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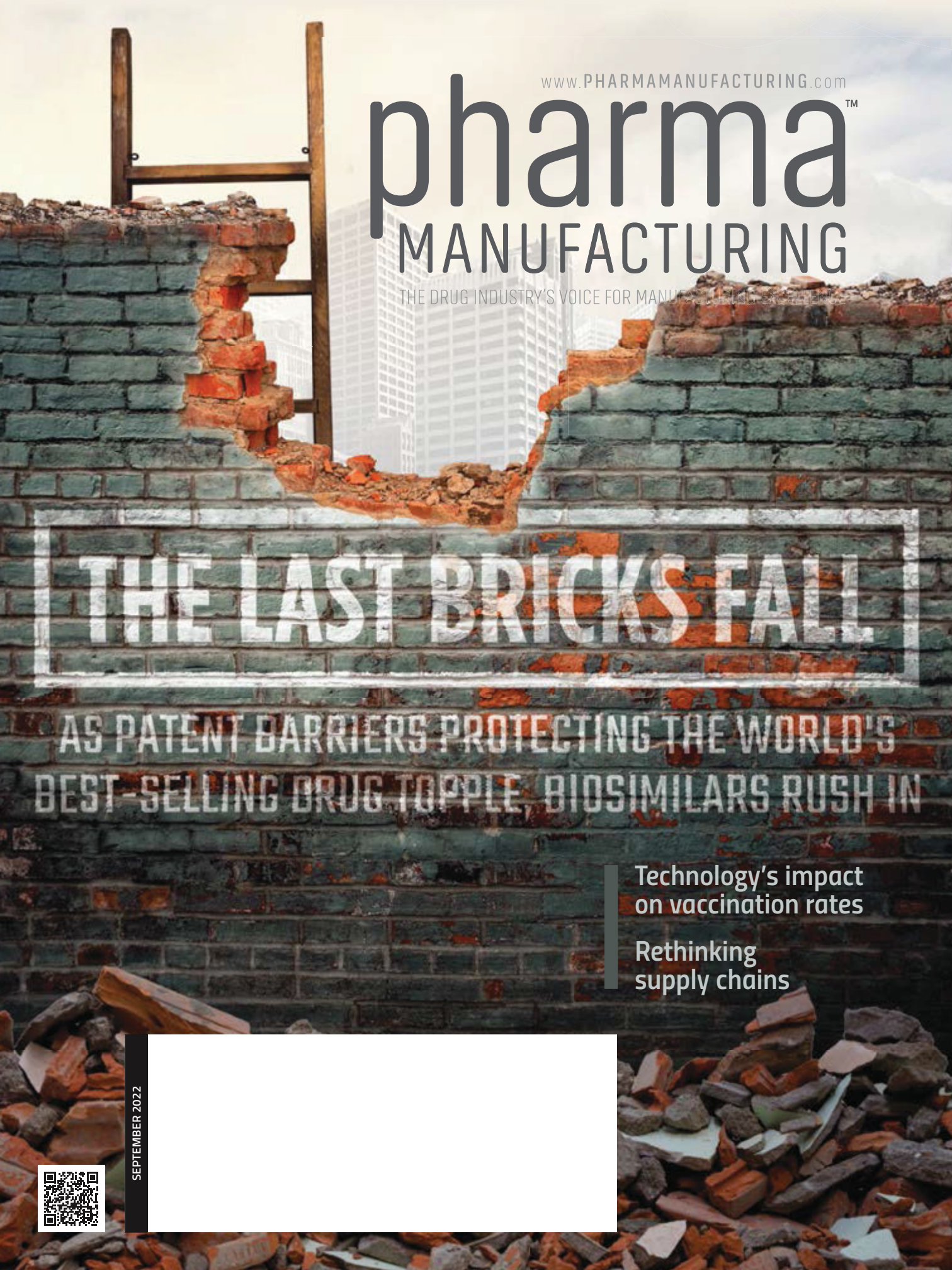

THE LAST BRICKS FALL

AS PATENT BARRIERS PROTECTING THE WORLD'S BEST-SELLING DRUG TOPPLE, BIOSIMILARS RUSH IN

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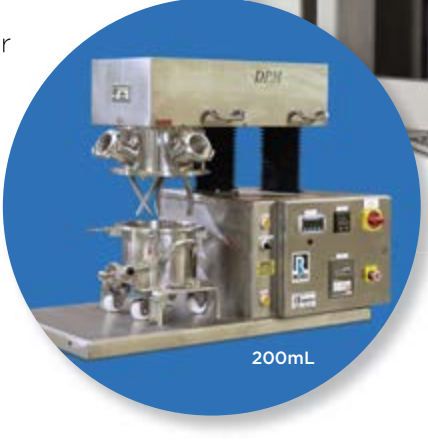

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Karen Langhauser
Chief Content Director

Another brick in the fall

Pharma's biggest hit is finally granting licenses to its patents

Music wouldn't be quite as interesting without the legal histrionics of rock bands.

In addition to having one of the best-selling albums in U.S. history, Pink Floyd is also known for its litigious drama.

Most of it surrounds a bitter feud between guitarist/vocalist David Gilmour and bassist/vocalist Roger Waters, which resulted in a years-long legal battle about who owns the rights to the name 'Pink Floyd' as well as show props like the band's iconic flying pig.

Gilmour and Waters' creative differences allegedly peaked during the making of the band's 11th studio album, "The Wall." Released in 1979, the album — which has sold over 33 million copies worldwide — was arguably both Pink Floyd's opus and their demise. The concept record, which included the famed tune, "Another Brick in the Wall," marked the last time the band's four long-time core members recorded an album together.

The legal woes over rights and royalties weren't exclusive to in-band feuds either. Pink Floyd had to take their own record label to court and at one point, the band was even sued by the school children who sang on "Another Brick in the Wall (part 2)."

Popular songs are not unlike blockbuster drugs in that the artists behind them will do everything in their power to protect their creations, which also ensures a continued flow of cash, even from aging hits.

News broke recently that Pink Floyd is selling the copyrights to its songs and recordings — and seeking a whopping $500 million for this back catalogue of hits. The band has been notoriously picky about allowing commercial use of its music (even turning down a huge offer from Instagram), so a sale would mean the band forgoes the right to decide where their music is used — and that we could hear a lot more Floyd in generic scenarios.

In pharma, perhaps no company has been more protective of rights than AbbVie, which has built a patent wall of protection brick by brick around its biggest hit, Humira.

Not only is Humira approved by the FDA in 10 different indications, but AbbVie has filed over 200 patent applications for the drug in the U.S. — 90% of them following Humira's initial FDA nod back in 2002. By 2025, the drug is predicted to have amassed sales of over $200 billion, solidifying its title of the best-selling drug of all time.

All told, it has been quite a run for Humira — and one that was certainly not without its own legal feuds. Despite facing antitrust allegations over its enforcement of the patent wall surrounding Humira — AbbVie's defense repeatedly held up in court.

As companies filed with the FDA for biosimilar versions of Humira, AbbVie took them to court for patent infringement. One by one in perfect cadence, AbbVie reached settlements with competing drugmakers, delaying competition.

But the patent song has finally come to an end: The settlements allow adalimumab biosimilars to enter the U.S. market in 2023.

Ultimately, what's more important than the ballad of Humira's fight to maintain stardom is its culmination — when biosimilars finally hit the market next year, lower prices should be music to the ears of millions of U.S. patients.

Gina Parry
Distribution & Pharmaceutical Sales Manager, VAI

3 tips for hitting the DSCSA deadline

Pharma can do better than 50% compliance

With the FDA's November 2023 deadline to comply with the Drug Supply Chain Security Act (DSCSA) looming, pharma manufacturers should have already started to prepare — especially since nearly half of them missed the last deadline.

Signed into law in 2013, the DSCSA combats the spread of counterfeit prescription drugs. As part of the legislation, the FDA outlined a long list of traceability and security requirements by which pharma stakeholders must abide. However, many organizations previously struggled to meet deadlines due to poor internal communication and what some perceived as unclear instructions from the FDA.

As your organization looks ahead to this next phase, here are three tips to keep in mind:

1. Communicate and plan effectively

Many companies struggled to adjust to phase one requirements due to poor planning. This time around, your organization needs to thoroughly understand the FDA's guidelines and should have already developed a company-wide plan. You should view this plan as a process of trial and error rather than as a series of boxes to be checked off. In practice, this means creating a buffer period before the November deadline to work out any issues.

Additionally, your preparation shouldn't take place in a vacuum. Constantly communicate with the manufacturers, distributors and dispensers along the supply chain that you work with to ensure everyone remains on the same page.

FUNNY PHARM

"Well, management did say they wanted more bodies on the production line..."

— Corin Angel

Funny Pharm comics are drawn by professional cartoonist Jerry King. Readers submit suggested captions to win. Above is a recent cartoon and winning caption.

Be part of Pharma Manufacturing's 20-year celebration!

To commemorate 20 years of *Pharma Manufacturing* magazine, our October anniversary issue will revisit key topics in the pharma industry and how they have changed over the past two decades. Coverage will include a special editorial section that will highlight change through the eyes of equipment/services suppliers. Companies that have been in the pharma business for 20+ years are welcome to submit a quote discussing how their specific area of expertise has changed.

Email our editors with your quotes today!

2. Update software and protocols

Phase two requirements are more comprehensive than the initial requirements, so you'll need to re-evaluate your systems to determine whether they're capable of complying. For example, instead of simply tracing packages at the lot level, you'll now need to track each sellable unit you receive and ship.

To accomplish this, your organization will require the ability to handle complex product information in real time. One option is to enlist the help of enterprise resource planning (ERP) software, which handles these moving parts for you and keeps your organization compliant.

3. Invest in new hardware

In addition to software updates, you may need to upgrade your hardware. For example, when it comes to tracking individual packages, the bar codes you'll have to scan will be different from the linear bar codes you're used to and that means you'll need new bar code scanners and RFID readers. Since purchasing and implementing new hardware can require a lengthy process, it's important to identify required hardware upgrades sooner rather than later.

If you need assistance, a third-party auditor can play an important role in helping you fully comply with phase two requirements. At a minimum, you should plan to perform an internal audit and leave no stone unturned when it comes to evaluating your progress.

Continuous improvement

As long as the problem of counterfeit drugs persists, pharma companies will need to improve their practices to increase visibility into the pharma supply chain. Revamping operations twice in one decade is no small task, but the benefits are massive for both your organization and for public health. By committing to meet the phase two requirements, you can lay the blueprint for continuous improvement in 2023 and beyond.

Ethan Smith
General Manager, Life Sciences, Nuvolo

Digitally aligning manufacturing and quality

By bringing together processes and data, pharma can create efficiencies that ultimately get high quality therapeutics to patients faster

The world has progressed into a digital age, and it's time for the pharma industry to catch up.

While plant floor equipment has benefited from automation, many of the processes that surround manufacturing remain paper-based.

Pharma Manufacturing recently spoke with Ethan Smith, general manager, Life Sciences at Nuvolo about how furthering pharma's digitalization journey can help the industry reap big benefits in quality and manufacturing.

Q: How is digitalization impacting pharma manufacturing?

A: Digitalization is massive for pharma across the board. This industry — and particularly manufacturing — has operated off documents (aka paper) for most of its existence. Regulators and inspectors from health authorities have historically asked to see and review documents during inspections. Employees are trained using documents. And information has been 'stored' — if you can call it that — in documents over the years.

Now, advances in cloud technology, the IoT movement, and new platforms offering enhanced integration capabilities are all driving the pharma industry and its manufacturing towards digitalization.

People now expect digital solutions at home and at work. From banking to getting groceries delivered, everything is happening digitally — and pharma manufacturing really needs to catch up with that overall trend.

Q: What is the ultimate goal of digitalization in the pharma industry?

A: Ultimately the pharma industry is here to deliver safe and effective therapies to patients. The goal of digitalization is to make that process simpler, faster and more secure.

That said, it's also important to recognize that digitalization is a journey, not a destination. There's no singular goal or solution that we can deploy and say we are done. It's a constant evolution, and I think we all know that technology waits for no one. These advances are going to continue to accelerate.

