid nanoparticles and the role they will play in the success of emerging therapies and vaccines.

Q: While they proved extremely effective in the fight against COVID, RNA-based therapeutics are not without challenges, especially in terms of formulation and delivery. Can you walk us through the importance of drug delivery for RNA?

A: RNA-based therapeutics and vaccines have certainly been in the spotlight with the development of COVID-19 vaccines during this pandemic, but actually, the first lipid-based gene therapy encapsulating siRNA was approved in 2018. The field has been gearing up for years now to harness the powerful and versatile nature of nucleic acid to treat and prevent diseases.

In the case of DNA therapies for example, a gene of interest can be delivered which can be used to purposely cause the sustained expression of desired proteins.

RNA can be used in different scenarios:

- *Large messenger RNAs:* mRNA can be used to only cause the transient expression of certain proteins, applicable in the case of protein-replacement therapies or COVID-19 vaccines. Once the mRNA is degraded, the protein expression then stops; and the mRNA does not integrate into the genome, providing a tighter control over when the treatment starts and stops.
- *Shorter RNA strands:* Small interfering RNA (siRNA) or short activating RNA (saRNA) can be used to silence or activate the expression of certain genes. This is particularly relevant when diseases are caused by the overproduction or insufficient production of a specific protein.

Overall, nucleic acids are extremely versatile in the way they can be used to modulate gene expression or protein production, but these are fragile systems that would degrade if administered as-is and then be cleared out prior to reaching the cells where they need to take action. This is when lipid-based formulations are crucial to promote their stability but also enable their efficient delivery into cells.

Q: What makes lipid-based delivery an attractive system for RNA therapeutics?

A: RNA, being highly negatively charged and very fragile systems, need to be protected to ensure they can reach the target cells and be released into the cytoplasm of cells in their active form. While other delivery systems are also studied for this purpose like viral vectors and polymeric systems, lipid nanoparticles stood out as a promising option. Indeed, LNPs demonstrated efficient stabilization of RNA and delivery into the cytoplasm of cells, but they also provide flexibility in the formulation and manufacturing of the final drug product. For instance, they can be customized to have specific encapsulation, release or targeting properties. Additionally, some lipids have immunostimulant properties and can act as adjuvants to also promote efficacy.

Q: The performance of lipid-based formulations is dependent on a few factors, one of which is the composition of the drug delivery vehicle. Why does this matter so much?

A: The composition of LNPs has a significant impact on the overall performance of the RNA-based drug product because the formulation affects the encapsulation efficiency of the RNA, its biodistribution, and how well it will be released into cells. For instance, the formulation would need to be optimized if a new RNA is to be encapsulated. Additionally, since the RNA is encapsulated within

> “There is going to be a paradigm shift in the way diseases are addressed — so lipid-based RNA therapeutics definitely have a very exciting future ahead.

lipids, these lipids are then in direct interaction with the biological environment from the onset of administration, and therefore their composition also dictates to which specific tissues or cells the RNA is going to be delivered.

Q: Another important factor is the quality and consistency of the lipids used in your formulation. Why is this so vital and what can be done to ensure high lipid quality?

A: Lipid type, source and quality are essential factors to be considered when designing lipid-based formulations because these have a direct impact on the impurity profile and properties of the final drug product. For instance, they might impact particle characteristics such as structure, stability, and release properties. Additionally, to ensure the reproducibility of the formulation and associated results, it is essential for these lipids to be synthesized from high-purity raw materials with consistent quality because these characteristics are then carried over to the lipids and then to the final drug product manufactured with those.

Of course, when considering the need for consistent and high purity excipients, chemically synthesized lipids have a significant advantage over natural lipids because they are made from a single type of lipids of known quality, while natural lipids can be composed of a mixture of lipids and might present batch-to-batch variability.

To ensure the high purity of chemically synthesized lipids with consistent quality and good handling properties, the purity of the starting materials needs to be tightly controlled and optimization of the manufacturing process and purification methods is often required. It is particularly important to control any impurities in lipids, as these can alter the characteristics of the final formulation like the stability and the RNA release profile.

Q: During the pandemic, with so many RNA therapeutics and vaccines being developed, the industry urgently needed a large supply of lipids. How did MilliporeSigma rise to the challenge?

A: Within our SAFC® portfolio, we have over 24 years of experience in the GMP manufacturing of lipids and an established center of excellence that make us a trusted supplier for these materials.

We also have extensive experience with the successful execution of a large number of projects for different clients. Additionally, our SAFC® portfolio has a dedicated contract manufacturing organization and a global network of facilities and experts to efficiently enable scale-up processes as needed. All of these facilities are frequently inspected by the FDA, EMA, other health agencies, and customers. Therefore, we had the appropriate network and expertise within MilliporeSigma to support pharma companies developing vaccines against COVID-19 right as the pandemic started.

We were already working with mRNA companies before the pandemic actually, and the progress made in this field during this time just encourages us further to support the growth and development of RNA-based therapeutics and vaccines. The recent acquisition of AmpTec further expands our presence in the mRNA field, and this also reflects our faith in the technology.

Our lipid team is also highly experienced, with over 85 years combined working in this field. They have the deep know-how to develop solutions for even the most challenging customer projects. As an example, we were able to meet the challenge of producing very large quantities of lipids for BioNTech’s COVID-19 vaccine.

Our goal is to provide the best support possible to our customers — both our existing customers and other companies advancing the mRNA therapeutics and vaccines and the science behind them.

Q:. What role will lipid-based RNA therapeutics play in the future?

A: Before COVID-19, there were already many activities ongoing in the development of RNA therapeutics. It is however certain that the emergency approval of mRNA-based COVID-19 vaccines with their successful clinical results has fast-forwarded the development of other mRNA therapeutics in an incredible way.

There is a lot of potential for this technology to be applied to other indications outside of COVID-19, for instance against other infectious diseases or for cancer vaccines, and we have seen a rapid increase in the number of preclinical investigations and clinical trials using RNA or DNAs to support that. As more clinical successes are published using this technology and as we prove that medicine can be designed to act at the genetic level, there is going to be a paradigm shift in the way diseases are addressed — so lipid-based RNA therapeutics definitely have an exciting future ahead.

Legal unea$e

Meagan Parrish
Senior Editor

How the generics industry is adjusting as the dust settles on price-fixing lawsuits

When federal prosecutors are breathing down a company's neck, it's not often that executives opt to wait and see how the whole situation will play out in court. The stakes are just too high, especially in criminal cases when penalties can be severe and executives could even get carted off to jail. Thus, the common legal wisdom is to settle — and settle fast.

So when Teva Pharmaceuticals walked away from settlement talks with the U.S. Department of Justice (DOJ) over criminal charges related to widespread price-fixing allegations, eyebrows were raised across the industry.

"I was surprised when Teva chose not to settle because of the huge consequences involved…and the danger of going in front of a jury," Rachel Peck, an attorney with Steptoe who specializes in white collar defense, cartels and antitrust issues, said.

But the company, it seemed, had some cards up its sleeves. It was the spring of 2020, and with the pandemic raging, Teva reportedly gambled that the federal government would not levy charges against one of the largest companies involved in supplying needed drugs. In fact, Teva had recently announced that it was donating 10 million tablets of hydroxychloroquine to wholesalers — a drug that, at the time, was still being lauded as a potential "game-changer" in the pandemic fight. The message? Teva was a government friend — not a foe.

The bet, however, didn't pay off. In August 2020, the DOJ formally charged Teva with conspiring to fix prices, rig bids, and allocate customers for generic drugs. According to the DOJ, consumers were overcharged at least $350 million, and unless Teva ultimately settles, the indictment has set up an eventual showdown in court.

It was the latest twist in an ongoing and large legal saga that has rattled the generics industry — often portrayed as the do-gooders in pharma. Although it started with a trickle of price-fixing allegations in 2016, it has since erupted into a flood of lawsuits targeting dozens of companies for allegations related to hundreds of generic drugs. And the lawsuits piling up around the industry now include state-led, class action and criminal litigation efforts.

Teva, which released a statement after the DOJ indictment saying that it rejected the charges and that it will "vigorously defend" itself in court, has been pitted as being at the center of one of the price-fixing conspiracies that allegedly permeated throughout some of the industry.

Yet, the charges speak to deeper problems that have boiled beneath the surface of the generics landscape for decades. Now, as the industry takes stock of how the various lawsuits are unfolding, generics companies may find themselves adjusting business practices to avoid further allegations. And the situation is opening up the door to talk about larger issues that could be creating the perfect environment for price-fixing schemes.

Clouds of collusion

The backdrop

Since the price-fixing allegations in the generics industry exploded in 2018, the situation has oft been referred to as the "largest cartel in U.S. history." But this isn't the first time that pharma companies have found themselves ensnared by allegations of widespread price fixing.

In 1999, the DOJ settled two major antitrust suits related to vitamins — one of most commonly used health care products in the country. According to the suits, major manufacturers colluded to artificially inflate the prices of vitamin supplements and additives used in processed food products. It was a situation that then Attorney General, Janet Reno, said impacted "every American consumer" on a "daily basis."

