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AFTER A YEAR OF HISTORIC DEALS, BARDA LOOKS TO RECRUIT MORE PARTNERS IN PHARMA

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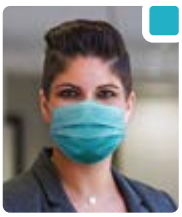
Karen Langhauser
Chief Content Director

A familiar face

BARDA went from obscure to iconic and has no plans to turn back



You probably don't recognize the name James Montgomery Flagg, but I guarantee you know his face.

At the peak of his career, Flagg was said to be the highest paid magazine illustrator in all of America. Flagg's version of Uncle Sam is one of the most celebrated icons in American culture. Between 1917-1918, the government printed off over four million copies of Flagg's "I Want You for U.S. Army" posters to boost recruiting efforts during World War I.

The face behind the illustrator's bold, powerful Uncle Sam? According to some accounts, it was Flagg himself. As one version of the story goes, Flagg aged himself with makeup, affixed a fake goatee to his chin and grabbed a mirror, using himself as a model. While the Uncle Sam character had existed decades before Flagg was even born, the depictions of Sam were inconsistent. Whether it had to do with timing, artistic ability, or simply having the right look, the Flagg self-portrait rendition of Uncle Sam stuck.

While James Montgomery Flagg was prolific in his day — even attracting the admiration of FDR himself — his style of illustration eventually fell out of fashion and his name faded into obscurity. But his face remained forever etched in American culture as the most iconic symbol of the U.S. government.

In 2006, the Pandemic and All-Hazards Preparedness Act gave birth to a small agency called the Biomedical Advanced Research and Development Authority. While BARDA is now well-known within the pharma industry and beyond, name recognition wasn't instantaneous. The agency spent much of its history as a little-known office buried inside the U.S. Department of Health and Human Services, quietly aiding the development of various medical countermeasures for a range of chemical, nuclear or biological threats.

When the H1N1 virus emerged in 2009, BARDA partnered with drugmakers to produce a bulk supply of vaccine antigen and adjuvant as well as investigational lots of a H1N1 vaccine. In 2012, after realizing that the national manufacturing capacity for pandemic influenza vaccines had fallen short during H1N1, BARDA oversaw close to $12 million worth of contracts with vaccine makers to preemptively produce master vaccine seed stocks for viruses with pandemic potential. During the 2014 Ebola outbreak, BARDA worked with pharma companies to advance therapeutic and vaccine candidates, as well as further expand the industry's manufacturing readiness.

But it wasn't until the novel coronavirus pandemic hit that BARDA's work was truly showcased. The office has been at the center of U.S. response, fielding over 4,000 submissions from companies with potential countermeasures. BARDA has cultivated its partnerships with pharma companies to accelerate the development of needed therapeutics and diagnostics tools. As a driving force behind Operation Warp Speed, the agency has become one of the most prolific government partners in pharma, making headlines for several billion dollar deals with leading vaccine makers. All told, the agency has invested $17 billion into combatting COVID-19.

James Montgomery Flagg was said to have squandered his fleeting fame on celebrity parties, fast cars and beautiful women. BARDA too is not without its flaws as a government agency, having suffered criticism for the demanding amount of oversight it requires on projects, a slow contract award process and internal management issues.

But the agency has certainly proven its worth during the past year. Hoping to nab a 2021 budget of $1.4 billion to fund more partnerships with pharma, BARDA will likely remain a familiar name — and face — in the industry.

industry dose

Karen Langhauser
Chief Content Director

When can international trade shows resume?

Organizers tried to schedule an in-person trade show, but exhibitors weren't on board

With much of the 2021 trade show schedule still pending, one group tried to decisively move forward.

Last month, Messe Düsseldorf announced that it had reached an agreement with its partners from trade associations, industry and the trade fair advisory board on a path forward for staging interpack, International Trade Fair for Processing & Packaging, from Feb. 25-March 3, 2021 at the fairgrounds in Düsseldorf, Germany.

The decision to proceed with the largest international packaging industry event — one that crosses into the pharma space as well as food, beverage, cosmetics and industrial goods — was a risk, and it seems most exhibitors weren't ready to take it.

Shortly after Messe Düsseldorf made the announcement, UCIMA, the national trade association that represents Italian packaging machinery manufacturers, issued a press release stating that, given the resurgence of COVID-19 and associated government measures, it was "inconceivable" to host interpack in February.

It turns out they were correct. Less than a month after announcing the already postponed event would take place in February, Messe Düsseldorf cancelled the show entirely. The 62-year old flagship event is typically held every three years, which means the next show will continue as scheduled for 2023.

How were they going to pull this off?

What made organizers think they could safely host an event that normally brings in close to 3,000 exhibitors and more than 170,000 visitors from over 150 countries?

Messe Düsseldorf has worked out a Hygiene and Infection Protection Concept based on current government ordinances. The 27-page guidelines include actions such as mask mandates, the use of distance markings, contactless payments, installing hand sanitizer stations and a ban on handshakes. The organizer says its modern indoor air-handling systems, combined with the use of natural air flow in the large halls from open doors and skylights, provide "plenty of space for safe encounters."

The new safety concept, called "PROTaction: Back to Business," was debuted last September at the first major trade fair to take place in Düsseldorf since the onset of the pandemic. Produced by Messe Düsseldorf in partnership with the Caravaning Industry Association, CARAVAN SALON 2020 — the world's largest RV trade fair and consumer show — was held from Sept. 5-13, 2020.

According to the organizers, 107,000 people safely attended the annual event showcasing vehicles and equipment, tents, mobile homes, camping equipment and tour operators.

Too much uncertainty

On Nov. 25, facing surging death rates, the German federal government and the German states decided to implement stricter COVID-19 measures, which will extend until at least Dec. 20. A decision to extend beyond that won't be made until mid-December, but the prevailing assumption is that restrictions will continue into 2021.

"This, unfortunately, does not give cause for hope that the situation will improve significantly over the course of the coming months. This will affect all Messe Düsseldorf events in the first quarter," explained Wolfram N. Diener, president and CEO of Messe Düsseldorf in the Dec. 3 press release announcing interpack's cancellation.

At present, EU citizens can travel to Germany, but U.S. citizens may only enter Germany if they "serve in an important role or if there is an urgent need for their travel." These exceptions include such groups as

PHARMA HAPPENINGS

Schedules for industry events in 2021 are still shifting. Here's a current look at the lineup and dates of pharma's biggest shows.

BIO International Convention

June 14-17 / Boston, Mass.
After hosting a number of virtual shows in 2020, the Biotechnology Innovation Organization's biggest meeting of the year is slated to return in the summer.

BIO International Convention

DCAT Week

July 12-15 / New York, NY
The Drug, Chemical and Associated Technologies Association is planning a pared-down version of its flagship event.

CPhI North America

Aug. 10-12 / Philadelphia, PA
Join more than 15,000 industry pros respresenting all aspects of the pharma supply chain from around the region.

CPhI north america

CPhI Worldwide

Aug. 31-Sept. 2 / Milan, Italy
The largest pharma manufacturing trade show of the year has a new date but is once again planned for Italy.