Q: Where are there still inefficiencies in the manufacturing process?

A: Pharma manufacturing execution — the actual running of the equipment to make the products — is all highly efficient.

However, what happens before and after production can be improved. Determining how much of a therapy to make is one thing that hinges on market demand. But once that's decided, other factors come into play, like shelf life, manufacturing capacity, and the availability of equipment, ingredients and intermediaries. This requires lots of manual effort.

Downstream, quality review is also a highly manual process that could benefit from digitalization. It can take months for a manufactured batch to be cleared through quarantine due to paperwork. However, if documentation is digitalized, that timeline can shrink, allowing therapies to hit the market sooner. This can prevent drug shortages and positively impact company revenue.

Q: What solutions can help address these inefficiencies?

A: Solutions to these kinds of complex challenges must be flexible, interoperable and most importantly, highly reliable to operate in the manufacturing space.

At Nuvolo, we aim to work within the landscape of the existing mission critical applications that support manufacturing, like manufacturing execution systems and quality management systems.

For example, in order to release a batch, the quality department needs to know that all of the equipment used to manufacture that specific batch on that specific date was: up-to-date on all of its planned maintenance; calibrated within an acceptable tolerance; and properly cleaned and set-up for the process. All of this information can be found in our GxP Asset Management product.

With the batch number and the product information from the MES or ERP system, we're able to provide the quality department with a validated report that documents that all of the equipment used was in fact 'ready for use' for manufacturing. Think of it as a green light status at the asset level.

It might sound relatively simple on the surface that, yes, this machine was ready to work when the batch was manufactured. But when lots of batches are being produced across multiple sites around the world that have multiple manufacturing lines within them, there can be hundreds of thousands of pieces of equipment involved.

Nuvolo allows for the quality department to get the same level of output without having to verify each piece of equipment by going line by line through that executed batch record individually. Instead, it's sourced as a digital record to supplement the quality review package.

team to streamline the batch review process. This saves time while maintaining — arguably enhancing — the level of quality and allows the quality team to focus on what they do best and what matters most: ensuring that all the process steps were followed.

The second critical benefit is that tracking batch numbers and products that each piece of equipment has produced creates new information and insights for the manufacturing function that owns these pieces of equipment. By

> There's no singular goal or solution that we can deploy and say we are done. It's a constant evolution, and I think we all know that technology waits for no one.

Q: What does the term 'digital alignment' mean?

A: Simply put, digital alignment is bringing together processes and data to make them operate more efficiently.

Technology platforms promote digital alignment because they inherently bring processes and information together since the information and processes coexist on the same platform. This is why we're seeing more larger pharma companies adopting an IT strategy centered around enterprise platforms.

Q: What are some of the long-term benefits of digitally aligning quality and manufacturing?

A: Bringing quality and manufacturing into closer alignment has three crucial benefits.

The first one is providing equipment information from a manufactured batch to the quality

including those batch numbers in the compliant audit trail of every asset, the manufacturing team can analyze the equipment's performance based on their company's products. This is an entirely new dimension for asset management, which has historically been managed just with downtime and runtime metrics. These new insights will help manufacturing teams as well as finance and procurement to make better decisions around when to repair, replace or supplement a device for manufacturing efficiency.

Thirdly, digital alignment of quality and manufacturing will prevent production delays by enabling the reservation of all the equipment that is needed for a production run in a single place where the maintenance plans and records for the equipment are also maintained. This ensures that a manufacturing site doesn't get ready to start a batch only to find out that one piece of equipment has an open maintenance order or is out of calibration and then those challenges turn into costly production delays.

Q: Are there opportunities to mature this alignment even further in the future?

A: Absolutely. It's definitely a journey and the companies involved in it — both pharma manufacturers as well as technology providers like Nuvolo — are going to continue to evolve and mature processes and solutions to the challenges that have existed in the industry for quite a while.

For Nuvolo specifically, we see maturing the employment of machine learning and advanced analytics using that data as the way to enable true asset performance management. For example, does one piece of equipment like a tablet press perform better when a manufacturer is making one of its products versus another product? Are there ways that manufacturers can use equipment better? Pharma requires very expensive assets to produce its products, so if companies can focus on product intelligence it will change the way the equipment is managed, maintained and ultimately purchased.

The advancement of cell and gene therapy and other personalized areas of medicine where a single patient is the actual batch is also on the horizon. Digital alignment will help improve yields and timelines, getting a patient's personalized therapy back to them as efficiently as possible. The clock is ticking for the patient, so being able to be more productive and more efficient here is massive.

At Nuvolo, we are excited to have some involvement in that by working with the industry to help find areas where we can continue to evolve and expand, as well as discover entirely new ways to further help the industry and patients.

Andrea Corona
Senior Editor

Precious things are kept inside castles, locked up in fortresses, or protected by walls. Be it a king or damsel or an entire city, barriers are built to shield our most valuable assets.

For pharma, few things have been considered more precious than one of the most profitable drugs in the history of humankind.

AbbVie's adalimumab, known to the world as Humira, is an immunosuppressive drug approved to treat many illnesses, including debilitating diseases such as rheumatoid arthritis, plaque psoriasis, Crohn's disease and ulcerative colitis.

Humira is a drug like no other — it's ability to treat a vast array of indications has earned it the nickname the 'swiss army knife' of pharmaceuticals.[1] Millions of patients have been treated with Humira worldwide, and it's estimated that it will amass a revenue of $240 billion by 2024.[2]

But the world's top-selling drug had humble beginnings as a mere phage system invented by the Cambridge Antibody Technology Group (CAT) in Cambridge, UK. The team, which included scientists from Knoll AG (later bought by BASF Pharma), used genetic engineering to create an artificial immune system that had the capacity to replicate human antibodies, working it out until they had a therapeutic product in their hands.

Four years later, BASF Pharma published the first positive results from a phase 1 clinical trial involving 140 patients with rheumatoid arthritis being treated with the drug candidate called D2E7 — and the rocket launched.

Seeing blockbuster potential in D2E7, Abbott Laboratories bought BASF's pharma business for $6.9 billion in 2001, which included the drug candidate. Shortly after, D2E7 received its first Food and Drug Adminstration approval on December 31, 2002, and was introduced to the world as Humira. In 2013, Abbott split in two, and AbbVie — now the owner of Humira — was born.

The first phage display-derived antibody approved in the U.S., Humira rose straight into stardom — within its first year, it had been approved in 38 countries and prescribed to 50,000 patients.[1]

In adition to being a life-changing medicine, due to what some call 'beautiful legal work,' and others a sinister monopoly, Humira has remained unrivaled in the market since the drug's conception. AbbVie protected the biologic with a web of patents for many indications, creating an intellectual property defense wall that no legal department could get through, extending the drug's market exclusivity far beyond what was granted by the FDA.

In the U.S., a year's supply of Humira costs around roughly $77,000 — and patients' out-of-pocket costs vary greatly depending on insurance coverage. In the EU, adalimumab biosimilars have been available since 2018, and have taken over more than half of the market share, which has not only resulted in lower prices for patients switching to biosims but also has driven down prices for the branded drug. In the Netherlands, for example, the market entry of biosimilars triggered discounts of up to 89% on branded Humira.

Now, with competition scheduled to enter the U.S. market in early 2023 — and potentially 11 products lined up to compete with Humira[3] — all eyes are on the adalimumab biosimilar charge, with many experts claiming that the future of biosimilars in the country will inevitably be shaped by the success or failure of these launches.

After years of battling through patent litigation, will these manufacturers have the fortitude to stand out in a soon-to-be saturated market?

AbbVie has filed a total of 247 patent applications for Humira — 90% of which were filed after the drug's approval.

A drug worth protecting

Adalimumab is a recombinant human IgG monoclonal antibody. Monoclonal antibodies — or single clones — are a type of antibody that targets a specific protein.

In the case of Humira, the mAbs specifically target the cytokine human tumor necrosis factor (TNF), which is implicated in generating inflammation as part of acute phase immune reactions. Since inflammation is behind many symptoms of autoimmune diseases, mAbs are powerful drugs.

Humira's success is amplified by the drug's ability to treat many autoimmune disorders, most of which require lifelong medication. Immune disorders are also very common, affecting more than 7% of the global population, with more than 23.5 million Americans being diagnosed each year. And that number is increasing.[4]

"Prescribers — mostly rheumatologists — suddenly had with Humira somewhat of a silver bullet. One medication that targets processes that occur across more than one disease," explains Dr. Sarfaraz K. Niazi, adjunct professor of Biopharmaceutical Sciences at the College of Pharmacy, University of Illinois in Chicago. Niazi is also a patent law practitioner with more than 100 U.S. patents in the biotech field and has developed a biosimilar to Humira, as well as two other biosims that have FDA approval.

"Humira is a highly effective, powerful drug," Niazi says, and the data agrees. According to results reported by AbbVie, nearly 20% of patients with autoimmune disorders can reach remission within four weeks of treatment.

With support from the science and healing potential of Humira, AbbVie did an incredible job building a money machine that fed itself. By investing in numerous clinical trials, Humira became the magic pen with which most autoimmune disorders could be treated, becoming a go-to for prescribers around the world.

In response to a drug pricing investigation by the House of Representatives, AbbVie reported investing a total of $5.19 billion in Humira R&D expenditures between 2009 and 2018 — approximately 4.2% of the company's Humira worldwide net revenue over that period.[5]

The investment paid off, and today Humira accounts for almost two-thirds of the company's revenue.

If the story had ended there, perhaps Humira would be looked at in a more heroic light. But in order to protect its favorite prize, AbbVie employed an expensive legal arsenal of resources to shield its technology from being replicated.

Building the patent wall

The FDA defines a biosimilar as a "highly similar" product with no clinically meaningful differences from an existing FDA-approved reference product. Manufacturers making biosimilars have to demonstrate that the product is not clinically different in terms of safety, purity or potency.

"A biosimilar is a receptor-binding drug that replicates the cell processes triggered by the reference product," explains Niazi.

Enacted in 2010, the Biologics Price Competition and Innovation Act (BPCIA) created an abbreviated approval pathway for biosimilar biological products. The act also outlined a path for biologic drugs to seek interchangeable status, if the drugmaker could provide additional data proving that a biosimilar product could produce the same clinical results as the reference product in any patient, including a detailed comparison of the history, as well as similarities and differences between the two. Importantly, interchangeable products may be substituted for the reference product without the involvement of the prescriber, whereas this is not the case with all biosimilars.

Currently there are 37 FDA-approved biosimilars in the U.S., 22 of which are commercially available on the market — and only three have received interchangeable status.[6]

Beyond the rubble: A look at the Humira biosimilars set to launch

Company	Product	FDA Approval	Launch	Seeking interchangeability	Conentration	Citrate Free	Latex Free
Amgen	Amjevita	YES	January 31, 2023	NOT YET	Low (50MGS)	YES	NO
Organon	Hadlima	YES	July 1, 2023	NO	Low (50MGS)	NO	YES
Boehringer Ingelheim	Cyltezo	YES	July 1, 2023	YES – granted on October 2021	Low (50MGS)	YES	NO
Coherus	Yusimry	YES	July 1, 2023	NO	Low (50MGS)	YES	YES
Viatris	Hulio	YES	July 31, 2023	NO	Low (50MGS)	YES	YES
Sandoz	Hymiroz	YES	September 30, 2023	NO	Low (50MGS)	NO	NO
Pfizer	Abrilada	YES	November 20, 2023	YES	Low (50MGS)	YES	YES
Organon	SB5-HC	NO	July 1, 2023	YES	High (100MG)	YES	YES
Fresenius Kabi	Idacio	NO	September 30, 2023	NO	Low (50MGS)	YES	YES
Teva/ Alvotech	AVT-02	NO	July 1, 2023	YES	High (100MGS)	YES	YES
Celltrion	Yurflyma	NO	July 1, 2023	NO	High (100MGS)	YES	UNKNOWN
Amgen	ABP 501 HC	NO	TBD	YES	High (100MGS)	YES	NO

SOURCE: CARDINAL HEALTH

While the BPCIA — which was included in the Affordable Care Act — was helpful in terms of stimulating biosimilar approvals in the U.S., it did leave some loopholes.