After Rhone-Poulenc SA, a French vitamin-maker, agreed to cooperate with the DOJ in exchange for avoiding prosecution, the case resulted in a $500 million fine being levied at Roche, and a $255 million fine for BASF. At the time, these were the largest antitrust penalties in U.S. history. The former marketing director of Roche's vitamins division also had to pay $100,000 and was sentenced to four months in prison.

The harsh penalties were indicative of the DOJ's efforts to beef up antitrust enforcement. Since then, a number of other industries, including construction supplier companies and major meat processing corporations, have been rocked by widespread price-fixing lawsuits and settlements. Although the impacted industries operate in vastly different markets, they all have one thing in common: identical and interchangeable products made with low profit margins.

"Cartels are hard to form when you have firms making different goods with different levels of quality, because there are all sorts of dimensions you have to squabble about. The raw materials may change, the costs may go up and down, etc." Alden Abbott, a senior research fellow at George Mason University's Mercatus Center, and a former Federal Trade Commission attorney, says. "This is why it's not surprising to see cartel conduct in a homogenous goods industry."

According to Chester "Chip" Davis, president and CEO of Healthcare Distribution Alliance and the former president of the Association for Accessible Medicines (AAM), the generic industry's largest trade group, it's a situation that can be traced back to the Hatch-Waxman Act — a regulation passed in 1984 to help propel competition in the generics space.

In the beginning, there was no question that Hatch-Waxman succeeded in streamlining approvals and bringing more generics to patients — a change the marketplace embraced. Yet, as Davis explains, unforeseen consequences later cascaded through the industry as the dynamics of the market shifted.

"Fast forward in time and you have major health care consolidation among pharmacy benefit managers, distributors and other buyers," he says. "So that original intent of Hatch-Waxman, where you have 12-15 different manufacturers and countless buyers hasn't stuck as the number of buyers has dropped significantly. And do you really need

> “I’m surprised it took this long for an investigation [into price fixing] to surface. The generic drug industry is ripe for this type of activity because you are dealing with interchangeable goods.”
>
> — Patrick Linehan

12-15 different manufacturers to get down to commoditized pricing? Many health care economists would tell you that you need about three to five to get down to that pricing. So I’m not sure that the health care system has appreciated how much the market has changed.”

A race to the bottom

On top of that, political and public pressure in the generics space to keep prices low has created an environment that Robert Field, a professor of law, and health management and policy at Drexel University, says could lead to “temptation to artificially inflate prices.”

“There’s a conflicting policy goal,” Field says. “We want the generics industry to be as robust as possible, but when you ask them to operate with these thin margins, there’s going to be a risk of engaging in behaviors such as price fixing.”

Given the diverging forces at play in the generics market, Patrick Linehan, a partner at Steptoe who specializes in white collar defense, cartel, and securities issues, says that it was only a matter of time before antitrust behaviors came to light.

“I’m surprised it took this long for an investigation [into price fixing] to surface,” Linehan says. “The generic drug industry is ripe for this type of activity because you are dealing with interchangeable goods and the competition is based on prices, not unique aspects of the products.”

Where the suits stand

In one of the first major exposés of the price-fixing allegations, a December 2018 article in The Washington Post painted a sinister portrait of antitrust behaviors by generics companies.

Citing investigators involved in the probe, the environment was described as a “sandbox” where companies played nice with each other and divvied up the market for certain drugs. Over dinner, cocktails and rounds on the golf course, companies allegedly used a form of shorthand to communicate about how they would work together to share the market and inflate prices.

At the time, the investigation, being led by the attorney general’s office in Connecticut, involved over

Tips for building an antitrust compliance program

Tailor the program to your business
Identify antitrust risks in your specific business model and create a program that targets those risks.

Create program materials
A robust antitrust program should include a code of conduct that communicates company values and antitrust ethics; a policy manual that includes an overview of antitrust laws and instructions on how to report suspicious behavior; and guidelines that describe hypothetical situations involving antitrust behaviors and how employees should respond to them.

Encourage a culture of compliance
An emphasis on antitrust compliance should come from the top and permeate through the ranks at the company. Practices among employees that could be seen as antitrust — such as discussing any pricing or cost information with competitors — should also be strictly prohibited.

Make antitrust reporting easy
Consider establishing an anonymous tip line for employees looking to report antitrust behaviors. Implement strong non-retaliation rules for whistleblowers.

Train employees regularly
Create protocols that are easy for employees to understand and implement, and then build regular training sessions that reinforce those skills.

Devote adequate resources to the program
A high-ranking compliance officer at the company should be tasked with overseeing the program. This employee should be allowed to operate autonomously and given adequate resources to implement the program effectively.

Reassess your plan
Antitrust compliance programs should be regularly audited and potentially revised to address new risks or detected incidents of antitrust behaviors.

a dozen companies — including Mylan, Dr. Reddy's Laboratories, Teva and Sun Pharmaceutical Industries. In a court filing, Teva said the allegations of conspiracies were "devoid of any facts." But two former executives at Heritage Pharmaceuticals — also named in the investigation — then pled guilty to federal criminal charges and have since agreed to cooperate with the DOJ.

This approach to unraveling industry-wide antitrust behaviors follows typical investigative patterns.

"For years, the DOJ has used amnesty agreements to get someone to snitch," Abbott says. "That's really how you crack a cartel."

The probes led by Connecticut's attorney general have now resulted in three multi-state lawsuits filed in 2016, 2019 and most recently, in 2020 with a focus on topical drugs. All told, the multi-state suits have named over 30 pharma companies as defendants along with dozens of industry executives. And given that every state is now involved in at least one of the lawsuits, it is one of the most far-reaching antitrust legal efforts in U.S. history.

"The scope is huge" Abbott says. "But the fact that all 50 states are involved is not surprising given that generic drugs are a big ticket item across the country."

Although the initial multi-state complaint named Heritage Pharmaceuticals as a "consistent participant" in collusion, the 2019 lawsuit placed Teva at the heart of the conspiracies.

"At the zenith of this collusive activity involving Teva, during a 19-month period beginning in July 2013 and continuing through January 2015, Teva significantly raised prices on approximately 112 different generic drugs," the complaint alleges. "Of those 112 different drugs, Teva colluded with its 'High Quality' competitors on at least 86 of them

> **“For years, the DOJ has used amnesty agreements to get someone to snitch. That’s really how you crack a cartel.”**
>
> — Alden Abbott

(the others were largely in markets where Teva was exclusive). The size of the price increases varied, but a number of them were well over 1,000%.”

Despite the evidence presented in the complaints, settlements with states have already begun. In June, Teva struck a deal with Mississippi to put the issue to bed for $950,000. As part of the agreement, Mississippi said it would no longer seek action in the multidistrict litigation against Teva — a conclusion the company cheered.

“We believe the modest settlement amount reflects our position on the lack of evidence for the allegations against us,” the company stated.

In addition to the multi-state lawsuits, some generics companies are also facing proposed class action suits from purchasers, shareholders and patients.

And, of course, there’s the situation with the DOJ. In addition to its charges against Teva, six other companies and four executives have been slapped with criminal charges by federal prosecutors. Of those accused, five companies — Taro Pharmaceuticals, Sandoz, Rising Pharmaceuticals, Heritage Pharmaceuticals and Apotex — have entered into deferred prosecution agreements and have agreed to pay fines and cooperate with the investigation.

But like Teva, Glenmark — another company accused — has held out on striking a deal with the DOJ and both companies have vowed to continue fighting the charges.

On the defensive

On an investor earnings call this February, Teva’s CEO, Kåre Schultz quipped that if there was price rigging in the industry, it would be the “worst cartel in history” given that prices for generics in the U.S. are lower than they are in Europe, according to a study by the RAND Corporation.

Through it all, Teva has continuously pushed back on price-fixing allegations, pointing to overall pricing trends in the industry as evidence that widespread collusion hasn’t occurred. Glenmark has presented a similar defense and argued that the charges lack merit.

“We strongly disagree with the charges being advanced by the Justice Department and do not believe the evidence supports the government’s case,” a Glenmark spokesperson told Informa Pharma’s Generics Bulletin in July 2020.

So far, neither company has responded to specific allegations made in the various legal complaints, but Field says that if they do head to trial, Teva and Glenmark could argue that their behavior did not impact prices.

“The most common defense would be that it didn’t affect competition,” he says. “On the other hand, the rule for price fixing is really strict and straight-forward.”

"If you see an agreement of price fixing, it's illegal. Period," Abbott says. "And if there is such evidence, there is not a good defense."

To prove collusion, Field says that the prosecution would have to show that pricing fluctuations were more than circumstantial and changed after communication between the companies. It's evidence that the Connecticut attorney general's office says it has. Earlier this year, in fact, the office unsealed images of a "Diary of Collusion" created by a former Sandoz sales exec — now cooperating with the investigation — that allegedly shows detailed notes of price information sharing between competitors.

Whatever defense Teva and Glenmark present, Abbott says the fact that other companies have turned state's evidence will make the charges difficult for the companies to contend with.

> **On an earnings call this spring, Teva's CEO said it could be a "significant period of time" before its civil and criminal cases head to trial due to the pandemic.**

"[The companies] could deny the charges and say they've been falsely accused," Abbott says. "But you could have executives from five other companies testifying against you…so that's a pretty risky strategy, in my view."