CPhI worldwide

Interphex

Oct. 19-21 / New York, NY
Pharma's capstone event has moved to new dates in the fall at the Javits Center in the Big Apple.

INTERPHEX

Read more about how BARDA is aiming to strengthen its bonds with pharma on p. 8.

> **Big Pharma has often looked at us as a government body that might move with glacial speed. But we have worked to show that if we award you with a contract, it is not just a contractual agreement — it is a partnership. We have experts in manufacturing, clinical and non-clinical operations that can partner with pharma companies. Because if they succeed, we succeed.**
>
> —Gary Disbrow, director, BARDA

health care workers, diplomats and humanitarian aid workers, according to the German Embassy in the U.S.

But it also appears as though interpack's exhibitors were not thrilled at the prospect of moving the fully booked 2020 trade event to early 2021.

Knowing that the number of visitors would be lower than previous years, Messe Düsseldorf had offered companies participating in interpack 2021 discounts on exhibit space pricing, as well as the option to terminate their contracts entirely. And it seems that many exhibitors exercised that right to cancel — a decision that was likely linked not only to employee safety and COVID travel restrictions, but also to ROI.

"An international exhibition like interpack requires very substantial investments, not just in economic terms but also in R&D and marketing activities," said Luciano Sottile, a member of UCIMA's board of directors, in a press statement. "For this reason we believe it is impossible to ensure an adequate return on the investment if the presence of a sufficient number of high-quality visitors cannot be guaranteed."

The future of trade shows

Global revenues for trade shows and exhibition organizers fell by two-thirds in the first half of 2020, according to UFI, the global association of the exhibition industry. Looking at 2020 as a whole, UFI predicted that revenues will represent only 39 percent of those of 2019.

But with several promising vaccines entering final stages of approval from global regulatory agencies, many are hopeful that pharma industry events can safely resume in-person by the second half of 2021.

Meagan Parrish
Senior Editor

BARDA WANTS YOU!

AFTER A YEAR OF HISTORIC DEALS, BARDA LOOKS TO RECRUIT MORE PARTNERS IN PHARMA

There didn't seem to be cause for alarm when a letter laced with a fine white powder crossed Robert Stevens' desk on Sept. 19, 2001. And several days later, when he turned up at a hospital disorientated and feverish in the middle of the night, no one made the connection between Stevens' flu-like symptoms and the mysterious letter he ultimately passed around to other coworkers back at the office.

At first, doctors suspected the 63-year-old photojournalist who worked at a tabloid called the *Sun* in Florida had contracted meningitis. But after an infectious disease expert zoomed in on his spinal fluid with a microscope, the real and startling culprit revealed itself. On Oct. 4, Stevens was diagnosed with pulmonary anthrax and the next day, became the first person to die from anthrax poisoning in the U.S. in 25 years.

For most Americans, the anthrax attacks that unfolded over the next few weeks of 2001 — which ultimately killed five and sickened 17— were a tragic but fleeting footnote to a year already upended by the shock and horror of the Sept. 11 attacks. But for the American national security community, they were a mini-dress rehearsal for a larger nightmare scenario they could suddenly see crippling the nation one day. The key takeaway? We were not ready.

Anthrax, smallpox, Ebola, the plague — in the hands of terrorists, these pathogens could be weaponized. On top of that, an awareness grew that we were also vulnerable to

natural hazards, like a fast-spreading deadly virus. With those threats crystalized in the minds of top defense officials, countering biological threats became a new priority. Within the next few years, the government threw more money at the problem, laying the groundwork for a series of initiatives that would eventually lead to the creation of the Biomedical Advanced Research and Development Authority (BARDA).

Launched in 2006, BARDA has spent much of its history as a little-known office buried inside the U.S. Department of Health and Human Services (HHS), aiding the development of various medical countermeasures for a range of chemical, nuclear, biological or viral threats. But once the coronavirus pandemic hit the U.S., BARDA's efforts suddenly took center stage.

Although the country is now rounding into 2021 with coronavirus vaccines and a potential end to the pandemic in sight, BARDA isn't planning to fade back into obscurity. With the need for pandemic preparedness heightened among industry and government, BARDA is looking to build on its momentum and track record of success to continue advancing the development of needed pharma products to protect the country from biological threats.

As it works to put the pandemic behind it, BARDA is sending out the call that it needs partners in pharma to keep up the fight.

Bridging the valley of death

With anthrax fresh on the minds of defense officials, one of the original government projects that led to the creation of BARDA was an effort to procure enough vaccines to protect Americans from a biological attack.

In 2002, the Bush administration dropped an additional $4 billion into the country's $633 million biodefense budget with the goal of procuring vaccines — particularly for smallpox and anthrax — for the national stockpile. Two years later, the initiative took on the name Project BioShield and included more than $5 billion in bait for the pharma industry to develop medical countermeasures such as a new anthrax vaccine.

America needed plans and supplies and importantly, we needed drugs. But they were the kind of drugs that have little to no market value until the worst-case scenario hits. The kind of drugs most pharma companies don't see much value in making. So, Big Pharma didn't bite.

At first, the government turned to smaller pharma companies, striking a deal to develop an anthrax vaccine with a now bankrupt company called VaxGen and then later with Emergent BioSolutions (which has since become one of BARDA's biggest biodefense partners).

But there was another problem: Too many drugs were plummeting into what is often referred to as the "valley of death" — the space between drug discovery and the decision to commit resources for development.

"It goes back to the anthrax and smallpox vaccines," explains Chris Stanley, the president and principal consultant at Harmony Consulting. "Billions were spent on those products, but there was no market. Not only that, they would have to turn over the drugs to the stockpile and then they would expire, so the government ended up with this excess inventory on their hands."

Recognizing that pharma companies didn't just need money — they needed a partner in the government to help usher needed products through the many phases of development, clinical trials and filing for regulatory approval — BARDA was created.

The goal was for BARDA to function more like a venture capital firm than a government office, providing funding to companies that have a solution in line with BARDA's aim of developing medical countermeasures. Yet, to succeed at that mission, BARDA also positioned itself as a true partner in product development, providing not only funding but subject matter experts that could help steer pharma companies through the quagmire of bureaucracies related to product development — something it has pulled off while dealing with government entanglements of its own.

Early challenges

From the onset, funding issues hovered over the new agency. Although BARDA was given a multi-year war chest of $5.6 billion, *The New York Times* reported in 2011 that in its first four years, the office had only received — in total — about half of its original annual budget.

More money eventually came in and BARDA succeeded in acquiring vaccines for smallpox and anthrax. Over time, BARDA's biological targets have also multiplied to include a number of emerging infectious diseases, pandemic influenza, nuclear threats like radiation poisoning and burns, and even the opioid epidemic.

BARDA's vision for the future

Some of the agency's stated goals

- Develop robust alternative skin and blood products
- Take viral hemorrhagic fevers off the table
- Bend the opioid epidemic curve
- Use novel approaches to combat antimicrobial resistance

> **"I don't think anyone understood the full extent of what the pandemic would be. But because of H1N1 and Ebola…we understood what we needed to do."**
>
> — Gary Disbrow

To combat these threats, BARDA has expanded its weaponry of various countermeasures under a growing list of sub-offices such as the Division of Chemical, Biological, Radiological and Nuclear (CBRN) Medical Countermeasures, the Influenza and Emerging Infectious Disease Division and the Pharmaceutical Countermeasure Infrastructure Division.