Tahir Amin, co-executive director of the Initiative for Medicines Access and Knowledge (I-MAK), says that because these bills are built into larger legislative acts, it's harder to crack them down and change them when necessary, such as in cases of patent misuse — of which critics, including Amin, have accused AbbVie.

"By drafting this legislation into large bills that might not be publicly associated with these issues, when you try to bring up changes to the BPCIA, people begin politicizing the legislation because it is part of the Affordable Care Act, making it difficult to extract that out," says Amin.

Protecting the largest pharma empire of all time takes money and foresight, and must begin at the first patent filing, according to Amin, who practiced as an intellectual property attorney for 10 years in commercial law firms.

"The way that first patents are created informs how the subsequent ones are filed," he says.

By carefully crafting the first patent, companies can set

themselves up for intellectual property protection success for decades. If they purposely obfuscate details, they can file new patents with slight variations and extend patent exclusivity.

It's a game of looking threatening, too. "These companies also focus on filing an excessive number of patents knowing that they might not need all of them but the sheer amount might scare drugmakers enough to keep them from developing their competitor product," Amin says.

And it has been precisely this type of patent reputation that has kept AbbVie in the spotlight for the last few years. While the original patent expired in 2016, AbbVie has filed a total of 247[7] patent applications for Humira — a portfolio it has aggressively used to knock down biosimilars challenging its market.

While most innovator companies insist vehemently that patents help protect innovation, Amin argues that FDA exclusivities provide enough market protection for companies to launch a product.

"Something that is not recognized or discussed enough is that when companies have a new biologic product, you get your BLA and receive 12 years of marketing exclusivity. So that is separate to any patent — nobody can come on the market for 12 years from the get-go," says Amin.

Within that period, other drugmakers can submit applications for biosimilar approvals but can't market them until the FDA exclusivity and any patent protection litigation is finalized.

The BPCIA mandates that biosimilar applicants disclose their FDA applications to the innovator companies within 20 days of filing that application. "And then the patent dance starts," says Amin.

Niazi, on the other hand, believes that AbbVie's construction of patents is "beautiful legal work." He argues that while the first few patents filed for Humira covered many of the 14 worldwide and 10 U.S. indications it currently has, the company cleverly filed varieties, such as an auto-injectable pen or a stronger dose — that made all the difference.

"They [AbbVie] were smart to listen to patients' requests once the product was live and make sure that their patent portfolio was reflecting the changes they were making in needle size, and such," Niazi says. AbbVie also removed the citrate buffer that causes smarting pain; according to Niazi, it was known all along, but AbbVie let the patients suffer and made this change only when the patent expiry came near — a cruel strategic move.

AbbVie's patent portfolios are aggressive indeed — when the drugmaker countersues companies attempting to bring a biosimilar to market, they litigate with as many patents as possible. "AbbVie's patent thicketing strategy on Humira has become almost legendary, albeit for the wrong reasons, when people realize that none of these companies were able to litigate through them," Amin says.

Patent litigation with generics is different from biosimilars due to the way that the drugs are developed in the first place. "Biologics are much more complex; they have way more patents because of the nature of the technology. There are many different ways to manufacture and develop it," says Amin.

The result? An even thicker patent wall.

And protecting the wall comes at a hefty cost. According to patent litigation statistics, defending a patent can cost between $2 and $4 million per patent.

> **"It wasn't just one case, with Humira, but actually all the litigations chipping way at this patent structure keeping the technology exclusive.**
>
> — Tahir Amin

Brick by brick, the wall falls

Most of the arguments against AbbVie focus on the company's misconduct and antitrust violations in connection with its aggressive enforcement of patents to prevent the sale of biosimilar versions of Humira in the U.S.

"It wasn't just one case, with Humira, but actually all the litigations chipping away at this patent structure keeping the technology exclusive," says Amin.

But the wall protecting Humira has started to fall, slowly but surely, brick by brick.

Leading with an impressive portfolio of biosimilars and a hefty legal department, the first to take on AbbVie was Amgen with Amjevita, which is lined up to be the first biosimilar to hit the market in January 2023.

Not long after the FDA accepted Amgen's biosimilar application, AbbVie sued for patent infringement claiming that Amjevita infringed on 10 Humira patents and asked the court to block the launch if and when the FDA issued an approval.

"Intellectual property litigation is aggressive, and more often than not just intended to scare drugmakers with smaller legal teams away," says Amin. AbbVie did precisely that, not only suing for the 10 patents but threatening to come after Amgen for 51 other patents as well.

While specific financial terms of the agreement were not disclosed at the time, the companies announced a settlement in September 2017, with AbbVie

Walls set to fall

Most anticipated blockbuster patent expirations

1 Entyvio — Takeda Pharmaceuticals
Key patent expiration: 2025-2026

Entyvio (vedolizumab) is an immunotherapeutic drug that prevents white blood cells from entering inflamed gut tissue, decreasing inflammation. It's currently approved in more than 60 countries worldwide for patients with moderate to severe ulcerative colitis or Crohn's disease.

While Polish CDMO Polpharma Biologics last year announced its development of a biosimilar version of Entyvio, Takeda stated recently that it's no longer expecting entry of biosimilars upon loss of patent exclusivity.

2 Keytruda – Merck & Co.
Key patent expiration: 2028

Keytruda (pembrolizumab) is an immune checkpoint inhibitor used for cancer therapy. First approved in September 2014 for melanoma, Keytruda now has 26 separate approvals for 18 different types of cancer.

Keytruda is Merck's most popular product of all time, and Evaluate Pharma forecasts it will become the world's top-grossing drug by 2024. In total, Keytruda's patent wall is made up of 129 patent applications. Xbrane BioPharma and NeuClone have Keytruda biosimilars in the pipeline.

3 Opdivo — Bristol Myers Squibb
Key patent expiration: 2028

Opdivo (nivolumab) was initially approved in December 2014 for advanced melanoma. Evaluate Pharma predicts that by 2026, Opdivo will hit $11.75 billion in sales.

While Opdivo hasn't come close to drugs like Keytruda in sales, biosimilar companies are still eager to enter the market, with Xbrane BioPharma and NeuClone announcing the development of biosimilar candidates referencing Opdivo.

granting Amgen patent licenses for the use and sale of Amjevita worldwide on a country-by-country basis.

Samsung Bioepis followed behind Amgen, becoming the second company to ink a settlement with AbbVie that allows it to launch its biosim in the U.S. on June 30, 2023.

While each company making a biosimiliar argued similarly, it was Boehringer Ingelheim who sparked hope that perhaps a Humira copycat could launch before 2023, when they initially refused to settle and counterargued that AbbVie intentionally overlapped and added on patents.

"Boehringer came up with this novel argument saying that many of these patents were bad faith and that they would deliberately have this strategy from the start. And we thought actually, this is a pretty novel argument from a legal point of view," says Amin.

Eventually, in May 2019, Boehringer agreed to settle and keep its product on the shelf until 2023.

While settlements and legal teams are expensive, defending the patents gives companies making the reference product control over competitive launches, allowing them to better prepare and forecast their financial future.

Also, reference-product companies can try to bargain with biosim drugmakers, who often sign away international markets when settling as they are focused on the U.S. rather than abroad. "Companies often decide to keep the U.S. one because the country's market is much more valuable because there's no negotiation, there's no pricing control. They can charge whatever they like," Amin says.

Alvotech, who is partnering with Teva Pharmaceuticals on the U.S. commercialization of its adalimumab candidate, has been the most recent one to settle, inking a deal with AbbVie in which the Iceland-based drugmaker agree to wait until July 2023 to launch its biosimilar. The companies had been in a lawsuit tug-o-war, with Alvotech accusing AbbVie of employing a "wrongful monopoly" on the drug and AbbVie later accusing Alvotech of recruiting one of its manufacturing execs to steal Humira trade secrets.

Climbing to the top

There are four main ways in which Humira biosims can set themselves apart from each other: dose concentration, interchangeable status, needle size, and a formula without latex or citrate.

Dose concentration matters because although both high-concentration and low-concentration versions of Humira are currently on the U.S. market, over 80% of prescriptions are for the high-concentration solution, providing an incentive for companies with a biosimilar that offers this option. None of the FDA approved biosims are offering high concentrations, but pending biosims, such as Organon's SB5-HC, Teva and Alvotech's AVT-02, Celltrion's Yurflyma, and Amgen's ABP 501 HC are all high concentration.

The second factor, interchangeable status, matters because it would allow pharmacists to replace Humira with a biosimilar without having to address the swap with providers. While there are only three interchangeable biosimilars on the U.S. market as a whole, two approved Humira biosimilars are seeking interchangeable status — Teva's AVT-02 and Amgen's second Humira biosim, ABP 501 HC.

Needle gauge makes a different in terms of patient comfort — the higher the gauge number, the smaller the needle. AbbVie initially designed Humira's needle gauge to be a 27-gauge needle, later coming out with a 29-gauge needle. Most Humira biosims are offered in a larger-gauge needle with only Boehringer Ingelheim's Cyltezo and Sandoz's Hyrimoz's needle sizes being 27-guage.

> **Biosimilars are not for the weak. The investment necessary to succeed in this market given the current regulatory expectations is massive.**
>
> — Sarfaraz K. Niazi

In adalimumab formulations, citrate and latex can both be used as excipients. Citrate, for example, acts as a buffer, helping the biologic retain its chemical and physical products. However, in Humira injections, it has been found to potentially cause pain, so drugmakers might be incentivized to remove it from the ingredient list. The only two biosims entering the market with citrate in their formulation are Organon's Hadlima and Sandoz's Hyrimoz — the rest are citrate-free.

With latex, the concerns have to do with allergies. While only less than 1% of the population is naturally allergic to latex, according to Mayo Clinic, repeated exposure to latex may increase sensitivity. In order to protect both employees and patients who might have a family history of allergy development, AbbVie and several of the biosims are offering latex-free formulations.

As to which drug will come on top, experts agree that to succeed in the biosimilar market you need timing, a lot of money, and legal teeth. "Biosimilars are not for the weak. The investment necessary to succeed in this market given the current regulatory expectations is massive," Niazi says. "But you see that the drugmakers going after Humira are seasoned veterans."

According to Niazi, due to the nature of patents, biosimilars, and trends seen in Europe, the drugmakers more likely to succeed are the ones who reach the market first. "Amgen is leading because in a way they were preparing for this by already having and working with a robust portfolio of biosimilars for years before going after the best-selling drug ever."

Amgen is betting on this head start, says Gary Fanjiang, vice president and general manager of Biosimilars, at Amgen.

"We believe our five months head start on biosimilar competitors will support early adoption of Amjevita and are confident that our success in the EU will translate to the U.S. market," says Fanjiang.

Amgen also has decades of experience — and Fanjiang says that will help set its biosim apart.

"We have over 40 years of experience manufacturing complex biologics and a history of reliable supply. We will also leverage our experience designing and delivering patient support programs for our innovator biologics to ensure patients receive the same level of support when starting Amjevita."

And while patients will also see a reduced-price tag, a crowded biosim market on top of AbbVie's settlements will mean that the change won't be as drastic as it has been outside the U.S.

"It's going to be a pretty saturated place in 2023. I don't know how much the prices are going to come down because companies must still make a profit from their drug, and some of that money will go to AbbVie," Amin says.

But despite the impressive number of roadblocks, biosimilars are still a highly profitable business opportunity for pharma. "Biologics offer a huge market in terms of the profit, numbers like nobody have seen before," Amin says.

Biosimilars' big moment

Despite it being a new market, the good news is that the industry has been through something similar — pun intended — before.

Although different in nature, biosim drugmakers can look at the introduction of generics as a rough guide of what disrupting a name brand market can be like.

Craig Burton, senior vice president of Policy and Strategic alliances for the Association for Accessible Medicines, and executive director of the Biosimilars Council compares the situation to the adoption of Prozac generics.