If found guilty, the companies could face much higher penalties than they would have had to pay under a settlement agreement. In its charges, the DOJ warned that the antitrust offense carries a statutory maximum penalty of $100 million, but that it could be increased to "twice the gain derived from the crime or twice the loss suffered by victims if either amount is greater than $100 million." The penalty calculation implies that Teva could be fined twice the $350 million the DOJ claims the drugmaker overcharged consumers.

DOJ criminal settlement timelines and fines

$7 MILLION
Heritage Pharmaceuticals
May 2019

$3 MILLION
Rising Pharmaceuticals
December 2019

$195 MILLION
Sandoz
March 2020

$24.1 MILLION
Apotex
May 2020

$205.6 MILLION
Taro Pharmaceuticals
July 2020

"If you look at the alleged co-conspirators that have settled, they are settling for high nine figures," Linehan says. "The numbers are off the charts."

The fines and potential jail time for specific executives named in the criminal suits are bad enough. But an even more damning penalty could await a company on the other end of a guilty verdict — being left out of federal programs for a number of years.

"Teva could be excluded from eligibility to participate in Medicare programs which would be a serious, and potentially fatal, penalty for a drug manufacturer," Linehan and Peck wrote last year in an article for Steptoe. "This consequence was likely one of the driving forces that led to five other drug manufacturers reaching deferred prosecution agreements with the Antitrust Division."

On a broader scale, the increased scrutiny might encourage all generics companies to begin to tip-toe around any behavior that could be viewed as shady.

Feeling the heat

Corporate changes

On Oct. 1, the DOJ announced a new string of civil settlements related to the ongoing price-fixing probe. This time, Taro, Sandoz and Apotex admitted to wrongdoing and agreed to pay penalties related to allegations that the companies paid and received compensation that violated the Anti-Kickback Statute. All told, the civil settlements will amount to $447.2 million in penalties being paid by the companies — and that's on top of the $424.7 million the trio coughed up to settle its criminal charges last year.

As part of the new agreements, the DOJ reported that all three companies will enter into a five-year corporate integrity agreement (CIA) that includes monitoring and price transparency provisions.

"They also require the companies to implement compliance measures including risk assessment programs, executive recoupment provisions and compliance-related certifications from company executives and board members," the DOJ reported.

According to Abbott, mandating these kinds of inhouse procedures are a common part of settlement agreements and are designed to shift the way companies fundamentally do business.

"The effort is to have inhouse antitrust training and reviews with larger companies where you reduce the incentives for sales managers and executives to do that sort of thing," he says. "But it has to be different than just going through the motions, like sending an email to employees — you have to train people."

Companies who take that step — either voluntarily or because it's mandated — could also receive some leniency from the DOJ if they found themselves in the agency's crosshairs.

"Beginning in 2019, the anti-cartel people at the DOJ instituted a new policy that in effect says 'We'll give you some credit if you had a truly strong inhouse antitrust compliance program,'" Abbott says.

An industry under pressure

As the drama unfolds and the industry watches, Field says he can imagine that other generic drug companies — including those not involved in the price-fixing allegations — could be thinking of ways to proactively prevent antitrust behaviors among their ranks.

"Potentially, it could spook some companies into thinking that they have to be more careful," he says. "And some may even evaluate whether or not they want to stay in the market."

Linehan also says that from his experience, these kinds of widespread allegations typically cause other companies in the industry to reevaluate best practices.

"It has happened with clients I've had in other industries," he says. "When there's an industry-wide focus from a law enforcement perspective, everyone is watching and adjusting the strength of their compliance program."

Specifically, Linehan says that drugmakers and their attorneys are likely to focus on closely monitoring communications with competitors. Companies could also make sure they have a robust whistleblower program and anti-retaliation rules to complement it.

Because pharma is already a highly regulated industry, Linehan points out that companies are used to implementing comprehensive compliance programs. But what's really key is that antitrust compliance efforts are supported at all levels of the company.

"You have to pick the right leadership and you need an engaged board. Then your compliance department should operate with a degree of autonomy so that the upper levels still fall within their net, and can ask the right questions of the executives," Linehan says.

The DOJ's "Evaluation of Corporate Compliance Programs in Criminal Antitrust Investigations," guidance also explains that in order for a company's compliance efforts to be considered effective, the program will have to include: a comprehensive design, adequate resources, an emphasis on promoting a culture of compliance, antitrust risk assessments, and monitoring and auditing techniques.

Will the fines work?

From a regulatory point of view, Abbott says that strict penalties may still be the best medicine for preventing price-fixing schemes.

"The best thing is to have very high fines," he says. "Because executives don't like to go to jail or be ruined financially."

But whether or not the current risk/reward calculation for potential cartels favors compliance is still a matter of ongoing debate.

In 2015, antitrust scholars released research showing that in 71 different cartel cases spanning across multiple industries between 1990 and 2014, the victims did not recoup their initial damages 80% of the time.[1]

In the absence of systematic changes, high penalties could just be treating the symptoms of shady schemes — and not the disease.

Re-imaging the industry

When asked how the generics companies can balance the diverging forces of maintaining low costs and an abundant supply of drugs, Field takes a mental step back and offers a re-imagining of the industry.

"Want me to be the king of pharma for a moment?" he asks with a smile. "I think we need more vigorous enforcement of manufacturing standards. That would raise production costs, but it would winnow out the strong from the weak."

Essentially, Field argues, the focus should shift from prices to quality. It wouldn't be an environment that every company would survive. But if the public and purchasers were willing to get on board with that shift, it would create a healthier and more sustainable industry.

"Large organizations like insurance companies and large retailers could use their negotiating power to demand higher quality, and there could be incentives for them to seek the highest quality, not just the lowest price," he says.

Just like there are cleanliness ratings for restaurants in some cities, Field says regulators could implement a system

that rewards better quality, such as publishing inspection results.

Davis says that society should look at the big picture around generic drugs. While admonishing any individual companies that have admitted to price fixing, he also cautions that the industry shouldn't be judged as a whole.

"I think like everything else nowadays, this is a situation that has become overly politicized," he says. "That's not to say that there haven't been certain behaviors in the market. But I think it has been outliers, rather than a systemic issue."

As the public conversation around the supply and prices of drugs continues, Davis says that the interest in reshoring generics production could be a step in the right direction — as long as it's backed up with appropriate incentives for the industry.

"The legislative packages providing front-end incentives to encourage more domestic manufacturing are great," he says. "But you're going to need a sustained change in the marketplace and policymakers have to understand the overall dynamics of the market."

In the current political landscape, it's a tough sell — drug prices are one of the few issues that can get Democrats and Republicans fighting on the same side. But the bottom line, Davis says, is that the public emphasis should shift from low prices to recognizing the value of generic drugs.

"One of the biggest health care issues right now is: How do we lower the price of prescription drugs? But with some drugs, you could make the argument that we're not paying enough…I always thought that if you can get a 30-day supply of some medications for less than a cup of coffee, I'm not sure if we, as a society, have our priorities right," he says. "My hope is that policymakers continue to recognize the value generic drugs are providing to our health care system."

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Joel Wayment
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Ensuring access to critical medications

Key considerations pharma manufacturers should explore before, during and after a supply chain disruption

In the past 18 months, two major events have forever changed how pharma manufacturers view, plan for and manage supply chain disruptions in the United States.

The first was COVID-19. As the world shut down, consumers realized everything they wanted could be purchased online while carriers, already struggling with labor challenges from the pandemic, were caught off guard as they faced increased demand — creating delays not just for the general population, but for the companies that rely on carriers and the supply chain to keep their businesses running. On top of that, international delays became an issue as other countries including China and Italy dealt with their own initial COVID-19 waves. For pharma manufacturers, the pandemic created significant barriers to getting their therapies to providers and patients on time.

The second major incident to cause massive disruptions was Winter Storm Uri, which impacted the southern and eastern parts of the U.S. in February 2021. Despite the fact that the U.S. faces around 20 named winter storms annually, Uri brought unique challenges, paralyzing multiple carriers and their main shipping hubs, resulting in six million COVID vaccines being delayed. Experts shared that the average dwell time — the amount of time a shipment sits waiting for pickup or drop-off — increased by 308% the week of the storm.

These incidents created challenges for pharma manufacturers, hospitals, pharmacies and patients who rely on a stable and predictable health care supply chain. Yet, even as the U.S. struggles to understand what is specifically a COVID-19 issue versus what is the future of the U.S. supply chain overall, pharma manufacturers know they have a responsibility to manage through more unexpected supply chain hurdles.

Here we will outline some key considerations and actions pharma manufacturers should explore before, during and after a supply chain disruption— whether they manage their supply chain directly or outsource to a distribution supplier — to prevent delivery delays or potential drug shortages and ensure life-saving medication is getting where it needs to go.

Before the disruption

The challenges created by the pandemic and Winter Storm Uri have clarified the need for pharma to better understand the risks of the supply chain channel strategy, and where they fit into the mix. Contingency planning must happen before a disaster strikes — and can help with both seen and unseen supply chain incidents.

Monitor what you can

While Winter Storm Uri came as a shock to much of the South, many winter storms and hurricanes can be seen up to a week in advance. By dedicating time to monitoring storms, manufacturers can make informed decisions with clients or logistics partners if they should: stick to the agreed-upon schedule, use next day air versus ground to get ahead of the storm, or send extra product to critical locations in case the storm causes a transportation issue immediately after.