Even before the pandemic, BARDA's accomplishments were impressive. To date, the agency has helped bring 56 new products through the hoops of regulatory approvals.

But new crises throughout its history have revealed new challenges.

According to Dr. Nicole Lurie, who served as the assistant secretary for preparedness and response at HHS, BARDA struggled to get enough vaccines manufactured during the 2009 H1N1 pandemic that ultimately killed more than 12,000 Americans. Realizing that the office needed to work more closely with pharma, BARDA sought to expand the industry's manufacturing readiness during the Ebola outbreak from 2014-2016.

BARDA insiders have also emphasized that without ongoing manufacturing readiness, the country would not be prepared for an outbreak — whether it's from a terrorist attack or a novel virus. In 2018, Joe Larsen, then the acting director of BARDA's Division of CBRN Medical Countermeasures, warned an audience at the 13th Annual Non-Dilutive Funding Summit that the way the government was responding to viral threats — investing in clean-up rather than prevention — was not the best path forward.

"Responding to an emerging infectious disease event is not something that is easily done or responsibly done with supplemental funding from Congress," he said. "If we had a few hundred million dollars a year to help prepare for these events, that might be a better approach than spending $9 billion responding to these events in an emergency, which is currently where we find ourselves in … We had hoped to move into a more thoughtful and pragmatic approach of trying to prepare for emerging infectious disease events, but we realize that is a hard political fight these days."

Because vaccine manufacturers typically only want to produce enough product for the seasonal market, it is difficult to create extra capacity that would be available in the event of an emergency. But at the time, Larsen said that the agency had dedicated enough funds to ensure that America at least had capacity ready to produce 50 million doses of a vaccine within six months of the detection of a new pandemic virus. Yet, in order to stay ready, that capacity would need to be maintained.

And all of BARDA's efforts to prepare the country for a viral pandemic were about to be put to the test.

The COVID crisis

Gary Disbrow, BARDA's current director, admits that in the early days of the coronavirus pandemic he was a little nervous about the situation. But at the same time, Disbrow says the office was ready.

"I don't think anyone understood the full extent of what the pandemic would be," he says. "But because of

H1N1 and Ebola, we had been in response-mode before. We understood what we needed to do."

To get ahead of the curve of the fast-spreading new virus, BARDA launched a portal called CoronaWatch that allowed companies to submit information about its potential countermeasure and request a meeting with BARDA and its federal partners. To date, Disbrow says that the portal has received over 4,000 submissions.

BARDA also immediately established an incident manager to oversee the office's coronavirus response and quickly turned to pharma for help, looking at vaccine and therapeutic platform technologies it had invested in for Ebola and H1N1 from companies such as Regeneron, Johnson & Johnson, Moderna, Merck and Sanofi.

The proof of this quick mobilization has been well on display. In the last year, the agency has become the most prolific government partner in pharma, making headline-stealing deals with a swath of major industry players. As one of the lead divisions involved in Operation Warp Speed — the government's multi-agency effort to deliver 300 million doses of a coronavirus vaccine by Jan. 1, 2021 — BARDA has cultivated its partnerships with dozens of drugmakers to help push vaccines towards the finish line. BARDA has also propelled the development of needed therapeutics and diagnostics tools, and all told, has invested an astounding $17 billion into combatting COVID-19.

In many ways, the pandemic highlighted how BARDA has redefined what a government outfit can be. While moving fast and staying nimble, it has become the pandemic partner you want in your corner.

"When the chips are down, you call BARDA," says Dr. James Cummings, president of Government and Public Health Solutions at ICON, a global clinical research organization, consulting firm and drug developer, that's also a part of BARDA's Clinical Studies Network.

This year, BARDA's flagship Industry Week event — which allows the office to make its pitch to potential industry partners — saw its highest ever attendance.

The BARDA supply chain

There's no company that knows what it's like to team up with BARDA more than Emergent. Since becoming the sole source of the anthrax vaccine, Emergent has developed into one of the country's top biodefense pharma companies with a portfolio that includes commercialized vaccines for cholera, smallpox and typhoid, an opioid overdose antidote, and therapeutics and vaccines for other viruses in the pipeline. But it's Emergent's molecule-to-market CDMO manufacturing services that have given it a starring role in the push to get Americans vaccines.

In 2009, Emergent poured tens of millions of dollars into renovating its Bayview facility in Baltimore, Maryland. A few years later, Emergent struck a deal with BARDA who co-funded an expansion at the facility so that it could be used for production in the event of a pandemic. This year, a BARDA task order leveraging that facility went into effect and it is now one of the country's main manufacturing plants for coronavirus vaccines being developed by Johnson & Johnson and AstraZeneca.

BARDA ventures

This year, BARDA launched its Division of Research Innovation and Ventures (DRIVe). The new division will use venture-style equity financing to invest in breakthrough technologies aimed at fortifying health security while recycling returns from successful ventures. So far, DRIVe has funded 25 companies with $30.7 million.

"Our pandemic response is the manifestation of our journey to diversify our offerings in the public health arena and our longstanding relationship with BARDA to develop a variety of medical countermeasures," Sean Kirk, Emergent's executive vice president of Manufacturing and Technical Operations, says. "That's where I'm sitting right now."

The value of the coronavirus BARDA deals have been major for Emergent. BARDA's vaccine-production task order for rapid domestic production is valued at $628 million through 2021, and in its third-quarter earnings statement this year, the company reported a record year-to-date performance of $972.4 million in total revenues.

According to Kirk, fulfilling its contracts this year has also strained the company in new ways, requiring many to work seven days a week. Kirk says he's on the phone with government officials every day and is "fighting hard to maintain the strong choreography between materials supply, staffing, tech transfer and ramping up of candidates."

For companies like Emergent, being a part of BARDA's efforts to create a network of manufacturing capacity means that in a national emergency, other contracts might be set aside to fulfill the government's needs.

"We ask for a lot," Disbrow admits. "We need to have access to capacity at a moment's notice."

To help maintain the ability to provide end-to-end product development, BARDA has also laid the groundwork to quickly test needed products. In 2012, the agency established a Clinical Studies Network (CSN) to assist in the development of needed therapeutics, diagnostics or vaccines. The idea is to give BARDA access to pre-vetted companies it can rely on to help combat emerging threats.

ICON, which has a background in clinical trials for a number of vaccines, diagnostics and therapeutics, was picked as one of the original five companies to be a part of the CSN and re-established its contract with BARDA in October. To be a part of the CSN, Cummings says that companies have to show that they not only have the infrastructure and know-how, but that they are compliant with government regulations.

"It's great to be a trusted partner," Cummings says. "We've been continuously engaged with BARDA and stand at the ready to support them if the need arises."