"When the first generic competitor to Prozac was made available to patients back in 2001, national newspapers and network television evening news programs ran stories about this milestone. Prozac was one of the most prescribed medicines, so this was truly big news; it was important for physicians and pharmacists and patients to know safe, effective and more affordable options were now available," explains Burton.

This, combined with the years of good reputation that Humira has amassed should help.

"With competitors to Humira about to launch, biosimilars are about to have their big moment," says Burton.

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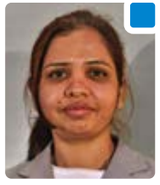


Formulating ophthalmic drugs the right way

Ophthalmic drugs bring their own set of manufacturing challenges and regulatory roadblocks

Ophthalmic drug formulation and manufacturing brings with it unique challenges and regulatory requirements.

Pharma Manufacturing recently spoke with Smita Rajput, Field Marketing Manager at MilliporeSigma about important factors to consider.

Q: What is driving growth in the ophthalmic drug market?

A: The driving forces for the market are the rise in the geriatric population as well as in age-related eye disorders. This has caused a surge in demand for ophthalmic drugs, and an increase in R&D and clinical study investment by various pharma companies. Added to that, we see government initiatives to raise awareness about eye diseases and treatments.

Q: What are the different types of ophthalmic drug delivery systems?

A: Ophthalmic drugs can be administered in four ways. The drugs can be administered through intravitreal injection, subconjunctival injection, subretinal injection or topical administration.

The topical drug delivery system is one of the noninvasive routes of administration and has minimum side effects. Topical administration also delivers therapeutic drugs in the anterior segment of the eye, so in the case of ophthalmic topical formulations, there are different types of drug deliveries available including solutions, emulsions, suspension, gels, in situ gels and ointments.

Q: What are some important considerations for ophthalmic drug formulations?

A: Ophthalmic drug delivery systems, including topically administered solution dosage forms, need to be sterile and free from visible particles. These formulations should also be isotonic with ophthalmic fluid. Otherwise, they result in irritation to the eye surface. In many cases, ophthalmic dosage forms are multi-use or they can be used over some time, so they need to be protected from microbial contamination during the in-use period.

Q: What are some of the biggest regulatory challenges of ophthalmic drug delivery systems?

A: Recently, regulatory authorities — specifically the U.S. FDA — have started considering ophthalmic formulations designed for administration as eye drops to be drug-device combination products. The regulatory compliance requirements for such combination products are much more complex than those for the drugs alone.

In addition to that, the FDA publishes product-specific bioequivalence recommendations to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing generic drugs and generating the evidence needed to support Abbreviated New Drug Application approvals. Since 2008, the FDA has posted numerous of these product-specific bio recommendations for ophthalmic drug products.

These recommendations describe different types of bio studies like clinical, pharmacokinetics, as well as in vitro that can be conducted for specific ophthalmic drug products. Ophthalmic product developers must fulfill all these product-specific requirements.

Q: Why is the API selection for ophthalmic drugs so important?

A: Bioavailability is a critical aspect of any type of drug delivery, and achieving bioavailability for BCS class II and class IV APIs is very challenging due to their limited water solubility. When designing ophthalmic drug formulations, a common technological problem is the low solubility of the active substance, which makes it impossible to achieve the desired therapeutic concentration if no countermeasures are applied. Also, suspension is not always an option due to irritant effects.

Hence, different solubility-enhancing technologies can be used which include cyclodextrin complexation, nanosuspension or nanoemulsion, co-solvent or micellar solubilizers. If you don't have options because you have to use the same BCS class II and IV drugs, then you need to look from the excipient or technology point of view in terms of what can be done to enhance the solubility of such APIs.

Q: What needs to be taken into consideration for the selection of excipients and filters when developing a manufacturing process for ophthalmic products?

A: Excipients play a very important role in the development of any dosage form. They have a direct impact on critical quality attributes, as well as critical process parameters of the manufacturing process.

Preservatives are a great example. They are used to protect the ophthalmic product from microbial contamination, but the quality and the impurity profiling of these preservatives will impact the critical quality attributes of the product — like stability or preservative efficacy.

Similarly, excipients impact the manufacturing process. For example, benzalkonium chloride tends to get absorbed into the filter membrane which can result in loss of preservatives, leading to lower concentration of the preservative in final drug product, and that affects the preservative efficacy.

To resolve this challenge, either the filter flush volume or the filter hold time needs to be increased. Both these approaches increase the manufacturing time with less yield. Here process efficiency gets compromised. In our R&D, we conducted several studies with our preservatives and filters with MOC of PVDF and PES against other marketed filters. We observed that the Millipore® Express filter membrane showed less adsorption and that the membrane gets saturated faster than other filter membranes. If a drug manufacturer is working on ophthalmic formulations with benzalkonium chloride as a preservative, then they can leverage our Millipore® Express SHF membrane to get a higher yield and reduce processing time.

Q: How are polymers used in ophthalmic formulations?

A: Polymers offer several benefits for drug forms. They can increase the contact time with the target tissue and reduce the drainage of the solution. Polymers also help to enhance the efficacy of the drug — if its viscosity is initially too low, polymers can help to further sustain the release of the active drug substance. They can act as solubilizers, inhibit crystallization and serve as a lubricant.

> Polymers can increase contact time with the target issue and reduce the drainage of the solution, offering several benefits for drug forms.

A variety of polymers can be used in ophthalmic formulations, including those of natural, synthetic or semisynthetic origin. In addition to selecting the right polymer for the formulation, aspects related to preparing the polymer solution, sterilization, and interaction with the other excipient in the final formulation must also be considered.

Q: What advantages does polyvinyl alcohol offer?

A: Polyvinyl alcohol (PVA) is a biocompatible synthetic polymer produced by the polymerization of vinyl acetate and partial hydrolysis of the resulting esterified polymer. PVA has been used in approved drug products and is generally recognized as safe (GRAS) by the FDA, does not have any immunogenic effects, and its long-term use has been demonstrated in many different formulations including oral, topical and ophthalmic.

It is water soluble, has a narrow range of viscosity, and has a high degree of swelling, offering the precise viscosity needed for formulations to remain in the eye cavity. The polymer has high adhesion and high correlation properties and also forms a transparent solution, which is important for medications administered to the eye. These are also important for retention in the eye cavity. With excellent lubricant activity, this polymer is well suited for lubricating eye drops.

Finally, PVA acts as a precipitation inhibitor of crystallization which means it helps retain the solubility of the API throughout the storage of the dosage form. With PVA being synthetic in nature, you can ensure that every batch will have high reproducibility which is very important for the ophthalmic dosage form.

Q: How is MilliporeSigma supporting the pharma industry in regards to ophthalmic drug delivery?

A: The SAFC® portfolio offers many products which can be used to manufacture sterile ophthalmic formulations, including a wide variety of excipients specifically designed for sterile formulations, aseptic filters, single-use systems, sterile connectors as well testing services for QC purposes.

For biologics, we developed a proprietary technology based on excipient combinations to reduce viscosity and maintain stability. Our R&D is continuously focusing on the ophthalmic sector to resolve the current challenges of our customers. Also, we are aware of the needs and challenges in the ophthalmic sector and support our customers not only with products but also with information needed to fulfill regulatory requirements and for risk assessment. In this evolving market and with increasing regulatory demands, we believe that having a strong and reliable supplier as a partner is a key element for success.

Olaf Zweig
EY Partner, Life Sciences

Derron Stark
EY Principal, Strategy and Transactions

Rethinking pharma supply chains

What it will take to build resilient and sustainable supply chains for the future

Since being declared a global pandemic in 2020, COVID-19 has impacted global supply chains with effects that are still being witnessed today. Each day comes news of "choked ports, out-of-place shipping containers, record freight rates and other problems that cause disruption and defy easy answer," acknowledged the World Economic Forum.[1]

Air transportation routes, as well as shipping, have suffered from the effects of the pandemic, with global air traffic falling by more than 90% in April 2020. With armed conflicts leading to airspace closures in early 2022, the effects of the pandemic and other disruptive global events seem set to continue for the foreseeable future.

Like other sectors, the pharma industry has had to absorb the impact of recent events on its supply chain operations. Throughout the pandemic, pharma has stood on the front line of the public health battle to develop and deliver vaccines and antivirals, working closely with governments and regulators. To their credit, these stakeholders have recognized the need for an unusual degree of regulatory flexibility during the pandemic, embracing a level of close collaboration with the pharma industry which will hopefully continue into the future.

But while acknowledging the industry's achievements during the crisis and the potential longer-term benefits it may yield in terms of improved collaboration, we must also recognize that COVID-19 was a serious challenge for the industry's supply chains. Leading pharma executives told us in the early months of the outbreak that their operations had already faced a 'stress test' of unprecedented dimensions.[2]

Now, more than two years after COVID-19's emergence, it is time to evaluate how pharma has coped with this test and what learnings for the future can be taken from its performance.

To this end, EY held discussions with 17 global heads of manufacturing and supply chain operations at companies that are members of the Pharmaceutical Manufacturing Forum (PMF). The goal of the discussions and subsequent analysis was to understand what the future for pharma supply chains may look like and what measures the industry can take to build greater resilience.

How pharma coped

"Pharma supply chains are essential for the national and health security and economic prosperity of the United States," stated Janet Woodcock, the then-acting FDA Commissioner, in June 2021. "The COVID-19 pandemic revealed just how vulnerable the supply chain is in this country," Woodcock added.[3]

This comment from a leader of pharma's chief U.S. regulatory body captured the fact that pharma's supply chains are suddenly in the spotlight. The heightened level of attention to pharma supply chains is by no means confined to the U.S. Anxieties over pharma's ability to supply key products have surfaced worldwide and major tensions, such as the disputes over resource priority for COVID-19 vaccines, have received significant media coverage.

Beyond the headlines, how vulnerable have pharma's supply chains proven to be? In practice, the absolute number of shortages is relatively small when placed in context. In the U.S., in 2020 and 2021, supply issues have been reported for under 1.5% of the 20,000+ prescription drug products registered with the FDA.[4] While shortages are reported by the manufacturers, stocks of products are typically kept by wholesalers, hospitals and pharmacies; hence, a reported shortage does not necessarily mean that patients are missing treatments.

Focusing on innovative pharma companies (i.e., the segment of the industry engaged in the research and development of new drugs), our interviews with PMF members revealed that this segment has confronted a number of challenges during the pandemic. In our discussions, senior executives at the industry's leading companies described difficulties acquiring sufficient levels

of certain raw materials and consumables. These included ethanol, toluene, acetonitrile, magnesium and neodymium, as well as specific single-use items such as biobags and other consumables required to maintain production output. For example, in 2021 there was a limited supply of the sterile filters used in biological drug manufacturing. Since vaccine manufacturers were depending on the same filters, the prioritization of mass vaccination programs resulted in a global shortfall. One respondent noted that "it has been even more challenging for small biotechnology companies to buy filters." With filter shortages expected to last for up to two more years, delays to development programs are likely to continue.

Yet despite these issues, our data suggests that, to date, PMF member companies succeeded in solving or mitigating the challenges they faced during the pandemic. Our analysis, presented on the left of Exhibit 1, shows that there is no significant trend indicating increased shortages of innovative pharma products in the 2019–2021 period.

This is confirmed by the overall assessment of the PMF members we spoke to (on the right of Exhibit 1). Companies maintained pre-pandemic service levels throughout. Where companies did face shortages, these affected only specific products experiencing demand surges due to COVID-19. Indeed, some companies told us that supply chains had performed better than in 'normal' times. With a reduction in reporting demands (including a lower level of internal and external auditing) and a heightened focus on productivity, some companies paradoxically found themselves operating more efficiently and with better service levels.

Supply chain policy interventions

For pharma, as well as for the policymakers, providers, payers and patients that constitute its major stakeholders, the ultimate aim is the same: to allow patients to access the right drug at the right time.

Industry supply chains largely succeeded in that goal in 2020–2021. Nevertheless, governments and regulators demonstrated during the pandemic that they are willing to intervene to help ensure the security of pharma supply. The three main economic and political global centers and trading blocs — the U.S., the EU and China — have all implemented wide-ranging measures since early 2020 aimed at securing supply of medical and pharmaceutical products.