Understand carrier engagements

Many times, manufacturers look at shipping as a linear movement

across the country, but it rarely is. It's vital to know how your products move through the supply chain, including how products get from one location to another, and what hubs are involved. The reason Uri was so devasting for the U.S. supply chain was how many carrier hubs were located in affected areas, including FedEx Express' primary distribution center in Memphis and UPS' hub in Nashville. The storm also closed port container terminals in Houston and brought trucks between the U.S. and Mexico border to a standstill.

It's important to talk to your logistics partners about the option to have engagements with multiple carriers. This gives you more of an opportunity to not have all of your product halted in one major hub area in the event something happens, giving your business a chance to pivot.

Know thy customer

Having a good understanding of how much inventory your customers carry could be the key to weathering the storm. If you know that the supply chain is about to be delayed by a number of days, this information can help make informed decisions about whether to ship out the supply immediately, or wait until after the disruption has been resolved.

Consider alternatives to typical supply/demand systems

There are many ways to ensure product is available to your customers so they do not need to worry when the supply chain is strained. With specialty drugs accounting for 73% of all medicine spending growth between 2011-2016,[1] the cost of drugs continues to be one of the largest concerns for hospitals and providers, who look for innovative ways to store the expensive drugs without paying for them upfront.

Consignment inventory can lighten the demand during times of crisis by enabling your customers to stock expensive drugs and therapies, without the upfront cost. By stocking product still owned by the pharmaceutical companies, there is less of a concern that supply chain disruptions may result in access issues for critical medications.

While it may seem too late to make critical decisions during a disruption, the actions companies take during these important moments have the potential to save lives.

During a disruption

While it may seem too late to make many critical decisions during a disruption, the actions companies take during these important moments have the potential to save lives.

Communication is key

The supply chain can be a fickle beast. A disruption that occurs in the Southwest could easily lead to delays in the Northeast, but customers may not understand that. They need to be aware of updated shipping and delivery timelines and understand why these delays are taking place. At the same time, manufacturers need to understand a customer's needs and priorities for medications. Communicating early can enable manufacturers to set appropriate expectations with customers so they can manage their existing inventory wisely.

Once the disruption is over, communication is necessary to understand whether non-standard delivery times (evenings or weekends) are acceptable for a customer. If you understand your customer's inventory, you can also prioritize which orders need to be shipped first to prevent critical drug shortages.

In some dire cases, by understanding customer inventory, manufacturers can alleviate supply chain delays by sharing inventory between customers directly.

Understanding your products and the cold chain

While it is rare, disruptions have the potential to result in a total shutdown of product movement. The blockage of the Suez Canal is a perfect, if not extreme example, of this taking place. Billions of dollars of products were stalled for a week as officials worked to free the ship. Had any of those ships contained drugs requiring cold storage and handling, the products may have expired during the canal blockage or ship backlog.

This example paints a picture not for just risk management, but for pharma manufacturers' need to understand their products' stability, and if it can be extended if cold storage cannot be maintained. Manufacturers may also consider investing in backup coolers that can last longer (120 hours) versus the normal-use (36-48 hours) coolers during times with a higher potential for disruptions like the holidays or hurricane season.

Collaboration with carriers

Carriers are on the front lines of supply chain disruptions. The better your partnership and collaboration with them, the better the outcomes will be as things do start to open back up or clear.

Collaboration with carriers can also help businesses understand if the delays will continue, and if manufacturers need to look into other options. Having a

team — whether in-house or an external logistics partner — is key to developing these relationships in time for a crisis.

Additionally, while less cost-effective, understanding options with couriers can also allow businesses to bypass the traditional supply chain and ensure medication is getting to where it needs to go.

When the storm has passed

Supply chain disruptions large or small can put significant pressure on pharma manufacturers and the customers and patients they support. While it's necessary to breathe a sigh of relief after they are over, there are still steps to be taken to ensure we are doing our part to assist with the fragile health care supply system.

Customer communication

Customer communication surrounding the disruption cannot end once the crisis has passed. They will expect more communication immediately after a disruption on when an order will arrive, if there are precautions that should be taken, and if they should expect delays on future orders based on a backlog of shipping delays. This is an excellent time to overcommunicate to customers on drug stability if the delay resulted in a longer period of time in transit than expected or allowed.

Review and assess

The final step is just as important as the first steps, and, in actuality, starts the process of managing through supply chain disruptions over again.

Now is the time to review what worked and what didn't with logistics partners, customers and carriers. The global supply chain continues to be disrupted, and as new players enter the market, we may see new changes — and new disruptions. Assessing what worked will lead to a stronger strategy for the next time, and ensure customers feel seen in the process.

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Maintaining compliance beyond the pandemic

Investing in employee readiness will be crucial to present and future success

The challenges the pharmaceutical industry faced in 2020 — from the COVID-19 pandemic to the chaotic economy to political pressures — look more and more like a new normal rather than a temporary crisis.

For example, the Biden administration invoked the Defense Production Act to speed up the production and distribution of COVID-19 vaccines, all but ensuring that pharma manufacturers will be busy for months, even years ahead. Industry business practices are transforming, with less travel and more remote work possibly remaining — even after the current crisis finally ends.

Subsequently, risk and exposure for the pharma industry are permanently changing, including in the areas of employee health and safety, data privacy and cybersecurity, and virtual interactions. A fundamental shift to other communication channels (e.g., email, video chat) opens up compliance concerns that pharma may not have previously flagged as a considerable risk.

Another potential risk that has emerged during the pandemic across a range of industries is the greater tendency for employees to not speak up when they see or learn of something that's noncompliant. Amid the ongoing economic crisis, people don't want to raise their hands out of fear of losing their jobs, and remote work has made it more difficult to immediately tell a manager about a problem. Without a strong "speak up" culture, both new and old risks become greater threats that could turn into something more catastrophic.

In this new normal, pharma manufacturers must address emerging risk, prioritizing prevention and mitigation strategies within organizational constraints. This includes training employees on appropriate behaviors now that they must conduct business differently.

Assessing, reassessing risk

Because so many stakeholders are suddenly facing new and updated exposure to risk amid the pandemic, an organizational approach to addressing risk must be a priority. Compliance teams should follow three steps in their strategies:

1. Partner with risk area owners and business leaders to understand what's changed since the pandemic began.
2. Update each exposure in your organization's risk registry and identify corresponding operational process changes to reflect the current reality.
3. Share and confirm alignment on these changes with all risk stakeholders, and take care to ensure communication doesn't get siloed — an ongoing process that can easily stall if you're not proactive.

Tapping technology for training

More than ever, measuring the success and failure of compliance training — especially with higher-risk topics and activities — is vital for pharma manufacturers.

Technology can help assess where employees have a solid understanding of appropriate behaviors as well as where clarity issues or behavioral gaps exist around important concepts. In the pharma industry in particular, it is critical for employees deemed to be performing higher-risk activities (e.g., sales reps interacting with providers) to receive tailored training based on simulations pertaining to their day-to-day, and for compliance teams to ensure understanding by segmenting the resulting behavioral data based on role or function.

In addition to identifying micro-cultures, this data can be provided to managers and function leaders to drive targeted, focused conversations on the ground and reinforce critical concepts.

Deep behavioral insights — something more than counting how many employees merely completed a course — go a long way toward measuring efficacy. When compared side by side with operational and transactional data, including helpline cases, audit findings and expense tracking, behavioral data can provide a window into hidden risk that is percolating within the organization.

For example, if you see behavioral insights coming from training simulation indicating employees in a particular function don't understand adverse event reporting, you check the corresponding helpline trends for the same risk. If you see zero reported incidents, underreporting is likely. Simply sending a targeted communication to this audience can surface self-reported issues that have previously gone unflagged.

The compliance program's ability to detect wrongdoing in this manner is a perfect example of a program working in practice per the updated Department of Justice guidance.* The guidance, which is intended as a reference of information and questions for prosecutors to ask companies when evaluating their compliance programs amidst investigations and subsequent charging decisions, provides a lens into how we should be structuring our programs.

In recent years, artificial intelligence has also emerged as a valuable tool within compliance training technology. AI can leverage an employee's prior interactions and behavioral insights from a course to tailor the current training experience — ensuring the time is spent on each person's individual needs and building upon past knowledge.

Compliance must be more than rules. It needs to focus on human behavior and emotions in real-world situations.

Humanizing training strategy

Many companies view compliance training as teaching employees an amalgamation of laws and regulations. This approach ignores the most important factor in the training process: the person experiencing the learning. Compliance must be more than rules. It needs to focus on human behavior and emotions in the real-world situations that employees may encounter on the job.

This fresh approach requires training that engages and empathizes with users, rather than trying to make them into junior lawyers. The right messaging can deliver important compliance knowledge and develop EQ as well as IQ and make the information stick long after a digital course ends. Even during a pandemic, people aren't necessarily tuning out training; they simply require content that is relevant to and resonates with them. Treat them with humanity and they will absorb and take action on what's being taught. Approaches such as spoken word, humor or sitcom-style microlearning reinforcement can be powerful here.