What's in it for pharma

This year, BARDA's flagship Industry Week event — which allows the office to make its pitch to potential industry partners — saw its highest ever attendance. Held in October, the annual event drew in 2,000 registrants — nearly twice as many as the year before. Although the event might have drawn a bigger crowd because it was held virtually, the increased attendance also indicates that more companies are looking to see how they can get a foot in the door at BARDA.

Given the wide variety of BARDA initiatives, contracts with the agency arise in numerous ways. But most of the time, pharma companies wait to see what kinds of technologies BARDA is looking for. Even though ICON is a part of the CSN, Cummings says that the company generally watches for BARDA announcements and puts in a proposal if the company can fulfill a need.

In more normal times, BARDA contracts are often born out of "Shark Tank"-like meetings.

Product feedback

To put the word out about projects it's looking to fund, BARDA has created a broad agency announcement that is updated as priorities change.

"They're trying to look in a crystal ball and see what the threats are

BARDA's response to COVID-19

500+
CoronaWatch meetings

102
Coronavirus-related partnerships

65
Products supported

$17 Billion
Investments in vaccines, therapeutics and diagnostics

and design countermeasures for them," Stanley, who has consulted companies on over $1 billion worth of BARDA contracts, explains.

According to Disbrow, BARDA currently has 15 material threats identified, which now includes the SARS-CoV-2 virus, in need of medical countermeasures.

If a pharma company has a solution in the works that aligns with one of BARDA's needs, it can submit a proposal to set up a "TechWatch" meeting. During these meetings, Stanley says that companies typically get 30-60 minutes to make their pitch and explain how much the development of their product will cost.

Usually the TechWatch meetings are with division heads from BARDA and other agencies in case the product would be a good fit for different government initiatives. And generally, BARDA is on the hunt for something that's not just useful, but is cutting edge.

"These are very geeky, incredibly intelligent people who want Star Trekkian technology," Stanley says.

If BARDA's interest is piqued during a TechWatch meeting, it invites companies to then submit a white paper or 10-page technical summary. If BARDA then wants to move forward, it asks companies for a full proposal, which Stanley says is an exhausting document to create that includes hundreds of pages with sophisticated cost modeling. Given the time and expense involved in both writing and reviewing full proposals, BARDA doesn't usually ask for one unless the project is likely to result in a contract.

From beginning to end, Stanley says the process usually takes four to six months. However, contracts have been approved at a much more rapid clip during the pandemic and in some cases were awarded in as little as nine days.

Agency expertise

For up-and-coming companies, a contract with BARDA can be a game-changer — not just because of the funds but also because of the access companies get to needed expertise.

"On the interior, they have just about every piece of what a pharma company has," Cummings says. "They have experts in preclinical, clinical and manufacturing at the table. And so all of these people can take a look at the entire lifespan of a product's development and get those solutions across the threshold."

BARDA's expertise in commercialization also makes it unique in the world of government partners.

"Many of their employees are industry people, so they know what it's like to navigate the challenges of product development," Kirk says.

Being hooked up with BARDA also means that companies are engaged with other government agencies.

"Generally at tech proposals, there are folks there from other agencies so that they can get a clear signal about the product you want to develop," Cummings says. "BARDA is a gathering point of other agencies, as well as a great standalone agency. I think that's a neat feature."

This inter-agency approach also helps position BARDA as a type of regulatory consultant for its partners. If, for example, the drug in development is headed for the strategic national stockpile, BARDA will provide the expertise needed to file for an emergency use authorization or approval with the U.S. Food and Drug Administration.

"BARDA has regulatory experts who work with the companies," Disbrow explains. "They have pharma experience and come from the FDA. So we know what the FDA is looking for, and our experts work with companies to review their documents so that they are of the highest quality, which reduces questions we might get back."

Kirk also emphasizes that working with BARDA goes towards a greater good.

"The thing I love most about them is that they are working in great service to our nation," Kirk says. "They are busting their butts every day to make a difference."

BARDA's next missions

"We still need therapeutics to treat those that are severely ill," Disbrow says of the ongoing COVID-19 pandemic, while emphasizing that BARDA's work in that arena isn't done. "For the next several months, there are going to be large numbers of people who will become ill."

This year's coronavirus outbreak won't be the last pandemic to cripple the world. So, even while BARDA still wrestles with COVID-19, its experts are keeping their eyes fixed on how to better prepare for other emerging threats.

Pandemic preparedness

Although it might be tempting to develop a product that may score a major government contract — an approach that Stanley has seen some companies attempt — BARDA aims to back products that have some commercial value and customers outside of the U.S. government.

"In the early days, BARDA would be more willing to develop products specifically for medical countermeasures," Stanley explains. "These days, BARDA won't accept any product that doesn't have its own commercial market."

In other words, BARDA prefers not to be a company's sole purchaser of its product.

It's a tricky proposition for some drugs that fall into the medical countermeasures category, especially when it comes to preparing for an outbreak that may or may not come. Yet, one way to balance that risk/reward scenario for pharma companies is to develop flexible platforms.

"We're looking at investments… beyond the 'one drug, one bug' to platform technologies," Disbrow says. "We want proven technologies that can switch to the pathogen of interest so that we don't have to switch technologies."

Overall, taking the lessons of COVID-19 and applying them to future planning is likely to be a prime focus for BARDA.

"Looking forward, I'm positive there'll be a huge push for pandemic preparedness," Stanley says.

Advanced manufacturing technologies and therapies

BARDA likes the latest gadgets and, much like the FDA, is likely to continue backing advanced manufacturing technologies in pharma. In particular, Stanley says they are likely looking for any technologies that could radically increase capacity or quality. In pharma manufacturing, Stanley says those kinds of technologies might include automated plants, modular manufacturing, rapid manufacturing or advancements in purification.

At Industry Week, government officials and representatives from BARDA divisions also spelled out some of their other goals for 2021, including the need for advancements in genomic sequencing, which can be used to help identify disease risks, novel antibiotics to combat microbial resistance, faster platforms for vaccine production, new therapies for Ebola and pre-symptomatic diagnostic tools.

Generics

Although BARDA picks its contracts based on technology rather than politics, lawmakers pushing to onshore generic drug production could again turn to BARDA to help the country procure drugs needed in public health emergencies. In the spring, BARDA struck a major deal potentially worth up to $812 million with Phlow Corp., a startup in Virginia, to manufacture generic drugs for the strategic reserve.

The deal raised eyebrows in the generics space because it was perceived that there were no bids on the contract. However, Disbrow says that Phlow presented at a CoronaWatch meeting and applied through BARDA's broad agency announcement, which includes funding opportunities for advanced manufacturing technologies. According to Disbrow, what made Phlow's proposition alluring was its commitment to using end-to-end continuous manufacturing.

"The company was willing to invest in advanced manufacturing and new technologies that the FDA supports," Disbrow says.

Although Disbrow couldn't say if BARDA is likely to make other major deals to spur domestic generic drug production, the political will to continue pushing for the onshoring of generics isn't likely to let up.

"I'm curious to see if the mission of BARDA will expand to include production capacity for essential medicines," says Bowman Cox, an analyst with Informa Pharma Intelligence. "Because [successfully onshoring] will take more than the deal with Phlow. And there seems to be a lot of willingness to put more public money into this sector."