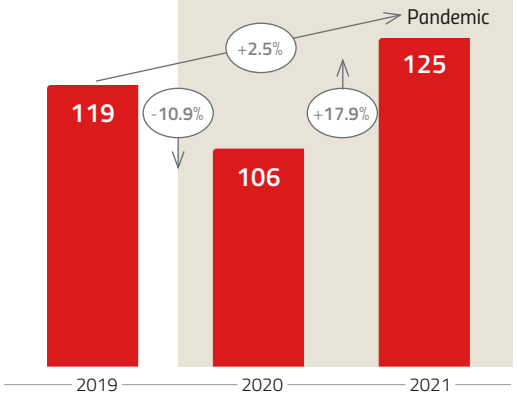
In recent decades, we have witnessed increasing globalization of pharma supply chains. The policies in the three major trading blocs suggest that we are seeing the start of a countertrend toward increased localization of supply chains and greater emphasis on regional or national self-reliance.

This change is part of a far broader ongoing shift in national strategic thinking, which may have been accelerated by COVID-19

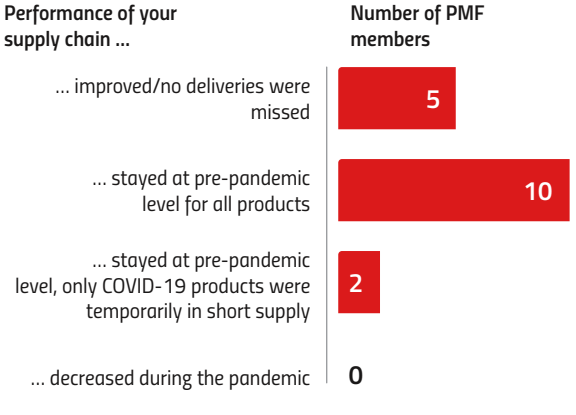
EXHIBIT 1

Performance of innovative industry's supply chain during the pandemic

Total shortage reports for innovative products in the US and EU4 (Germany, France, Italy, Spain)



Innovative supply chains' service levels during the pandemic



but is driven by deeper underlying factors that predate the pandemic. Among these factors:

- The globalization model is changing, with major trade regions increasingly seeking autonomy, resulting in sector supply mandates, including changes to trade, regulatory and tax policy
- Global trade agreements have declined in relevance as regionalized trade and bilateral agreements assume greater importance; the diminished role of the World Trade Organization underlines this shift[5]
- All stakeholders increasingly acknowledge the importance of sustainability and the need to measure the impact of companies' environmental, social and governance commitments, supported by the increased ease of tracking metrics such as carbon footprints and other externalities

> While there exists various possibilities for rethinking pharma supply chains, it is important to emphasize that there will not be a single or simple path forward from this point.

Moreover, it hardly needs stating that COVID-19 will not be the last major crisis that must be confronted in the 21st century. Recent developments in Europe emphasize the dangerous tensions present at geopolitical fault lines. The long-term impacts of the present military turbulence for the pharmaceutical sector specifically remain unclear for now, but supply chain operations across all industries will inevitably be affected by an increase in logistical complexity and cost. We can also anticipate that trade with regions at the center of ongoing military disruption will be negatively affected by difficulties in exchanging currency and/or executing bank transfers, as well as a lack of trusted institutions to serve as contract guarantors. Moreover, pharma companies may confront increased IP and cyber challenges if warring nations decide to breach norms on patent protection or block key external data connections.

Beyond these immediate impacts, the larger consequences of the military conflict — from sanctions and escalating inflation to the broader human and economic dislocation — will be felt across the global macroeconomic landscape. This will have ongoing and potentially significant consequences for industry supply chains. Beyond the current crises, moreover, the world will inevitably also face other, less predictable shocks in the future. From new pandemic outbreaks to cyber attacks (or even cyber war) to the effects of climate change, developments are all likely to aggravate geopolitical tensions further. As a result, we can expect states to continue pursuing self-reliance through supply chain localization over the coming decade.

Next steps

There is reason to believe that pharma will have an enlarged role in these national strategic calculations. In the wake of the national public health crises unleashed by the pandemic, governments are beginning to acknowledge pharma as a 'strategic sector' vital to economic and national security. The raft of recent policy measures to secure pharma supply chains taken in the U.S., the EU and China are evidence of this growing recognition. Ensuring a sufficient supply of pharma products to support public health objectives is becoming an increasing priority worldwide.

We can therefore expect to see policymakers explore a broader range of interventions in the industry's operations. Exhibit 2 sets out the range of possible measures policymakers may choose to implement in the future. Our analysis estimates the political likelihood of each of the possible measures governments may implement (plotted on the x-axis across the bottom) and their potential impact on supply chain operations (shown on the y-axis).

The measures were obtained and evaluated based on EY research into recently-passed laws, bills and statements from policymakers and competent authorities. Based on this assessment, six of the measures identified have the highest potential impact on the industry. These 'Tier 1 policies to monitor' appear in the upper right quadrant of Exhibit 2. The majority of these measures would encourage greater national or regional 'localization' of supply chains.

Already, pharma companies themselves are exploring multiple initiatives to increase supply chain resilience. For example, a number of companies have implemented multi-sourcing and leverage local contract development and manufacturing organizations. These measures can benefit resilience and are relatively simple to implement.

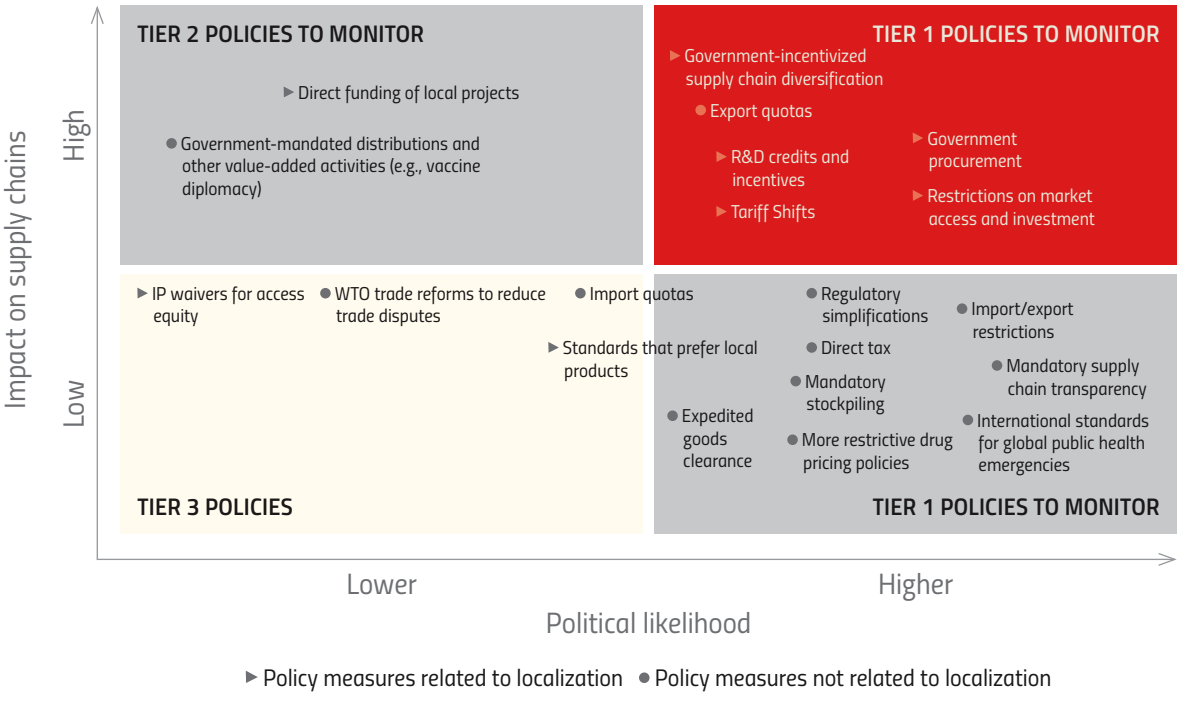
Certain other possible approaches may have a greater impact but will require longer-term investment and commitment to realize.

At this point, the industry and its stakeholders need to evaluate what measure, or combination of measures, can deliver the results they seek. They have a range of viable options available to them to increase supply chain resilience. Among these options, they can consider:

- Pursuing varying degrees of localization and other complementary or alternative approaches, including

EXHIBIT 2

Overview of potential policy measures across three trading blocs (U.S., EU and China) and their impact on pharma supply chains



establishing a hub-and-spoke manufacturing model
- Setting up joint manufacturing, or a joint physical warehouse (where antitrust regulations permit)
- Establishing a procurement clearinghouse (an order management vehicle that could consolidate and forward pharma companies' orders for common raw materials and consumables to suppliers and propose reallocations between companies, balancing excess stock in one area with shortages in another)
- Improving end-to-end supply chain visibility and transparency
- Optimizing regulatory requirements such as introducing regulatory notification principles instead of product approval

Each of these measures carries associated costs and benefits, and as companies consider their options, there won't be one single approach adopted industry-wide. However, although different companies will pursue different specific supply chain strategies, we can anticipate certain broader general trends.

The most significant of these will be the transformation of the fully globalized supply model to a hybrid model, balanced more strategically across global, regional and local sites. This hybrid model will aim to enhance supply resilience through companies building redundant capabilities with multiple suppliers, working with CDMOs and developing internal sites or holding more inventory.

Because these and other resilience-boosting measures are likely to be implemented, the supply chains of the future will be more expensive to operate, at least until the introduction of newer enabling technologies. In the long term, these increasingly complex supply chains will need to be supported by increased digital capabilities, including automation, artificial intelligence, and end-to-end supply chain systems.

Greater collaboration and cooperation between pharma and its stakeholders will be key to successfully building resilient and sustainable supply chains for the future — and delivering the outcomes sought by patients and by all parties in the ecosystem that serve them. While there exists various possibilities for rethinking supply chains, it's important to emphasize that there will not be a single or simple path forward from this point.

For a full list of references, visit pharmamanufacturing.com

Pascale R. Leroueil
Vice President, Healthcare Sector
William Davidson Institute at the University of Michigan

Quantifying technology's impact on vaccination rates

How reducing technology-addressable vaccine barriers affects coverage rates

Every year, businesses and organizations spend billions of dollars on vaccine development, with millions going specifically toward the development of new vaccine technologies. These technologies can offer simpler and safer administration methods, improved thermostability, and fewer required doses, which can in turn offer wide-ranging benefits such as lower costs for vaccine storage, reduced chances for adverse events, and increased efficacy.

Many of these benefits are captured during the development process through laboratory experiments, clinical trials and health economic studies. One benefit that is rarely quantified, however, is the expected increase in vaccination coverage rates.

The design and development of vaccines is already incredibly expensive and complex — there are high capital costs associated with every decision along the development pathway. And the vaccine business relies heavily on scales to make it work. Having a strong, data-backed understanding of how many vaccines can be sold in any given market before starting to manufacture a vaccine is incredibly important.

For decision-makers in the vaccine development and manufacturing space, it's important to understand that vaccine technologies play an especially significant role in determining demand and coverage rates. For example, say a country has access to a microarray, patch-based vaccine delivery system that could replace the standard syringe and needle delivery system. What might that do to vaccination coverage rates in that country?

Initially, the answer might be "not much." But once you consider the operational implications of who is administering a particular vaccine, the implications for the delivery system can change dramatically. For instance, a vaccine that requires a mid-level skilled health care worker such as a nurse to administer compared to a less skilled worker, such as a community health worker, could lead to significantly higher coverage rates, especially in countries with fewer mid-level skilled health care workers.

Anticipating demand for different vaccine presentations early in the development process is an incredibly powerful tool that can be utilized for more intentional decision-making. The type and magnitude of potential benefits make it possible to channel resources toward vaccine technologies and presentations with greater promise.

Key barriers to vaccination

The COVID-19 pandemic shined a huge spotlight on the barriers to vaccination that exist for many people across the world.