Senior leadership must take an active role in setting the tone for compliance and a culture of learning. During any crisis — and especially this one — employees take their cues from the executives making the big decisions. Leaders who continually promote value-based messages and connect with their employees inspire those employees to care about learning because, ultimately, compliance is good for the organization. This effort also promotes the "speak up" culture that is so essential in the permanently altered workplace. Managers may struggle to figure out how to do this on their own — this is why compliance teams must make it a simple lift by providing them with behavioral insights and a library of microlearning resources that can be utilized to drive conversation, conduct small team challenges, and deliver a consistent message across the organization.

Mid-level managers — the leaders who most often guide and interact with the employees expected to execute the principles learned in training — must

* On June 1, 2020, the Department of Justice updated its guidance document, Evaluation of Corporate Compliance Programs, superseding previous guidance from April 2019 and February 2017.

also contribute to this humanized compliance. If teams and departments become too insular, microcultures can form, and the actions and ethics of employees may stop conforming to compliance best practices and the organization's mission. (A "speak up" culture can also disappear in this scenario.) Managers can be instrumental in countering these microcultures with the examples they set as well as by encouraging two-way communication when compliance challenges arise with their reports.

Compliance for now, training for the future

All eyes have been on pharma manufacturers as the world looked to them to help end the pandemic. The industry has responded with unprecedented innovation and efficiency. This success inevitably means faster decisions, higher pressure to perform, more scrutiny and more room for error to go unnoticed, which means pharma manufacturers must update their risk strategies as well as rethink how they approach preparing their workforces through training and communications.

Over the years, compliance training tactics such as video and narrated PowerPoint that were once thought to be groundbreaking have stopped resonating with users. A new, humanized strategy in which employees are valued rather than lectured to, and learn by doing instead of watching or reading, offers the best path.

A new, unknown normal awaits on the other side of the pandemic. Investing in employee readiness will be crucial to investing in the present and the future. Is your compliance program and employee training up to the challenge?

Summarized updates from the 2020 DOJ Evaluation of Corporate Compliance Programs

Risk assessment

Endeavor to understand why the company has chosen to set up the compliance program the way that is has, and why and how it has evolved over time.

- Updates and revisions: Is the periodic review limited to a "snapshot" in time or based upon continuous access to operational data and information across functions?
- Lessons learned: Does the company have a process for tracking and incorporating into its periodic risk assessment lessons learned either from the company's own prior issues or from those of other companies operating in the same industry and/or geographic region?

Policies and procedures

- Addition to design: What's the company's process for designing and implementing new policies and procedures and updating existing ones? Has that process changed over time?
- Accessibility: Have the policies and procedures been published in a searchable format for easy reference? Does the company track access to various policies and procedures to understand what policies are attracting more attention from relevant employees?

Training and communications

- An acknowledgment that training programs may contain shorter, more targeted training sessions to first identify timely identification and reporting of issues
- Form/content/effectiveness of training: Whether online or in-person, is there a process for employees to ask questions arising out of the trainings? Has the company evaluated the extent to which the training has an impact on employee behavior or operations?

Confidential reporting structure and investigational process

- Effectiveness of the reporting mechanism: How is the reporting mechanism publicized to third parties? Does the company take measures to test whether employees are aware of the hotline and feel comfortable using it?
- Resources and tracking of results: Does the company periodically test the effectiveness of the hotline?

Third party management

- Assess whether the company knows the risks posed by third party partners
- Management of relationships: Does the company engage in risk management of third parties throughout the lifespan of the relationships, or just during the onboarding process?

M&A

- Ensure a process for timely and orderly integration of the acquired entity into existing compliance program structures and internal controls
- Due diligence process: Was the company able to complete pre-acquisition due diligence and if not, why not?
- Connecting due diligence to implementation: What has been the company's process for conducting post-acquisition audits at newly bought entities?

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Outsourcing goes international

Biopharma offshoring is predicted to reach near-record levels in an unexpected surge

Outsourcing in biomanufacturing has long been on a steady upward trend. This year, there are few indications of significant slowdown. This is partly due to COVID-19 — according to our recent research, 70% of the biopharma industry is planning to increase their future outsourcing in an effort to address supply chain risks.

Small companies continue to be major sources for innovation, and many have an active pipeline of products in development. Since many smaller companies have no manufacturing capabilities, and often don't plan to develop those core competencies, these companies need the technical expertise of contract manufacturing organizations (CMOs) to help bring their products to clinical stages, and eventually to commercial manufacturing operations. Larger, more established companies will also continue to search for partners to get their established products outsourced in order to free up internal capacity for new, upcoming products in their pipelines. This trend is not all that surprising.

But what is surprising from our Annual Report of Biopharmaceutical Manufacturing[1] is the growth in international outsourcing, or offshoring. Our survey found that nearly two-thirds of respondents indicate they expect to increase their levels of offshoring in process development.

Increase in offshoring of biologics

In the 2021 Annual Report, we evaluated responses over 10 years (from 2011 to 2021) regarding the percentage of biomanufacturers/developers that plan to offshore (outsource internationally) at least some (any) of the indicated activities within the next five years.

While all areas of manufacturing reported record or near-record levels of outsourced and expected outsourced activities, in 2021 alone, there was a significant increase in planned offshoring for all areas. An example of this can be seen in process development specifically, with 64.4% of developer respondents reported expected offshoring, up significantly from 34.9% in 2020, and the second highest recorded amount in this area since collecting data (2019 levels were 69.1%).

"Biomanufacturing operations" is another example where respondents report a significant increase in expected offshoring in the next five years, with 69.3% of respondents, up significantly from 34.9% in 2020, and the highest recorded amount in this area since collecting data. All other areas tracked for offshoring trends indicated record levels of expected offshoring. Offshoring continues to be an attractive option for companies looking to expand their reach outside their

PHOTO BY CHARLES DELUVIO ON UNSPLASH

domestic markets, for those seeking second source manufacturing processes, and for other reasons.

Offshoring is still perceived to provide cost-savings. However, we found that other benefits, traditionally not associated with international CMOs, are also important to those looking to offshore their manufacturing. These features can be harder to quantify than calculated cost-savings. Factors such as quality and reliability, as well as regulatory competence, are increasingly being associated with offshoring among emerging market CMOs as well.

These factors are recognized as critical for decision-makers to consider when choosing an international partner. In a 2020 survey, we asked respondents: "Which of the following factors would you consider MOST IMPORTANT if outsourcing to new regions, such as China, India, and Brazil?" We found that factors associated with quality and reliability were on the top of the list. The top five selected leading factors were:

- Meets international GMP standards, 67.2% of respondents
- Protect intellectual property, 52.5% of respondents
- Comply with my company's quality standards, 50.8% of respondents
- Pricing/cost of services, 37.7% of respondents
- Demonstrated ability to do the work, 34.4% of respondents

Based off these results, it is clear that respondents that are offshoring expect similar levels of demonstrated quality that are in line with GMP standards — and this is significantly more critical than any potential cost savings.

Favorite offshoring destinations

Regulatory concerns in outsourcing continue to be on the minds of biomanufacturers today.

The necessary expertise primarily exists in more established markets. A lack of regulatory and GMP manufacturing expertise required by decision-makers in developed countries can create considerable hurdles for developing market CMOs.

Perceived lack of regulatory and GMP manufacturing expertise trickles down to the decision-making process when choosing which country to favor when offshoring manufacturing. In our annual report, we evaluated the "strong likelihood" or "likelihood" of U.S. respondents considering countries for international outsourcing. We identified 18 major countries that may be likely candidates for international outsourcing. For U.S.-based companies, the top four results can be seen in Exhibit 1.

In 2021, Germany leads the group with 24.6% and China comes second with 21.3% of respondents indicating them as at least likely candidates for offshoring. For China, this differs sharply from the situation eight years ago when the country barely registered as a possible outsourcing destination.

For European decision-makers, the U.S. and Germany tie for first, with 42.9% of respondents indicating the countries would be a "likely" or "strong likely" international outsourcing destination.

So far, most outsourcing to CMOs in developing countries has involved less-regulated biosimilar and/or biogeneric drug manufacturing. These types of services have typified offshoring from developed to developing countries so far. While increasing overall, it can be seen that at least for the near future, offshoring of manufacturing tasks to CMOs in other countries, particularly to developing countries, will continue to be selective and not a major threat to U.S. and European CMOs for other areas of the market. This could change as these developing countries invest in capabilities to accommodate the regulatory requirements in larger markets, making them more attractive destinations for some of the more critical and more regulated manufacturing projects.

> "The issue of regulatory competence is especially a concern when developers consider outsourcing core activities.