Disbrow agrees that there is momentum for more onshoring on both sides of the political aisle.

"The pandemic highlighted supply chain issues," he says. "It is only going to continue to stress the system as we move into large-scale vaccine manufacturing."

The Strategic National Stockpile

Although the Strategic National Stockpile (SNS) is officially managed by BARDA's parent organization, the Office of the Assistant Secretary for Preparedness and Response (ASPR), BARDA plays a key role in maintaining the country's reserve of critical supplies by supporting the development and procurement of needed drugs.

But the COVID-19 pandemic revealed shortcomings of the nation's reserves for drugs and medical supplies.

In May, the Trump administration announced the "SNS 2.0" initiative designed to better maintain supplies for the pandemic, and improve management and distribution. HHS and ASPR then sent a request for input to pharma stakeholders looking for feedback on how the agencies could achieve certain goals for the SNS such as ensuring there is better coverage for pandemics, bolstering domestic manufacturing of needed products, and improving real-time supply chain visibility.

Going forward, the government has set the stage to partner more closely with pharma to create a next-generation SNS with stronger digital capabilities to track movement in the pharma supply chain.

One tool that could be more broadly implemented is a supply chain "control tower" that was used

this spring to track shipments of critical drugs.

"Pharma distributors would be able to share information so the government can get a clear view of how the supply chain is evolving," Cox says.

And while agencies that play a hand in controlling the SNS look for ways to revamp the system, Cox says that there is likely to be a general push to increase inventories throughout the pharma supply chain.

"In the years leading to the pandemic…manufacturers pushed just-in-time delivery," he explains. "If you have a global enterprise and you're trying to hit financial targets, one way to keep improving profitability is to whittle down inventory."

In light of the shortages experienced during the pandemic, Cox says that this philosophy is likely to shift.

"When the pandemic hit, manufacturers that had been doing a poor job of whittling down inventories were suddenly being celebrated," he says.

Show BARDA the money

Of course, BARDA's ability to move any initiative forward remains reliant on its budget. For fiscal year 2021, BARDA's requested budget was $1.4 billion — a similar figure to years past. The massive influx of cash in 2020 that allowed BARDA to strike major deals related to the coronavirus came from supplemental Congressional funding. For now, it remains to be seen if Congress will pad BARDA's wallet again in 2021.

"We are hopeful we'll receive supplemental funding," Disbrow says. "I think Congress knows that BARDA is doing a heavy lift right now. And we hope they see that it's a good investment. We deliver on what we say we're going to do."

With whatever funding BARDA gets, Disbrow says that the agency will continue to work with its current pharma partners and hunt for more as it focuses on teaming up with the industry to protect the country.

"We need to find situations that are a win-win for both parties," he says. "That is key to moving forward and forging those strong partnerships. Because if they succeed, we succeed."

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Karen Langhauser
Chief Content Director

Focus on: Italy

Lacking a central strategy, the pharma industry finds success by playing to its strengths

Leonardo da Vinci, Gianni Versace, Massimo Bottura — these names come to mind immediately when someone mentions Italy. Famed for its culinary delights, high-end fashion, and rich history in arts and culture, it should come as no surprise that Italy is one of the most visited countries in the world.

Tourists likely aren't flocking to Italy to see its pharma manufacturing facilities, but nonetheless, the drug industry is carrying its weight in the Italian economy. Known for its reliability and robustness, the Italian pharma industry has been a stable driver of economic rejuvenation.

According to Farmindustria, pharma's largest trade association in Italy, the industry has been, and still is, the leading sector in terms of job growth, production and exports — representing a "force for the entire economy."

All of this comes in spite of significant obstacles — cultural barriers and a lack of government backing chief among them — that the industry will need to overcome if it wants to remain competitive on a global scale.

Battling it out

Based on 2019 data, Italy is the biggest pharmaceutical producer in the European Union, both in terms of total manufacturing capacity, as well as in manufacturing capacity per capita, according to Lorenzo Positano, managing director and partner, Boston Consulting Group.

"It's a bit of a race between us and Germany each year," says Positano, who leads BCG's health care practice in Italy, Greece and Turkey.

According to annual reports compiled by the European Federation of Pharma Industries and Associations (efpia), Italy claimed the crown in 2017, Germany grabbed it in 2018 and now Italy has wrangled it back.

Italy's pharma production value reached €34 billion (USD $41.2 billion) in 2019. Much of the sector's success can be attributed to its exports — over 80 percent of the drugs made in Italy leave the country. Italian drug exports, which Farmindustria refers to as the "engine of pharma companies" were up 57 percent in 2019.

Quantity has not come at the expense of quality, either.

"Italy has a 60-year history of successful pharma manufacturing," says Positano. "The industry is very mature in terms of manufacturing quality. Our workers have strong skills. Essentially, pharma production in Italy is cheaper than in Germany, but the same quality."

The quality of workmanship is affirmed by the numerous multinational drugmakers, such as Novartis,

GlaxoSmithKline and Pfizer, who choose to manufacture in Italy. Italy is also the EU leader in contract development and manufacturing organizations; the sector has seen steady growth in production for the last decade and Italian CDMOs now rank first in manufacturing value. Capitalizing on access to the European market, leading global CDMOs, including Patheon (Thermo Fisher Scientific), Recipharm and Catalent, have commercial manufacturing facilities in Italy.

Recognizing that the quality of human resources is key to producing quality products, pharma companies based in Italy seek to maintain a top-notch workforce by offering modern corporate welfare programs with an emphasis on work-life balance.

The Italian pharma industry employs 66,500 people, 43% of which are women

Source: Farmindustria, 2019

Lack of federal focus

During the past decade, federal governments around the world have set lofty goals and pushed initiatives targeting life science industries in their respective countries.

In 2011, the Russian government launched Pharma 2020, with the goal of reducing the amount of pharma imports from 90 to 50 percent. In 2016, the United Arab Emirates unveiled the 2030 Dubai Industrial Strategy, targeting pharma as a vital manufacturing sub-sector and laying the groundwork for it to contribute 25 percent of the country's GDP by 2025. In 2018, the Canadian government introduced the Health and Biosciences Economic Strategy, with the goal of doubling the size of the health and biosciences sector and becoming a top-three global hub by 2025.

Notably, this type of long-term national strategy is absent in Italy.

"There is no central strategy or agency that pushes pharma innovation in the country," says Positano. "No organization has been done at the federal level to put together champions and focus on scaling up specific technologies across the country."

According to Positano, the heart of the issue may be cultural. "The scientific culture is not a part of our heritage," says Positano. "Our primary schools don't teach the scientific mentality — they are more focused on the arts, literature, history," he says.

Italy's investment in education in general is well below the EU average, particularly when it comes to higher education.[1] Several federal school reform initiatives over the years have attempted to correct the problem. The high cost of university education coupled with low returns once graduates enter the job market has led to a lower number of graduates. Many of those who do graduate with science degrees leave the country seeking better positions abroad; for years the country has been trying to slow the trend of a large fraction of its top researchers leaving Italy.[2]

Evolving competencies

What is on the horizon for the pharma industry as it fights to stay on top? One area where Italy is fine-tuning its skills is orphan drugs — the development of drugs for rare diseases.