For example, the refrigeration requirements for some of the COVID-19 vaccines were a significant obstacle in many countries. Many ministries of health simply couldn't afford the ultra-cold storage freezers required for the vaccines, or the electrical grids were not reliable and stable enough to keep the freezers continuously running. Similarly, the need for multiple doses and limited access to skilled health workers created additional challenges toward full inoculation.

The result? Staggering levels of COVID-19 vaccine inequity across the globe. Reducing such barriers when developing vaccines will not only help to increase coverage rates and demand, but it is also critical in protecting lives.

Barriers to vaccination come in two main categories: those directly addressable by vaccine technologies

EXHIBIT 1

Example of the conceptual framework used to estimate vaccination coverage

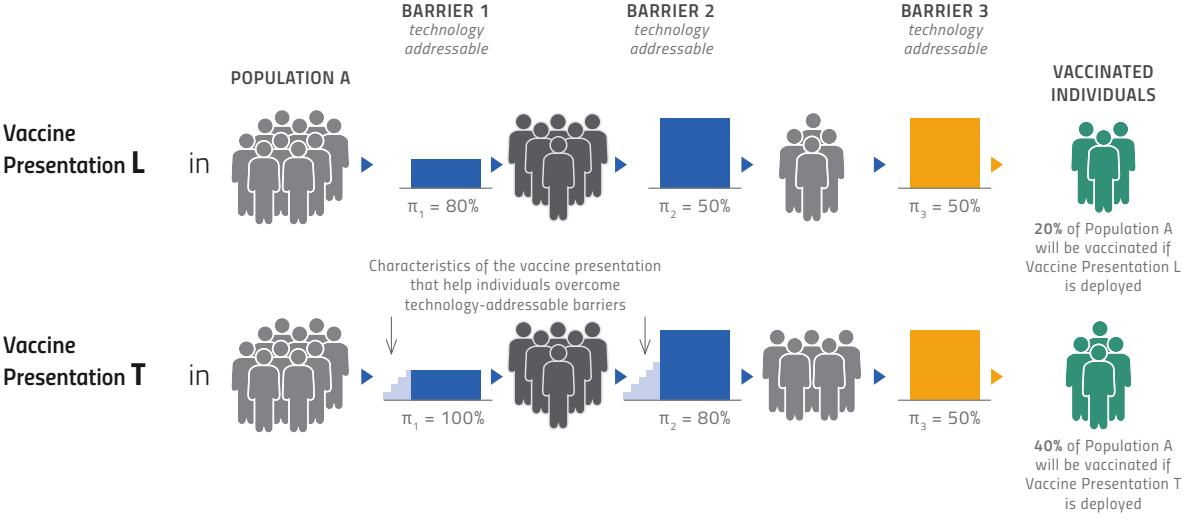
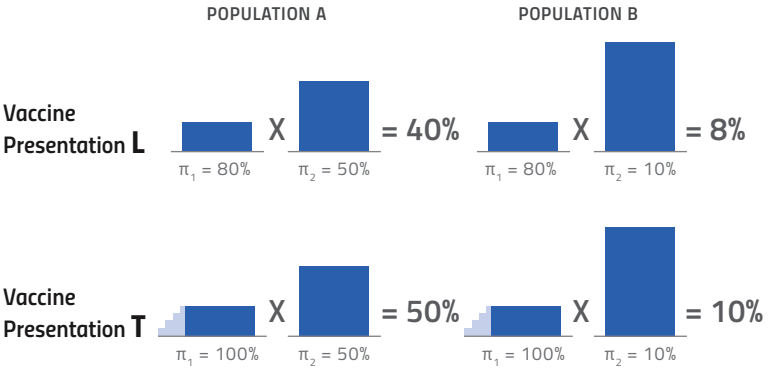


EXHIBIT 2

Importance of aligning vaccine technology with barriers faced by a population

In this example, new technology in Vaccine Presentation T affects only Barrier 1 and therefore has a lower impact in Population B, for which Barrier 2 is much more prominent.



('technology-addressable') and barriers that are 'non-technology-addressable'. The non-technology-addressable barriers are factors inherent within a country's current health system. For instance, this could include factors like the number of physicians and/or nurses, conflicts such as civil war and the amount of government health care funding available, to name a few. With non-technology-addressable barriers, there is an assumption that the environment will not change drastically over time between the current state and a future state. With those inherent non-technology-barriers factored in, it's then possible to estimate the potential impact of reducing the technology-addressable barriers.

As exemplified earlier with the patch-based vaccine, some technologies could mitigate or remove barriers, leading to increased demand for vaccines and higher coverage rates. Global health partners in this space, including the World Health Organization (WHO), defined five technology-addressable barriers:

1. Vaccine schedule: The probability that a member of the vaccine-eligible population does not receive vaccination due to an inability to comply with the existing vaccine schedule.
2. Temperature storage requirements: The probability that a member of the vaccine-eligible population does not have access to vaccines properly stored in a functional cold chain environment since their manufacture.
3. Administration requirements: The probability that a member of the vaccine-eligible population does not have access to an individual who can administer a vaccine using the most complex administration method.
4. Acceptability of presentation: The probability that a member of the vaccine-eligible population (or caregiver) exhibits vaccine non-compliance due to specific characteristics of the vaccine presentation. (For example, potential issues due to the use of pork products in the manufacturing process of the vaccine.)
5. Doses per container: The probability that a member of the vaccine-eligible population is refused vaccination due to provider's unwillingness to open a container.

Our research identified a sixth technology-addressable barrier: Number of doses. This was necessary to include since data shows that the number of people fully vaccinated drops off as the number of required vaccine doses increases. The assumption here is that a vaccine with more than one dose requires an individual to overcome the other five barriers multiple times, further reducing coverage rates.

Each of these technology-addressable barriers includes a range of scenarios and presentations that affect coverage rates, from low to high. In breaking down the effects into five different categories, including low, medium-low, medium, medium-high and high, we were able to build an effective model for estimating vaccine coverage rates. The model focuses especially on low- and middle-income countries (LMICs), but can be applied to any region of the world.

To further put this into perspective, let's look at one of the biggest barriers of vaccination in African countries: temperature storage requirements. While we previously mentioned this as a barrier for the COVID-19 vaccine in particular, cold storage requirements for vaccines present a broader challenge for other vaccines as well. Requiring an unbroken frozen chain of -15 degrees Celsius or lower would create the highest barrier for vaccine coverage. However, making a vaccine that requires controlled temperature, with the ability to tolerate up to 40 degrees Celsius for at least three days, would have a large effect of up to 50% on coverage rates.

A model for estimating vaccine coverage rates

Context is everything when it comes to the impact of vaccine barriers on a population's coverage rates. As noted, in certain countries, developing a vaccine that doesn't require refrigeration could have a huge effect on the volume of vaccines one is able to sell. In other countries, where refrigeration is consistently available, that might not be the case.

As a vaccine manufacturer, there might be some intuitive guesses early

on for what could increase demand. Wouldn't it be helpful if we could make a vaccine that can be delivered by a community health worker instead of a nurse? Wouldn't it be nice if we made a vaccine that was packaged with fewer doses per box? These are fine approximations at first, but they obscure the interaction between the characteristics of the vaccine with the characteristics of the environment. What is a country's infrastructure? What does the country's health care system look like, and how much would it benefit from different technological improvements?

Our model takes that environment into consideration by leveraging publicly available data from sources like UNICEF, which offers insight into vaccine presentations in various countries, and DHIS2, which provides a wealth of data on the environmental contexts of various countries.

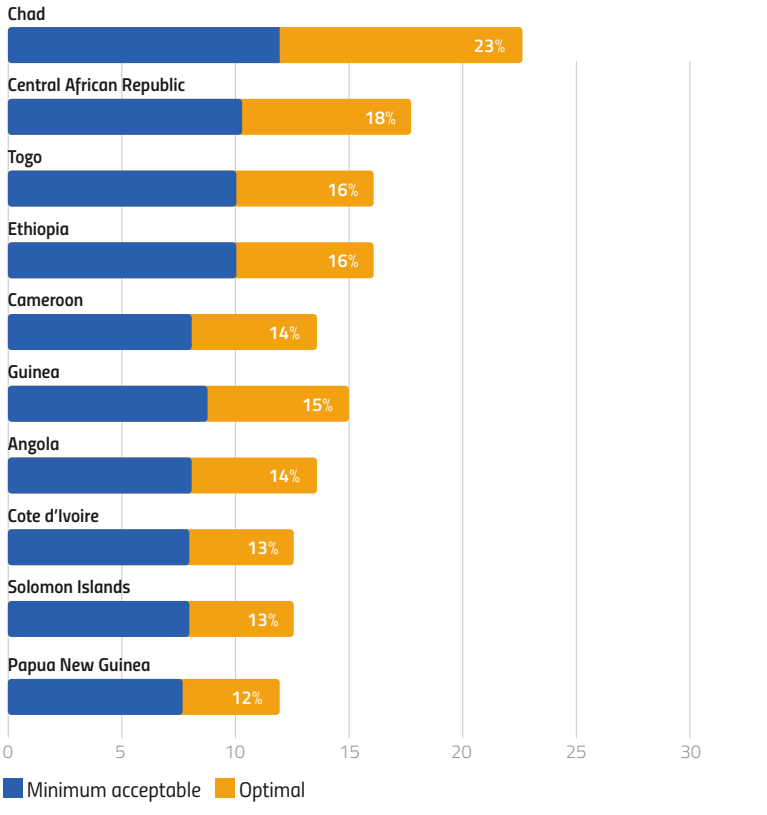
The model turns a relatively simple assumption into numbers that show the increase in coverage rates. It produces something to the effect of, "If country X had access to vaccine presentation Y, it could achieve a vaccination coverage of Z%." The model employs 'probability theory,' which essentially says if the probability of A happening is a, and the probability of B happening is b, the probability of both A and B happening is a x b. The math is slightly more complicated, but the general idea is that the probability of a person in country X with access to vaccine presentation Y getting vaccinated is the product of the probabilities of a person overcoming each of the six barriers defined above.

One benefit of this approach is that it can be used at any point along the vaccine development pathway. Whether someone is thinking about research and development or considering manufacturing vaccines for a particular region, this approach allows them to estimate the maximum demand for a specific vaccine presentation in different deployment contexts.

EXHIBIT 3

Incremental change in vaccination coverage rate when using MR-MAP (relative to a subcutaneous measles vaccine)

Ten countries with the highest estimated increase in coverage rate when using micro-array patch for a measles-rubella vaccine (MR-MAP)



Take, for example, a vaccine for malaria. If you are trying to figure out the potential volume — measured by the potential increase in coverage rates — across the globe, this model allows you to input the vaccine presentation and see where the highest potential volume for that vaccine exists. This would help in determining where manufacturing can focus.

In a different scenario, there could be three presentations of a malaria vaccine — syringe, patch and aerosolized — and a commitment to manufacturing in, say, East Africa. The model can show which of the three presentations would have the largest potential volume, giving concrete numbers into how these vaccine technologies would affect coverage rates in the context of countries in that region. In both of these scenarios, this high-level view helps in directing focus and investment early in the decision-making process.

As mentioned, this model is particularly specialized in estimating vaccination coverage rates in LMICs for three reasons:

First, while access to vaccines for childhood illnesses, such as measles and polio has increased dramatically

during the past 50 years, in many LMICs, vaccination rates are still well below targets. These lower rates signify an opportunity for vaccine manufacturers to reach these markets and increase coverage with new vaccines.

Second, LMICs are the types of data-limited environments in which an answer that relies on data is especially helpful, without having to invest significant funds towards deep market analysis.

Finally, a greater proportion of the barriers to vaccination in LMICs are technology addressable compared with high-income countries.

This approach of tackling technology-addressable barriers can also be expanded for use in any pharmaceutical or medical technology. In principle, one could extend this method to almost any product or service, whether it is health-related or not. What would need to change are the barriers and the definitions behind them. For example, when thinking about methods of getting an ultrasound, access to refrigeration is probably not a barrier to treatment, but access to reliable power through a stable electrical grid probably is.