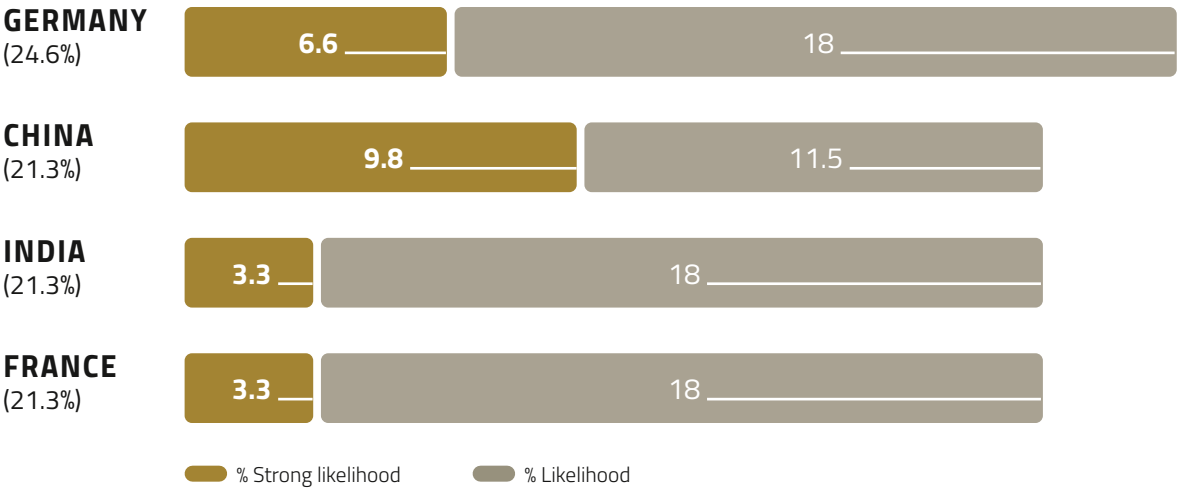
However, China in particular with its ongoing investments from Western CMOs and its emerging domestic industry will likely become a global player in the CMO space for biologics within five to 10 years and potentially emerge as a top choice for offshoring regulated and less-regulated manufacturing.

Offshoring to help gain a foothold in China's developing market

One often overlooked benefit of offshoring is that it allows developers to quickly gain a visible foothold in a developing market. An example of this can be seen in China. BioPlan recently published an extensive study and directory of CMOs in China (PRC).[2] As a result of an increase in growth of its domestic biopharmaceutical industry and bioprocessing activities, China's CMOs have also rapidly expanded their capacity to meet demand in China and have become increasingly attractive options for Western companies looking to offshore. This increase has occurred to meet demand from the large domestic population, particularly in terms of the expansion of biogeneric monoclonal antibodies manufacturing for domestic consumption.

EXHIBIT 1

Select countries seen as "strong likelihood" or "likelihood" as outsourced capacity destinations by 2026



SOURCE: 18TH ANNUAL REPORT AND SURVEY OF BIOPHARMACEUTICAL MANUFACTURING CAPACITY AND PRODUCTION

While a large part of this increase can be credited to the growing number of biopharmaceutical developers and the potential of the domestic market in China, this expansion has also occurred due to outsourcing from Western companies. CMOs currently play a big role in how Western biopharmaceutical developers will gain a foothold in China, utilizing their production capabilities to meet the domestic demand in the area. This has been spurred by changing central government laws and regulations that traditionally ruled out drugs being manufactured by CMOs and other third parties. This interest among Western companies for outsourcing bioprocessing to China CMOs has been increasing over the decade. China was cited by 40% of respondents as an outsourcing destination, compared with only 2.8% back in 2009.

Regulatory concerns for CMOs outside the U.S. and EU

The issue of regulatory competence is especially a concern when developers consider outsourcing of core activities for which regulatory requirements related to manufacturing are more stringent, such as GMP manufacturing.

Regulatory approvals for marketing products for the U.S. and EU markets are increasing for other developed and developing countries. However, as it currently stands, most rest-of-world facilities have only approvals or inspections related to making products for local and regional markets, or simply operate with no regulatory approvals or inspections. As a result, many of the activities offshored to these emerging countries are not for GMP operations.

However, this is changing. For example, biosimilar products made in India and China will increasingly become available in major markets, and several Chinese companies are launching biosimilars in the U.S. and EU markets. At the same time, as other countries increase their regulatory approvals, they will increasingly become candidates for offshoring opportunities as well. Eventually, the current leading developing Asian countries with CMOs now considered and used by Western customers will likely see much of their business shift to new CMOs in even lower-cost countries.

As the markets for developing countries continue to evolve, offshoring trends will continue to increase to help Western companies meet the demand represented by these emerging markets. We anticipate that the trends mentioned here will continue for five to 10 years, with the potential for continuity past that.

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Center for Breakthrough Medicines

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A right-first-time approach to development

Commonly overlooked issues may have a deep impact on cell and gene therapy commercialization timelines

The industrialization of cell and gene therapies (CGTs) is a prominent issue in the biopharma industry. These novel medicines have rapidly advanced to the stage where both significant efficacy and safety have been achieved in the clinic. Unfortunately, the existing manual, labor-intensive, open lab-scale manufacturing solutions for viral vector production and genetic modification of cells are not practical to properly commercialize these innovations.

Equipment vendors, raw material suppliers and drug developers are working together to address these issues. While some challenges, such as scalability and capacity are well-known, there are others that have received minimal attention, yet can have a deep impact on timelines.

Even when the goal is racing to be the first-in-human-studies to demonstrate a proof of concept, companies need to stay focused on striving for a right-the-first-time approach in their process development efforts. These efforts can be made internally or by connecting with an experienced contract development and manufacturing organization.

Investing in robust cell lines

Unlike the monoclonal antibody (mAb) field where manufacturing is standardized using platform technologies and producer cell lines, the CGT field is still in early growth stages and just beginning to define good systems for viral manufacturing. Most viral vectors are currently produced in human HEK 293 cells. In general, cells are not designed to make viruses and require additional helper function using recombinant techniques.

To do this properly, time must be invested in developing robust cell lines to consistently achieve the yield, quality and potency required. Having these robust cell lines offers stability and high viral production capacity, which is essential to a streamlined process. Rather than using multiple different cell lines with limited viral production abilities, it is better to take the time to understand the specific viral vector requirements and develop a well-characterized cell line that can meet expected production demand.

Start with good plasmids

Proper sequencing of plasmids is necessary to ensure that no unwanted mutations are present. Tradition methods such as 2x Sanger sequencing, however, cannot efficiently pick up mutations that can impact viral vector quality.

The emerging and best approach is to use next-generation sequencing (both long and short read sequencing) to efficiently validate sequence integrity of plasmid ITRs and LTRs to obtain a clear picture of genetic

sequencing information encoded within these plasmids. ITRs and LTRs determine not only the packaging of DNA for the virus (full vs. partial vs. empty capsids), but also the in vivo potency and long-term stability of the resulting gene or gene-modified cell therapy.

In addition, when plasmids are produced in incorrect bacterial strains, the master cell bank can contain undesirable, low-level sequence variants that are not detectable using Sanger sequencing. This situation can significantly impact time to market, as regulatory bodies often consider such "contaminated products" as mixed drug products that could impact approval.

Most autologous CAR T-cell therapies are produced by modifying patient T cells using lentiviral (LV) vectors, which are RNA viruses. These viruses can show decreased potency issues due to a phenomenon referred to as cryptic splicing, in which the gene of interest being placed into the T cell is aberrantly spliced resulting in reduced expression.

Conventional polymerase chain reaction (PCR) analysis cannot detect cryptic splicing, so the genome appears whole. The use of next-generation sequencing is therefore essential to ensuring the production of clean, high-titer viral vectors with high potencies for use in the production of modified cell therapies.

Explore the entire formulation space

Just as important as understanding the cell line and raw materials is fully exploring the entire formulation space for CGTs prior to entering the clinic. Often the rush to get to market will encourage some companies to skip this important step in developing a drug with all the required quality attributes. But when gene therapy formulation is an afterthought, it can require great time and expense on the back end for reformulation or even further process development.

It is true that for certain gene therapies, very specific drug product design is necessary as dictated by the indication and route of administration. Eye diseases are a primary example. Delivery into the eye necessitates very small drug volumes and therefore very high viral vector concentrations. There is an added layer of complexity with early clinical trials given that the dose range is often wide; formulations need to be not only stable at high concentration, but amenable to dilution to the lowest dose required for the study.

Both high concentrations and dilution processes can be detrimental to viral vectors. Effective formulation of gene therapy products prior to phase 1 trials is the best strategy for overcoming these challenges. It is particularly useful to have extensive experience working with different adeno-associated virus (AAV) serotypes and other viral vectors. This knowledge can be leveraged to predict which excipients will afford the optimum formulation.

What about subvisible particles?

Gene and gene-modified cell therapy developers should monitor the presence of subvisible particles beginning at the earliest development stages. As drug products move to later development stages, regulatory expectations regarding subvisible particles (which have immunogenicity potential that can lead to drug degradation) become stricter and more extensive.

Learning in phase 2 that a CGT candidate is suboptimal because it contains subvisible particles is too late. The formulation may need to be modified or the entire process revisited, both of which can add significant cost and delays. The best approach is to determine how filtration, dilution and other unit operations affect subvisible particle generation at the beginning of process development. Applying this knowledge throughout the later stages of development can help avoid issues associated with excessive subvisible particle content in the final product.

Build in flexible manufacturing solutions

Most cell therapies developed to date have targeted blood cancers due in part to the challenges associated with treating solid tumors, which requires selectively delivering cells to the tumor site and getting them to penetrate deep into the

Kayla Pasake, Research Associate; Dana Cipriano, Vice President of Testing and Analytical Services; and Allyssa Staboleski, Senior Scientist, Center for Breakthrough Medicines

tumor. The tumor microenvironment resists attack and targets tumor cells without killing host cells, which can be difficult due to a lack of well-defined, tumor-specific antigens.