About 30 million people living in Europe and around 2.5 million Italians suffer from a rare disease.[3] The development and authorization of treatments for rare diseases is both expensive and complex, and due to the small number of patients affected, the return for drugmakers is small — making it an area fraught with unmet needs.

"A lot of Italian pharmaceutical companies are pursuing orphan drugs. It is an area where pharma companies really have a competitive advantage and a lot to be proud of," says Positano.

This dedication isn't a new trend. Decades ago, Italy established itself as a pioneering country for rare disease expertise in Europe. One of the first orphan drugs to be approved by the U.S. Food and Drug Administration after the enactment of the 1983 Orphan Drug Act was developed by an Italian biotech, Sigma-Tau Pharmaceuticals, for the treatment of genetic carnitine deficiency. The Italian academic research sector has the highest number of scientific publications in the global field of rare diseases.[4] In 2001, Italy became the first country in Europe to implement a population-based public health registry dedicated to rare diseases.

Italy is home to over 170 pharma factories

Source: Farmindustria, 2019

Recently, Italian pharma company Chiesi Farmaceutici launched a U.S.-based subsidiary in Boston with a focus on advancing research and new product development for rare and ultra-rare diseases.

A newer push cited by Positano is in the area of digitalization.

Because of pharma's importance to the manufacturing sector, the industry has not been left out of the federal initiatives related to digital transformation. With the aim of helping Italian companies seize opportunities brought by the fourth industrial revolution, the National Industry 4.0 Plan 2017-2020 provides incentives and direct funding for companies investing in related R&D and smart machinery.

The most notable transformation will likely be seen in the pharma workforce.

"Historically, the Italian pharma industry was based on a strong physical commercial workforce," says Positano. "And now you see them accelerating the transition towards digitalization."

According to Farmindustria, the pharma workforce is poised to transform. Of the 20,000 employees that have been recruited into the pharma sector since 2014, 81 percent are aged under 35, and over 90 percent have either a university degree or a high school diploma.

Pharma companies are making in-house preparations by setting up advanced analytics teams comprised of engineers, scientists and data analysts. Farmindustria predicts that the effects of digitalization on pharmaceutical production will be the creation of new opportunities, not the loss of jobs.

The pharma industry's flexible and dependable workforce will continue to position the industry for success and enable pharma to continue to play a strategic role in the country's economy.

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Improving the risk-reward calculus for clinical trials

How natural language processing and machine learning can boost success in drug development

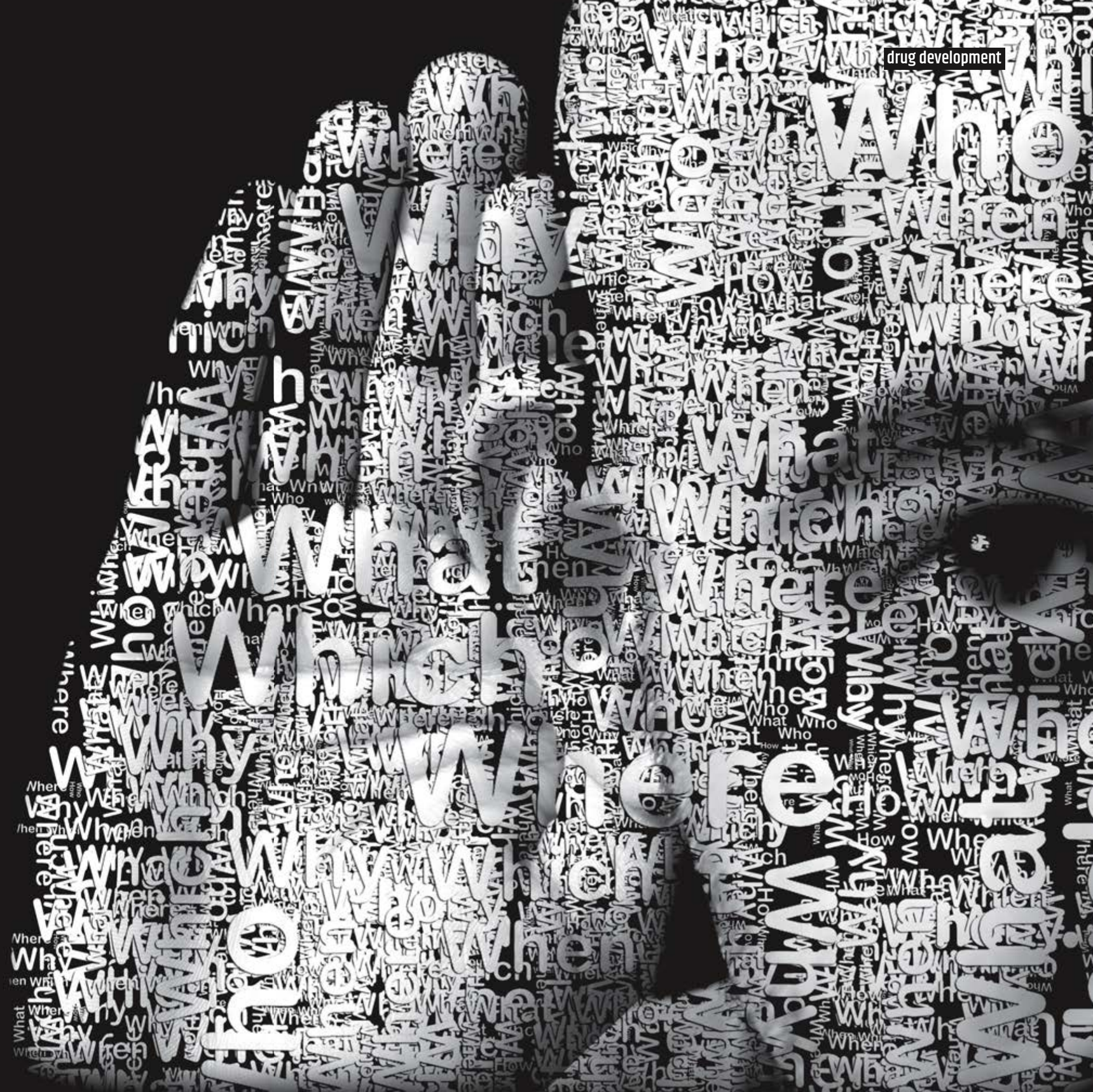
Bringing a new drug to the market is a monumental undertaking in terms of risk, resources and time. Typically, it involves budgeting $2 billion and an average of 10-12 years. A huge amount of these funds and some five to seven years are spent on clinical trials. Yet the risk-reward calculus for clinical trials remains dicey.

Despite an ever-increasing knowledge base and great technological advancements, a high percentage of clinical trials still fail. The reasons for this are manifold, ranging from questions of safety and efficacy to tightened regulations, to lack of funding and low patient recruitment rates.

According to an analysis published in *Nature* last year, the chances of success for a compound entering trials is under 10 percent. This result is falling in line with other estimates over the last couple of decades.