The model in action

This model is currently in use with major donor organizations working in vaccine-related spaces, helping guide their investments. For vaccine manufacturers, it's equally, if not more important, to consider how reducing these six technology-addressable vaccine barriers will affect coverage rates. Money and time are limited. Having an idea of a particular vaccine's market share before taking the leap into an investment is strategically helpful.

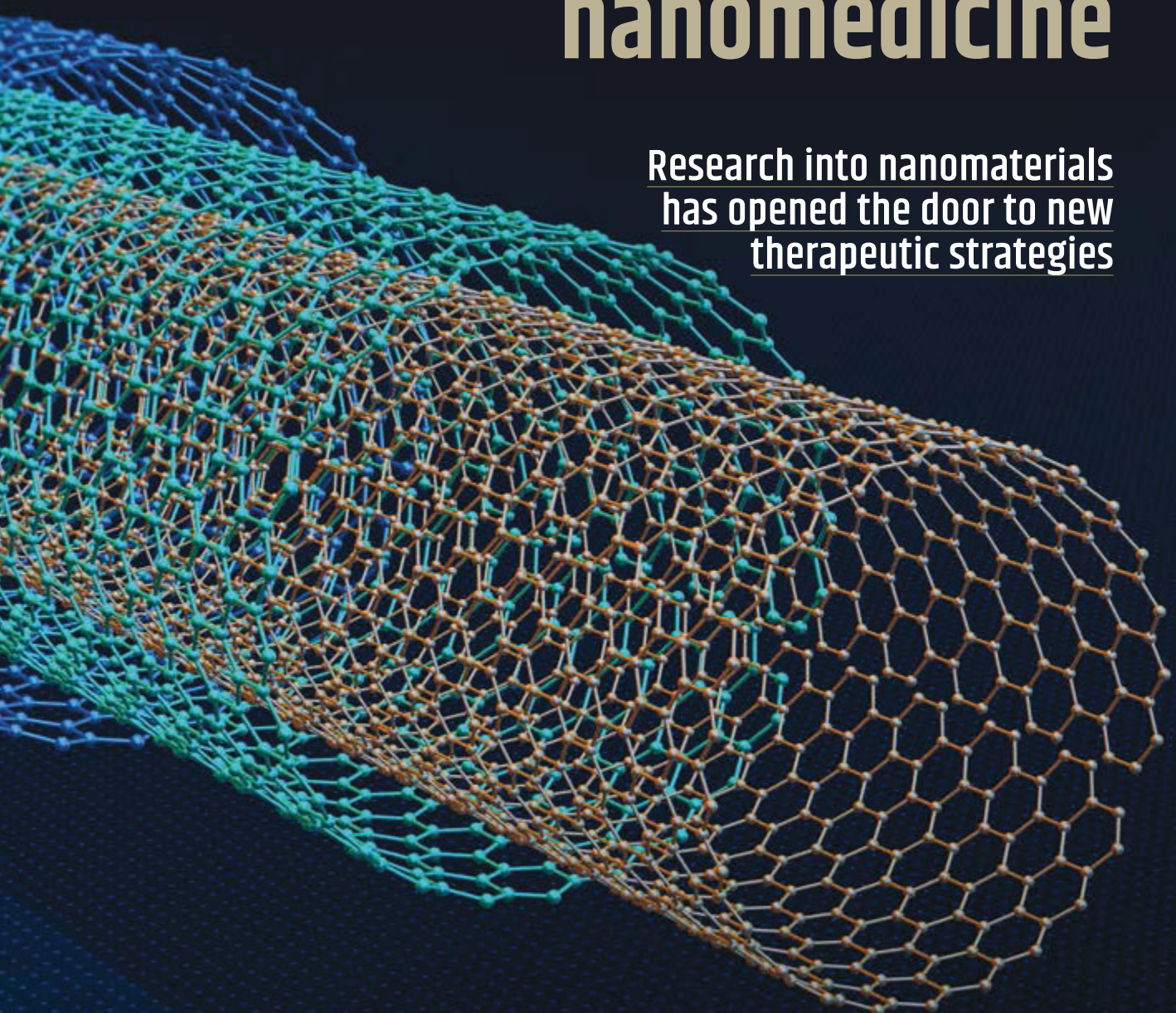
While reducing technology-addressable barriers certainly helps increase coverage rates in both high-income countries and LMICs, there is a significant market and need for effective vaccines in the latter. Those with resources in the vaccine space should seriously consider developing more platforms that help reduce barriers for countries with the fewest resources.

The COVID-19 pandemic has made it clear that identifying ways to increase vaccine coverage rates across the world is critical to our survival as a global population.

Megan Muroski
Senior Product Manager, MilliporeSigma

Advancing nanomedicine

Research into nanomaterials has opened the door to new therapeutic strategies



Many nanoparticles, including graphene nanoribbons, have been developed and studied over the past few decades. Much excitement has been generated around their potential use as both therapeutic and diagnostic tools.

Numerous nanoparticle formulations for medicinal and diagnostic purposes have been developed because of recent breakthroughs in nanotechnology. Using diagnostic nanoparticles and other graphene-derived nanostructures, researchers have been able to visualize pathologies and advance knowledge of crucial (patho-)physiological concepts underlying various diseases and disease treatments.[1]

A wave of new research is exploring how the industry can utilize graphene nanoribbons (GNRs) in drug delivery and beyond to allow for more precise therapeutic treatments.

The promise of graphene nanoribbons

The poster child of nanotechnology is undoubtedly graphene: a two-dimensional hexagonal lattice made of sp2-hybridized carbon atoms. Graphene exhibits several exceptional properties: It is the strongest material ever tested and exhibits extraordinarily high thermal conductivity and vanishingly low electrical conductivity.[2] Graphene forms the basis of a wide variety of graphene-derived nanostructures that have already been used in countless applications throughout science, technology and engineering. Graphene and graphene-derived nanostructures are the subject of considerable scientific research to develop novel technological solutions.

Strips of graphene with widths of the order of tens of nanometers are known as graphene nanoribbons.[3,4] Inheriting the properties of graphene sheets but exhibiting electron confinement properties across its short axis, the properties of graphene nanoribbons are no less exceptional. GNRs show promise in a variety of applications and have generated attention from researchers in domains including chemistry, physics, materials science and medicine.[5] These fields are interested in graphene nanoribbons due to their high aspect ratio, electronic properties, conductivity, and propensity for functionalization.[6]

Graphene nanoribbons have already been used in several applications, including bioimaging, DNA sequencing, batteries, conductive films, polymer composites, sensors, and energy conversion or storage devices.

The electrical and mechanical characteristics of GNRs are exceptional. Mechanical, chemical, photo- and acoustic sensors, instruments for the direct sequencing of biological macromolecules including DNA, gene and drug delivery systems, and tissue engineering are among the application fields.[1]

Graphene nanoribbons as drug delivery agents

Researchers have demonstrated the viability of pH-controlled drug uptake and delivery using graphene oxide by creating self-assembling supramolecular hydrogels from graphene oxide and metformin hydrochloride, an important drug for diabetes treatment.[7] The resulting hydrogels showed increased drug-release rates in acidic media, suggesting that similar approaches could be used for controlled drug release in the stomach.

Much research into graphene nanoribbon or graphene-based drug delivery technologies focuses on cancer treatment. In these roles, graphene-based solutions provide the opportunity to deliver more targeted cancer treatments, thus decreasing the systemic toxicity associated with conventional cancer treatment drugs.[8] GNRs have a large surface area, which lends itself well to functionalization with chemical groups or physisorbed moieties. Oxidized nanoribbons (oGNR) and reduced graphene nanoribbons (rGNR) are envisaged as unique drug delivery agents in cancer and tumor therapy, with early research demonstrating the potential of these materials in delivering cancer treatment drugs to tumor sites.[9]

Graphene nanoribbons have also been utilized as mediators in photothermal therapy for cancer treatment, in which non-ionizing radiation (usually infrared) is used to kill cancer cells. By functionalizing reduced graphene oxide nanoribbons with polyethylene glycol (PEG), researchers could attach markers to human glioblastoma cells for selective fluorescence imaging. This resulted in high performance in subsequent near-infrared photothermal therapy.[10] In another report, researchers used phospholipid-PEG-modified graphene oxide nanoribbons to treat glioma cells in combination with chemotherapy and photothermal therapy. The results showed that drug chemotherapy and near-infrared hyperthermia could function synergistically, opening up new avenues of research for novel cancer treatments.

Beyond therapeutics

Researchers have also been exploring applications of graphene nanoribbons across various sectors of biomedicine.

Bioimaging

Carbon nanomaterials can cross cellular membranes and exhibit enhanced Raman scattering, strong near-infrared absorption, high photoluminescence yield, and photoacoustic response.[11] Coupled with a huge potential for functionalization and strong biocompatibility, these materials — including graphene oxide, graphene nanoribbons, and carbon nanotubes — show tremendous promise as contrast agents in imaging applications. It is possible to improve existing contrast agents with graphene and its derivatives and create whole new probes and agents for biomedical imaging. These promise to improve our ability to monitor processes in living cells, tissues, or even entire bodies using a variety of approaches.

Neurophysiological rehabilitation

Based at Rice University in Texas, the James M. Tour group has carried out extensive research into the potential therapeutic benefits of graphene ribbons in neurophysiological rehabilitation.[12]

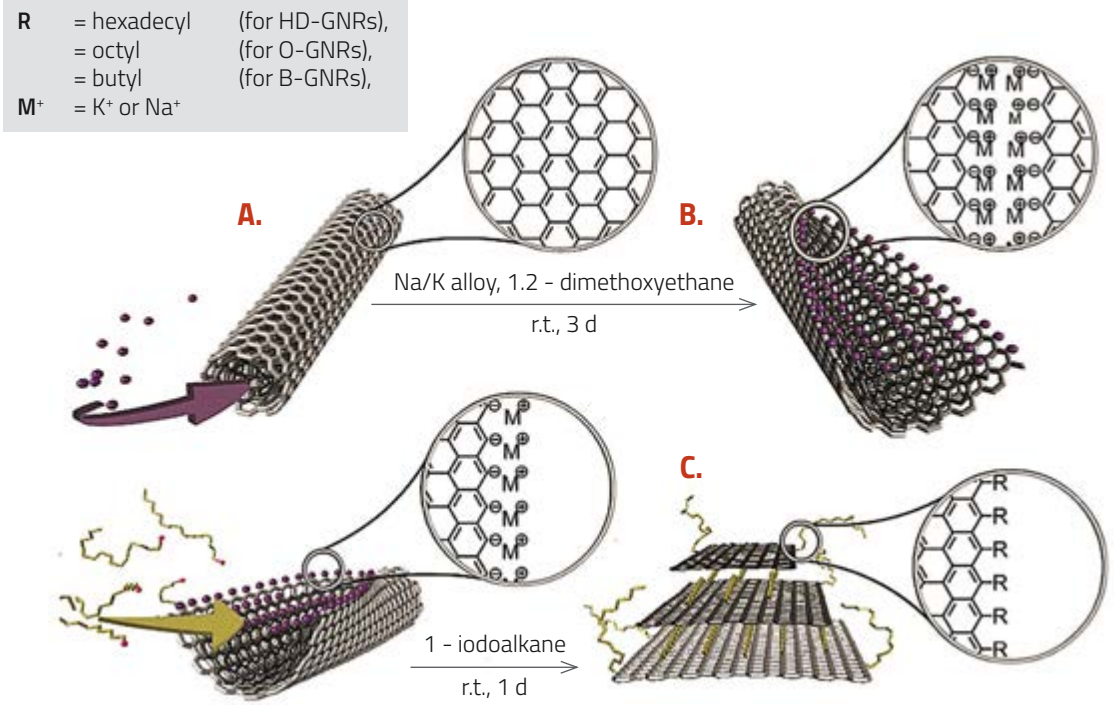
Recent research from the group demonstrates that nontoxic polyethylene glycol graphene nanoribbons can create a favorable microenvironment for spinal cord healing following injury.[1,12] PEG-Graphene nanoribbons' main structural elements provide a microenvironment that is receptive to healing. The composite material fills the space left by severed axons to create a nanoscaffold that can facilitate the transmission of neuronal signals across the lesion while allowing growth along the framework.