New technologies such as bispecific CARs and tandem CARs take advantage of certain features of tumor cells to ensure targeted delivery and penetration. Determining the maximum tolerated doses for such cell therapies (which often need to be high to tackle the large numbers of cancer cells) is difficult, however. Dose-escalation studies are generally needed.

Such trials are particularly challenging with autologous cell therapies given that there is one batch per patient. In addition, side effects with cell therapies typically can take days or weeks to manifest. Therefore, cohorts often overlap, with higher doses administered to patients in the next cohort without knowing the full response of the previous cohort.

It is not uncommon in the middle of these escalation studies (and in the middle of manufacturing additional product) to find that further dose escalation is not possible. The challenge then becomes manufacturing de-escalation.

The best solution is to establish a flexible process that allows for changes in production levels. One option is to adjust cell concentrations, while keeping the intended volume/container the same. However, a modular approach to product containment, where every batch consist of several sizes of containers, allows 2x-5x de-escalation. The former presents additional analytical challenges that are not an issue in the latter strategy.

Ideally, during early phase development, multiple scenarios are simulated with respect to potential dosage demand. The key is to find the optimum balance between what might be needed for the clinical studies and what is possible on the manufacturing floor. That is not always obvious, because the cells used to produce these autologous gene-modified cell therapies come from very sick patients and don't always grow well.

A modular approach to drug product presentation helps to address clinics' need for access to the exact volumes of products required for infusion. It allows delivery of the specific dosages needed throughout the entire dose-escalation study as efficiently as possible.

Bridge the analytics gap

Process and product understanding is essential to successful development of high-quality CGT products. Integration of state-of-the-art analytics from bench-top technology development through GMP manufacturing accelerates process development and scale-up.

The advanced analytical techniques used today, including proteomics, mass spectrometry and other very detailed, high-sensitivity, high-accuracy methods, help drug developers understand how changes to the process impact post-translational modifications (glycan modifications, deamidation, etc.), viral particle stability, contamination profiles (host-cell DNA, host-cell proteins, etc.) and other product attributes. This knowledge is crucial to enabling the development of robust, highly reproducible, high-yielding processes that afford high-quality cell and gene therapy products.

The maximum benefit from these technologies is only gained, however, if they are immediately accessible and there is no need to send samples out to third-party analytical labs. The need to use multiple vendors with multiple timelines dramatically slows process development.

Having a full suite of state-of-the-art analytical capabilities places control in the hands of the drug developer where it belongs. It allows rapid evaluation of the impact of process changes on product attributes beginning at the earliest stages of development. Issues can be eliminated before processes reach the pilot/demonstration scale and thus the potential to experience catastrophic failure late in the development timeline can be avoided.

With integrated analytics on site, products and processes are well characterized and well validated and specialized formulation solutions are not needed to compensate for performance issues.

Working towards industrialization

Considering the complexities around industrializing CGTs, innovators and sponsors should endeavor to implement right-first-time processes that utilize industry best practices. CDMOs should provide expert teams that are integrated with customers to ensure that every step of the process from plasmid design to fill/finish is well planned. Robust support for product design activities must include optimal formulation to meet the intended target product profile (presentation, route of delivery and compatibility with devices).

For gene therapies, the viral vector targets will guide the creation of an optimum manufacturing and formulation design space. Experience with a range of cell therapies is leveraged to select the appropriate types of cells used, indications, volumes and overall anticipated doses. Closed, automated cell therapy manufacturing processes are used to produce, store and ship products in both vials and bags, under required cryogenic conditions.

The ability to access next-generation technologies via a CDMO can also be beneficial to drug developers. CDMO activities are built around the mindset of achieving better process and product characterization using an integrated analytics approach that helps to continue building knowledge of the product attributes that are critically important to mitigating risk and ensuring success for CGTs at any quantity.

product focus

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

Capping multiple SKUs

When it comes to packaging complexity, handling multiple stock-keeping units (SKUs) remains an ongoing challenge to manufacturers. Now, TurboFil Packaging Machines has introduced the Acrobat Chuck Capper, a servo-driven chuck capper ideal for manufacturers producing a variety of caps and bottles.

Made with proprietary technology and parallel belts, the capper helps lower the cost of changeovers to different bottles. The Acrobat's servo motor offers precise, repeatable torque control and counterclockwise thread seating for difficult threads. Its novel "chasing chuck" system also automatically locates the next bottle along the belt.

The system's positive placement and cap-specific stainless steel serrated pneumatic chucks help assure gentle handling of different products. According to the company, the Acrobat can handle caps up to 3" in diameter including flat, port, hinged, child-resistant, continuous thread, twist top, metal lug, tilt top and tamper-evident varieties. At just 73" X 75", the system is also compact to help optimize floorspace.

Overcoming formulation challenges

Using highly concentrated protein solutions presents drug developers with specific difficulties in formulation and manufacturing. To help overcome these issues, MilliporeSigma has launched an excipient technology platform that reduces viscosity while maintaining protein stability.

Called the Viscosity Reduction Excipient Platform, the core of the solution uses a combination of one amino acid and one anionic component. The company says that a variety of excipient combinations are then available as part of the platform to address specific needs for protein-based therapeutics including "viscosity reduction beyond reduction with single excipients" and "improved balance of viscosity vs. stability."

According to MilliporeSigma, the synergistic effects of the excipient combinations used in the platform deliver several advantages including: reducing the viscosity of highly concentrated protein therapeutics such as mAbs to enable subcutaneous formulation; increasing concentration of plasma protein-based therapeutics; improving the ability to handle high concentration formulations in downstream processing; enabling competitive differentiation via protected intellectual property and technology licensing.

High-speed cartoning for pre-filled syringes

As the demand for pre-filled syringes, vials and other delicate pharma containers continues to climb, manufacturers are dealing with pressure to keep pace in all phases of manufacturing and packaging. With that goal in mind, IWK Packaging Systems has introduced a modular, high-speed top-load cartoning line called the IWK TL Series that the company says offers numerous advantages over conventional top-loading cartoning equipment.

According to the company, the IWK TL Series offers safe, reliable product handling that eliminates glass-to-glass contact through an intelligent transport system not typically found in top-load units. To account for variability in operations, manufacturers are able to employ an individually adaptable setup instead of using a fixed distance between carton holders.

The IWK TL Series is also modular with a monoblock design that allows for mixing and matching various stations per product-specific needs including product feeding carton erection and divider insertion units prior to transport to end-of-line closure, reject and discharge modules.

All told, the company says that the series provides reliable product handling with a novel transport system, station flexibility for shifting needs and quick changeover to minimize downtime at a time when there are "continued efforts to produce billions of COVID-19 vaccine doses."

Improving particle characterization

In drug development, orthogonal particle characterization methods are regulatory requirements, especially for protein-based biologics. Although light obscuration (LO) instruments have traditionally been used to provide size and count data, the technique is not enough to ensure product quality and stability.

Now, Yokogawa Fluid Imaging Technologies' new LO instrument bridges the gap between compliance and formulation with a single solution. Called the FlowCam LO, the instrument combines Flow Imaging Microscopy (FIM) with LO to generate data for compliance standards while allowing verification with high-resolution images.

"Over the past ten years FIM has become one of the essential tools used in the biopharmaceutical industry due to its ability to accurately identify and classify subvisible particles in liquid media," the company said in a statement. "With automated high-resolution imaging, particle identification and morphology are confidently and readily determined and displayed in real-time, speeding up formulation development."

Automating synthetic biology workflows

With the pressure on drug developers to quickly innovate needed therapies, CODEX DNA has created a benchtop solution that accelerates the design-build-test phases of the product development cycle.

As the world's first and only hands-free and fully automated synthetic biology platform, the BioXP 3250 system is designed for DNA assembly, cloning and amplification. It also enables automated high-throughput synthesis of genes, clones, variant libraries and mRNA — and works overnight.

"Our users now have greater flexibility to generate full-length genes or long DNA constructs at unprecedented rates, reducing iteration cycle times," the company says. "The BioXp system is designed to improve productivity, reduce turnaround time, increase throughput and scale, enhance quality, and enable complete workflow control for both synthetic DNA and mRNA formats."

Grace Linton
Process Architect, CRB

Christa Myers
Process Engineer, CRB

Five engineering trends shaping pharma

These shifts could forever change how we formulate, evaluate and distribute therapies

2020 was a good year for cell and gene therapy (CGT) manufacturers. Financial investment in CGT companies skyrocketed by 200% and the researchers behind CRISPR/Cas9 brought home a Nobel Prize. As the world gathered courage to face the pandemic, CGT innovators responded by gathering momentum.

Similar momentum was building across the pharma industry. The blistering speed of vaccine research made headlines, but extraordinary breakthroughs were quietly taking place in all corners of the industry. Bold thinking and modern facility designs brought new approaches to facilitating progress.

Of all the positive changes, the following five trends will play a particularly important role in forever changing how we formulate, evaluate and distribute therapies.

Adaptive manufacturing will change facility design

As the fight against COVID-19 intensified, oncology vaccine researchers adapted their mRNA platforms to support COVID research. This is just one example of how the ability to pivot in response to a shift in demand or a breakthrough in research will become an increasingly important determinant of success. Companies will have to move fast to stay competitive — and be flexible.