"No other major business type operates under such a high failure rate," writes David Lowe, a medicinal chemist working on preclinical drug discovery. In the end, regardless of whether the truth is closer to 10 percent or 14 percent, as suggested in a survey of clinical success rates across the drug industry done by researchers at the Massachusetts Institute of Technology, it's safe to say that pharma companies that enter the clinic get a pretty low return on their considerable investments.

Drug development productivity — the ratio of the number of new drugs approved to R&D spending each year — has declined steadily over the past decades. Eroom's Law, as the reverse of Moore's Law, suggests that the cost of developing a new drug has doubled approximately every nine years since the 1950s. Even with inflation rates taken into account, the rise in costs is still tremendous.



Can new technologies help?

Artificial intelligence (AI) is an umbrella term covering a number of technologies, including machine learning (ML) and natural language processing (NLP).

Currently, academic research labs, biotech corporations and technology companies are using machine-based learning to predict pharmaceutical properties of molecular compounds and targets for drug discovery. AI has also proven to be helpful in the enablement of faster diagnosis and tracking of disease progression by using pattern recognition and segmentation techniques on medical images like retinal scans.

However, when it comes to speeding up and improving the success rates for clinical trials, natural language processing offers some very promising opportunities.

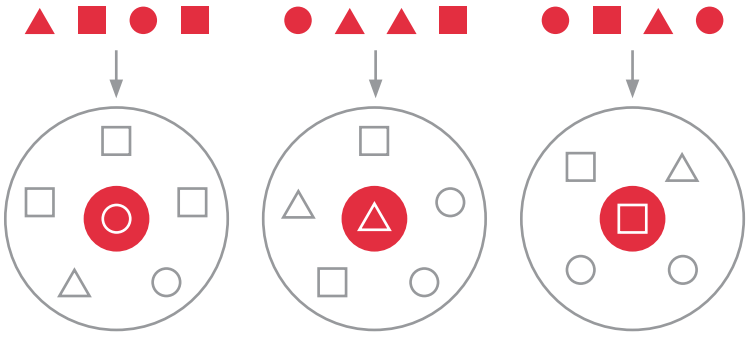
Turning unstructured data into valuable insights

NLP is an area of artificial intelligence and computational linguistics, and essentially a way in which a computer can extract meaning from written or spoken language. It includes information retrieval and extraction, lexical and semantic analysis, pattern recognition, tagging and annotation, and data mining techniques. Rudimentary forms of NLP have existed for many decades. The reason it now offers astonishing benefits is recent progress in statistics, processing speed and the ever-growing amount of available data. Until now, 80 percent of medical data was said to remain unstructured and untapped after it was created.

Modern NLP techniques can help extract valuable information from the ever-growing volume of data. They can be used across virtually any type of textual documents such as electronic health records, clinical trial data, lab reports, white papers, medical and health care regulatory filings, or scientific publications. While a standard keyword search only retrieves documents that researchers must then read, NLP "reads" the documents and can be used, for example, for automated entity recognition, categorization of topic and themes, the summarization of long text bodies or even multi-document summarization, intention detection or sentiment analysis. When extracted in a structured format, these findings enable fast reviews and analysis. For researchers, this often means enormous time savings and an improved basis for decision-making because they can go from finding and reading documents to a data-centric view, uncovering actionable insights from previously hidden relationships.

Relation extraction

Sources like PubMed, ClinicalTrials.gov or Google Scholar contain texts with mentions of authors, clinics, conditions, patients, treatments, adverse events, etc. Using NLP, these bits of information can be grouped together in categories such as people, institutions or drugs to gain a better understanding of their relations.



In drug development, NLP can speed up processes at all stages. Early in target discovery, researchers might search existing specialist literature for recent developments regarding their therapeutic area of interest. Alternatively, they might want to search patient interviews to gain a better understanding of their needs or patent literature to find out more about the competitive whitespace for certain disease targets.

To automate processes, gain deeper insights, reduce risks and lower costs — thereby securing a decisive advantage over their competition — plenty of leading pharma companies have already integrated NLP into their everyday work.

"In the clinical domain, researchers have used NLP systems to identify clinical syndromes and common biomedical concepts from radiology reports, discharge summaries, problem lists, nursing documentation, and medical education documents. Different NLP systems have been developed and utilized to extract events and clinical concepts from text ... Success stories in applying these tools have been reported widely," stated the authors of a research review of clinical information extraction applications, published in the *Journal of Biomedical Informatics.*

Speeding patient recruitment

A critical area to leverage NLP is against the long-standing challenge of poor patient recruitment for clinical trials. Patient recruitment is the largest cost driver of clinical trials. Current estimates suggest that almost 85 percent of clinical trials fail to retain enough patients for successful study conduct. Recruitment

and retention-related concerns have been associated with massive delays, with over 90 percent of clinical trials failing to comply with predetermined completion dates, due to poor participant accrual and excessive subject dropout. For a blockbuster drug, such delays can result in capital losses of up to $8 million per day.

The shortage of volunteers may be due to a lack of awareness among the general population, or perhaps issues of trust within the industry. Many patients are unaware that participation in a clinical trial is an option at the time of their diagnosis. Moreover, many members of the general public lack familiarity with clinical trials and are unaware of opportunities for participation by healthy volunteers. Negative attitudes about participation, which are widely spread, can usually be changed by offering more information.

To be able to contact the right subjects at the right time, clinical research organizations (CROs) need to work closely with physicians, as they are able to offer various treatment options to their patients, including clinical trial research. To find out who is best suited to reach out to potential trial participants, CROs can fall back on a popular approach used when marketing products: the social graph technique. The term refers to a method of data analysis derived from using social networks to find influencers — people engaging with the largest and most relevant audience on social media. It is most often represented as a map with nodes (influencers and followers) connected with lines (various kinds of subscriptions on social media).

To create social graphs useful to CROs, multiple data sources can serve as reference points. For example, they can be developed from or enriched by the data obtained from public datasets, such as PubMed, ClinicalTrials.gov, or H-CUP, and web sources such as Google Scholar, vitals.com, ratemds.com, etc. A great number of medical practices keep anonymized records of their overall patient flow public and many doctors like cosmetologists, nutritionists, and plastic surgeons are even active on social media. With the help of NLP, the data from these datasets can be structured, semantically parsed, and pre-processed with extracted keywords and relationships between nodes.

When ranked by impact and visualized in the form of heatmaps, CROs can easily find the doctors with the most relevant audiences, based on their area of expertise and geographical location, and then advertise to them directly. These doctors can then inform their patients about an opportunity to take part in a clinical trial that could help solve their health issues. As the CROs do not know anything about personal medical details and cannot address the patients directly, the patient's privacy is preserved at all times.

Identifying top-tier trial sites

NLP can also help improve the chances for successful clinical trials by supporting the evaluation of their feasibility. One of the most important aspects of a clinical trial is selecting high-functioning investigator sites because they can dramatically affect product approval, study costs and timelines. Too often, the identification system for sites is not very mature. As a consequence, the decision of whether a site is deemed suitable is often simply based on the availability of the necessary infrastructure and know-how to fulfill the activities specified in the clinical study protocol. Only one-third of all sites manage to attract enough patients, with many of them falling considerably short.