The Tour group has already demonstrated in five rats that applying 0.5 mL of a 1% PEG-Graphene nanoribbons solution in PEG 600 at C5 vertebra following total cervical transection led to a 24-hour restoration of about 30% of the pre-surgery somatosensory evoked potentials (SSEP) amplitude, a measure of brain and spinal cord response.[6] Within two weeks following surgery, one animal without SSEP measures regained use of its forelimbs and hindlimbs, scoring 19 out of 21 by week three on the

EXHIBIT 1

Scheme for unzipping and functionalization of GNRs

(A) intercalation of potassium between the walls of multi-walled carbon nanotubes; (B) splitting process of MWCNTs and formation of GNRs with active carboanionic edges; (C) in situ functionalization and intercalation of GNRs with alkyl groups



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Basso, Beattie, and Bresnahan (BBB) motility scale.

Biosensing

The field of biosensing involves the detection, identification and quantification of biological substances. Biosensors are particularly important in bioanalytical chemistry, where they can shed light on the interactions that occur in complex biological processes.[5]

The unique electronic properties of graphene oxide nanoribbons present opportunities for the development of optical biosensing technologies. Optical biosensors use light to probe molecular interactions and have numerous applications in clinical diagnostics, drug discovery, food process control and environmental monitoring.[13]

In addition to high conductivity and excellent electrochemical stability, graphene nanoribbons have good light transmittance, making them ideal candidates for optical biosensor elements. Graphene nanomaterials have brought a new surge of interest in optical biosensor research, with GNR hybrid materials using graphene nanobelts (or reduced graphene oxide nanobelts) exhibiting excellent optoelectronic properties that can be used in biosensing applications.

Research in 2015 showed that graphene nanoribbons coated with a cobalt coordination polymer could provide a wide linear range and low detection limit in H202 sensing.[14] Other approaches include using modified graphene nanoribbons as signal amplifiers for photoelectrochemical biosensors driven by natural light.

Widespread potential

Due to their amphiphilic properties, graphene-oxide nanoribbons — the oxygenated derivative of graphene nanoribbons — provide numerous opportunities in the field of biomedicine. For cutting-edge biomedical applications, they can be modified noncovalently and covalently to provide a huge range of functionality in diagnostic and therapeutic applications.

From sensitive biosensing to precisely targeted drug delivery, the potential applications of graphene nanoribbons (and other graphene-derived nanostructures) are widespread and promise to have a significant impact throughout life sciences.

For a full list of references, visit pharmamanufacturing.com

Andrew Harris
Director of Engineering & Architecture, DPS Group

Mark Canter
Director of Biotechnology, DPS Group

Process design considerations you shouldn't overlook

The global mAbs market was valued at $147 billion in 2020 and is projected to reach $390 billion by 2030. This growth has led to demand for large capacity requirements.

The design and construction of a new manufacturing facility can be a costly proposition. The following are four factors that can reduce an organization's CapEx and OpEx costs during the design of mAbs facilities and the production of therapeutics in those facilities.

1. Design accommodations for reprocessing downstream batches to minimize/eliminate lost batches
During design and development for a mAb process, the possibility of equipment failure is considered — but what does that failure mean for the product sitting there at risk? What happens when you have millions of dollars worth of product sitting in a tank, a post-use filter integrity test failure triggers an action limit, and you must reprocess to save the batch?

mAbs facilities run like railroad trains. There is a set schedule with typical facilities producing batches every three or four days. If a train is derailed, every other train is held up. The entire batch will be lost if there's no well-engineered system to go back upstream to reprocess.

Consequently, overall equipment design must preserve optimal process performance under normal conditions — while also integrating mechanical, automation and cleaning strategies for successful reprocessing when disruptions occur. This can be as simple as a swing elbow or flex hose solution to transfer the product back upstream, or as complex as permanent valving with associated automation.

2. Optimize for filtration requirements at a large scale to minimize consumables changeout
Implementation of process intensification technologies to achieve ever-higher titers has resulted in high cell densities that challenge harvest and clarification operations.

The most efficient technology for separating cell debris from the product is a centrifugation cell separation step, which removes roughly 95% of the solids. The residual cells and cell debris that break through centrifugation must be filtered. Because of the multi-product nature of manufacturing current and future products, some plants are very conservative in sizing filtration capacity. That often leads to large rooms filled with depth filters and holders. And because filters themselves are single-use, there can be a massive, operator-intensive flow of consumables coming in and going out.

Unfortunately, there is no real solution other than to be more aggressive with filtration sizing and to optimize the process, reducing the number of consumables.

3. Advantages of a single-use bioreactor may not outweigh stainless steel's initial cost
There are expensive challenges associated with implementing a single-use seed train in a large-scale facility — most significantly, correctly handling the logistics design for both new and waste single-use components.

Single-use equipment also carries a potential for leaks. Closed connections are essential, but this can be challenging with single-use equipment; tube welders are no longer commonplace, and aseptic connectors can be expensive. Some plants opt for redundancy in single-use components to reduce the risk of not being able to run. However, this can lead to supply chain issues and increased warehousing requirements.

Each plant must perform its own economic and logistical analysis to determine what makes sense for its building and design.

4. Involve operators in the design process to reduce human error
The most significant risk in any mAbs facility is people. If workers don't follow standard operating procedures or are not adequately trained, a simple mistake could become a costly production problem.

The earlier operators are involved in the facility's design and construction, the more successful the outcome will be. It is not uncommon, however, to launch a project and not see any operations people until the die has been cast. And making changes amid a detailed design phase can be expensive.

Of course, it is a cumbersome task to anticipate and address all the potential pitfalls at every step of the project, from design to production. Still, the more pharma can rationalize expectations, the more successful the industry will be at balancing costs and risks.

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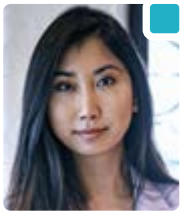

How pharma can overcome inflation

Hint: It's not by raising prices

Amidst rising inflation, supply chain bottlenecks, labor shortages and talks of a looming recession, it's no wonder manufacturers are starting to feel the squeeze of today's economy on their margins. In fact, due to inflation alone, 73% of manufacturers from across industries expect to increase the prices of goods through 2022.

Pharma manufacturers are no exception. Unfortunately for the pharma industry, the stakes are particularly high. With debates over prescription drug costs continuing, pharma may risk public backlash if they hike prices higher to offset economic pressures.

But there is a way for pharma to reel in excess costs and increase user adoption without sacrificing margins — while still passing on the savings to patients: Launching a direct-to-consumer (DTC) e-commerce brand and selling prescription drugs to patients online.

Tapping the telehealth boom

Prescription drug e-commerce platforms aren't a new concept. Consider the recent success of brands like Hims and Roman that make it seamless for patients to consult with a physician, get prescriptions and have medications shipped to their door — all without leaving their couch.

Patients are resonating with this simplified model. In fact, the use of telemedicine/telepharmacy products is up 38 times from early 2020. Particularly in the wake of the pandemic, patients are looking for easy ways to get the products that they need while skipping a costly, time-consuming, and potentially health-risking visit to the doctor's office and local pharmacy.

There's no reason why pharma manufacturers can't take advantage of this momentum by launching their own DTC e-commerce brand. Here's a few perks of selling direct:

Cut out the middleman

Going DTC allows pharma manufacturers to bypass middlemen in their supply chains, meaning they'll spend less time and capital negotiating with third parties, including pharmacy benefit managers (PBMs). This can be particularly valuable as controversy continues over the role of PBMs in rising drug costs in the U.S.

Increase patient adoption

Whether they are selling branded or off-patent drugs, cutting out the middleman presents a tremendous opportunity for pharma companies. Patients seeking out drugs they know well, like Viagra, may not get the name brand at the pharmacy, but they can purchase name-brand drugs directly from the pharma manufacturer instead — driving higher patient adoption. Selling off-patent drugs DTC can be incredibly profitable for pharma as well.

Pass off savings to patients

When pharma manufacturers move to a DTC model, they can increase profit without raising prices. It's a win-win for both manufacturers and patients. Patients are paying the same, or in some cases, significantly less, than what they would at the pharmacy, while manufacturers offset the effects of inflation and other economic pressures on their bottom line.

Increased brand recognition

Launching a DTC brand can help manufacturers foster more meaningful connections with patients. Instead of reaching brands through a third party, patients will be building relationships with brands directly.

Because prescription drugs require patient upkeep, manufacturers who can foster a seamless and enjoyable patient experience will see higher customer return rates. Manufactures learn more about their customer base through these interactions and can use these relationships to inform marketing strategies.

Up until now, pharma companies often lacked the expertise in necessary parts of the supply chain — like telehealth, distribution, digital marketing — and passed these services on to third-parties. However, new e-commerce solutions, digital marketing platforms and backend tools have made it easier for pharma companies to take ownership over the entire supply chain.

While the effects of inflation may not be going away any time soon, transitioning a portion of business to an e-commerce model may be one way to combat higher prices. As patients' reliance and acceptance of telehealth and telepharmacy continues to grow, it's time for pharma manufacturers to consider a promising future in e-commerce.

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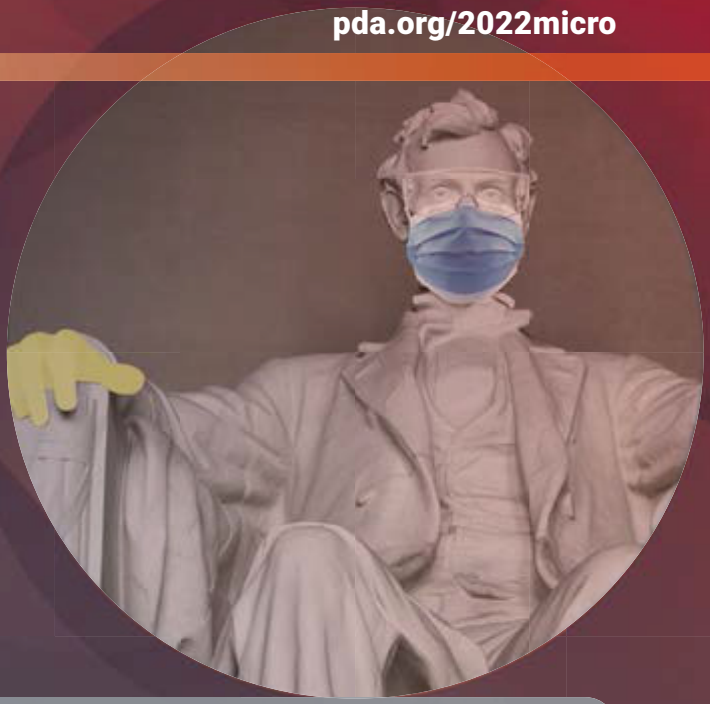
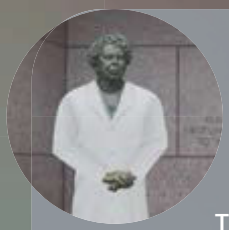
Leading through Science: A Monumental Undertaking





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  - **Erica L. Carpenter, MBA, PhD**, Research Assistant Professor of Medicine, *University of Pennsylvania School of Medicine*
- Ask the Regulators
  - **Renée S. Blosser, MS**, Microbiologist, CVM, *U.S. FDA*
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CONNECTING PEOPLE SCIENCE AND REGULATION®

SABIN Metal Corporation

PHARMACEUTICAL CATALYST RECYCLING EXPERTISE

REFINING • PRECIOUS METALS • RECYCLING

With best-in-class techniques and over seven decades of experience, we deliver the highest possible metal returns for our customers.

We recover and refine platinum, palladium, gold and other precious metals from catalysts and materials used in the manufacturing of pharmaceutical products. This includes precious metal catalysts used in hydrogenation on various intermediaries.

Find out more about Sabin Metal Corp's services, operations, and why a partnership with us is the right choice at *sabinmetal.com*