This need for flexibility will drive project owners away from the traditional, dedicated facility. To get the most of their capital expenditure, they'll instead turn towards facilities designed for the unknown, capable of adapting smoothly and cost-effectively to change.

Procurement strategies will address supply chain turbulence

The pandemic exposed — and considerably worsened — challenges that already existed in the supply chain.

Now, leading experts are rethinking how projects are scoped, scheduled and budgeted in order to address these chronic challenges. For example, a lean and agile design process makes it possible to pre-order long-lead materials early in the capital project life cycle, ensuring that when construction finishes, project owners aren't held up by delays in equipment delivery.

Supply chain ethics questions will lead to solutions

COVID-19 has turned our attention to global distribution challenges as leaders attempt to distribute vaccines in areas where robust cold chain logistics and crucial infrastructure don't exist.

To address these and other ethically charged supply chain challenges, we need sustainable solutions that support the distribution of all drugs to all who need them. Take microneedles, for example. By making it safer and easier for people to self-administer an intravenous drug, this technology could bring vaccines to communities with limited medical resources.

Precision medicine will own the spotlight

The field of precision medicine is evolving at a staggering speed, and it has broad implications for how pharma innovators design, build and operate a new generation of testing labs and commercial facilities. These facilities will focus on the aseptic production of small, personalized batches — sometimes as small as a single dose. This radical change will impact everything from process design to cleaning and decontamination protocols.

The research life cycle is accelerating

Because of COVID-19, we now know that innovating new products quickly is not only possible, it's essential.

Now that the world — and pharma companies — have had a glimpse of how quickly we can move together, there's no going back. Pharma's appetite for removing silos and fostering an open, productive exchange of knowledge between researchers, regulators and manufacturers will grow as time goes on, and the availability of new life-saving therapies will grow with it.

To support this trend in terms of accelerated capital project delivery, the industry is embracing methods like design-build, Enterprise Project Management (EPM), and Integrated Project Delivery (IPD). As project owners experience the benefits of these lean and collaborative project delivery methods, they'll increasingly nudge out the more traditional design-bid-build delivery systems.

Change may be constant, but the scale of change? That's always in flux, and right now the pharma industry is verging on some of the biggest, most promising shifts in living memory. To seize this moment, project owners and their partners need to understand the latest regulations, monitor emerging technologies, and take advantage of practical, on-the-ground solutions designed for this rapidly evolving field.

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Paul Dunn
Chair, International Hologram Manufacturers Association

Holograms: The medicine for compliance

Integrating holograms with track and trace can help pharma security

Regulation continues to drive concerns for those involved in pharma manufacturing, production and distribution. This has led the sector to protect itself from criminals and counterfeiters through the Drug Supply Chain Security Act (DSCSA), among other legislation.

Since 2017, pharma manufacturers have been required to print a unique product identification code on all prescription drug units of sale and homogenous cases distributed in the U.S. The move came against the backdrop of continued increases in counterfeiting and the illicit supply or falsification of products, which in turn, have threatened brand values, market capitalization and supplier reputation.

Recently, new guidance documents have been published that provide recommendations for complying with the DSCSA in order to identify and trace drug products as they move through the supply chain. The development is designed to strengthen the FDA's hand in helping to protect consumers from exposure to drugs that may be counterfeit, stolen, contaminated or otherwise harmful, while improving the detection and removal of potentially dangerous drugs from the supply chain.

Failure to comply with the requirements of the law, which include product and transaction information at each sale in paper or electronic format and the inclusion of unique product identifiers on individual drug packages, can result in penalties.

The ISO 12931 standard talks about the "performance criteria for authentication solutions used to combat counterfeiting of material goods" but specifies that "track and trace technology when used alone is not considered to be an authentication solution."

However, when used in conjunction with an optically variable device (OVD) such as a hologram, track and trace technology can become a potent added value security solution.

What holography brings to the table

Indeed, the International Hologram Manufacturers Association's view is that a product identifier initiative by itself cannot be considered an authentication solution under ISO 12931. However, integrated hologram track and trace can provide manufacturers with the tools to be fully compliant with the legislation; incorporating features that help users generate unique sequential, encrypted or random serial numbers, or identify and mark products overtly or covertly either via special self-adhesive labels or directly onto pharma products using a variety of print technologies.

The capacity of holograms to incorporate other forms of data and product tracking information will become increasingly important as technology pushes forward and the nature of anti-counterfeiting evolves. This enables them to be used for a widening range of pharma authentication and brand protection roles, linking on-pack product identification with supply chain management, market enforcement and forensic support services. In this way, the identity and distribution of goods can be controlled through a total system solution involving security authentication features, tracking mechanisms and investigative services.

Of notable value to the brand owner (and a strong financial incentive) is the fact that the information generated at the labelling stage can be linked to the company's ERP system, enabling business functions such as manufacturing, supply chain management, finance, projects, HR and customer relationship management to be captured and better managed.

The move towards outsourcing the production of pharma products not only reduces manufacturing costs but also impacts the control of brand security and visibility. Here holograms can be integrated into the supply chain security process to allow companies to maintain control of their products: from the sourcing of labels or proprietary components to the manufacturing and shipment of finished goods.

They can also be integrated with secure web interfaces to help eliminate rogue ordering of products while authorized distributors can pick, pack and ship items in carefully measured quantities to customers, with the product's movements throughout the supply chain, fully tracked and documented. It's therefore important to encourage brand owners to take the necessary steps to create awareness about holograms — and their multifarious applications and benefits — to fully unleash their potential.

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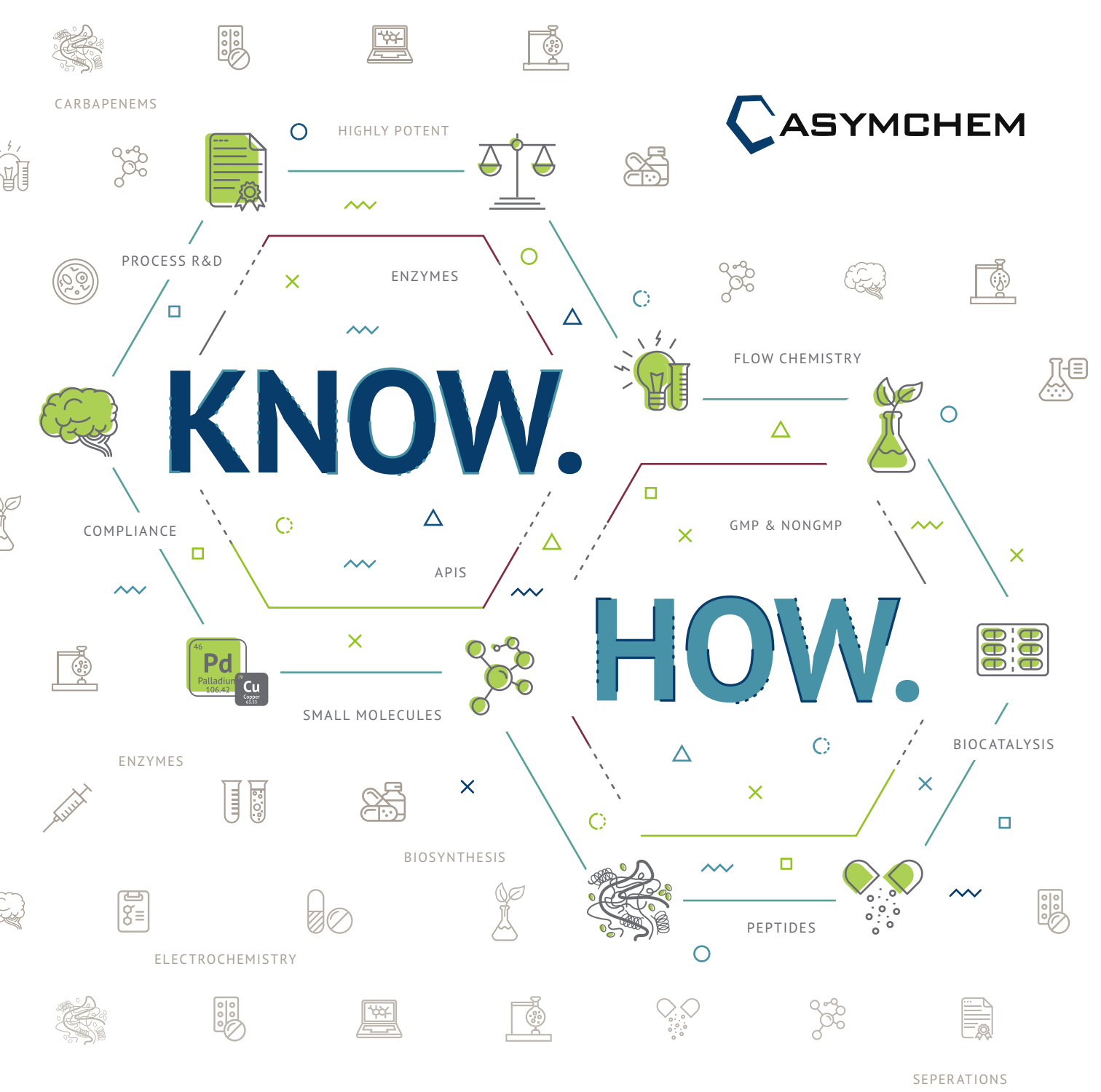

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