To improve the process of finding clinical trials that perform well, it makes sense to include criteria such as an investigator's expert status (e.g., how many articles has he published and how often are they quoted) or prior experience in clinical trials with similar treatments. Other critical factors could be the site's location and its previous success rates in enlisting subjects, the proximity of comparable studies, or the epidemiological data of the specific patient population. Information like this can be gathered by combining targeted database population, electronic health records, insurance databases, prescriptions, etc. and using NLP techniques to make sense of the data's semantic relationships.

A semantic relationship could be, for example, asking the solution for sites at which an advanced kind of brain surgery is performed. The system can then gather all relevant sites and a site-scoring algorithm can automatically rank them according to parameters such as the frequency of this special operation, the expert-status of the responsible doctor, the overall site experience with this procedure, or former enrollment rates. The value of this approach is the accurate prediction about the site's match and the huge time savings for researchers who do not have to do this work manually.

Combining technology and technique

The volume of unstructured data produced in the pharma industry is increasing exponentially, which offers great opportunities. But far too much of the information contained in medical records and other documents remains untouched. However, when sorted and analyzed, this data can be used to gain trail-blazing insights.

NLP can help to do exactly this and therefore can be useful during every stage of clinical trials. Combined with techniques like the social graph, for example, it can help meet clinical trial patient guidelines and quickly gather large pools of eligible patients. For this reason, investing in these kinds of AI technologies will not only benefit pharma companies by securing competitive advantages, it will also fundamentally improve the quest for new and better medicines by speeding up clinical trials and reducing their costs.

CRB

Noel Maestre
Director of SlateXpace

Peter Walters
Director of Advanced Therapy Medicinal Products

Top 6 trends for ATMPs in 2021 and beyond

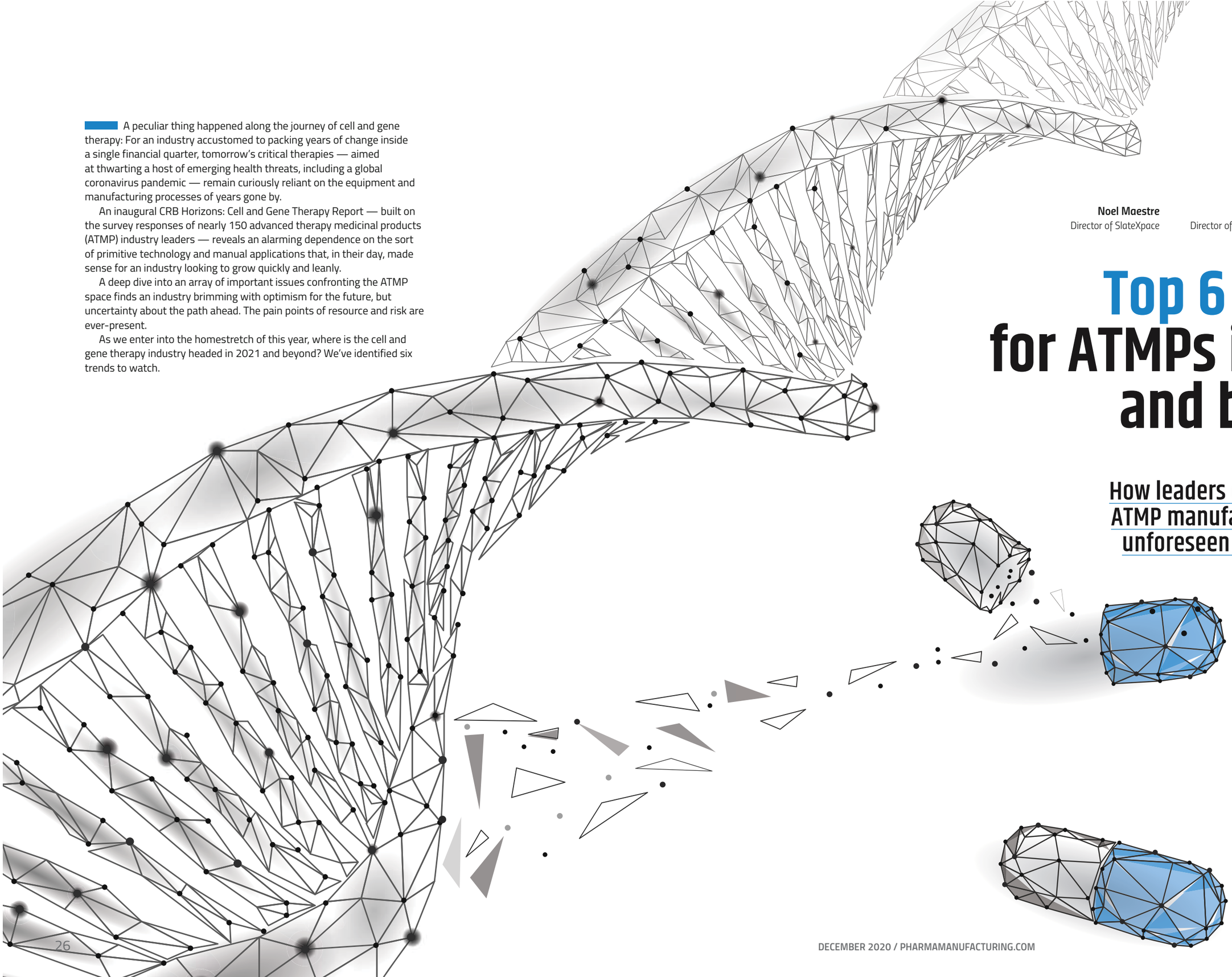
How leaders can future-proof ATMP manufacturing to meet unforeseen threats head-on

A peculiar thing happened along the journey of cell and gene therapy: For an industry accustomed to packing years of change inside a single financial quarter, tomorrow's critical therapies — aimed at thwarting a host of emerging health threats, including a global coronavirus pandemic — remain curiously reliant on the equipment and manufacturing processes of years gone by.

An inaugural CRB Horizons: Cell and Gene Therapy Report — built on the survey responses of nearly 150 advanced therapy medicinal products (ATMP) industry leaders — reveals an alarming dependence on the sort of primitive technology and manual applications that, in their day, made sense for an industry looking to grow quickly and leanly.

A deep dive into an array of important issues confronting the ATMP space finds an industry brimming with optimism for the future, but uncertainty about the path ahead. The pain points of resource and risk are ever-present.

As we enter into the homestretch of this year, where is the cell and gene therapy industry headed in 2021 and beyond? We've identified six trends to watch.



A quickstart guide to multimodal

ATMP startups that are new to therapeutic manufacturing might not be fully aware of the challenges they'll face as they move from the lab to the cleanroom. More mature companies with a history of dedicated, stick-built manufacturing sites and rigid procurement processes might have reservations about initiating a non-traditional capital development project.

For both types of companies and everyone in between, the first step in navigating this opportunity and unlocking its advantages is knowing which questions to ask. For example:

- **Scheduling and cost control:** How can you balance the pressure to get up and running as quickly as possible with the need to manage your costs, particularly while your products are in the early investigational stage?
- **Compliance and closed processing:** What will it take to ensure end-to-end regulatory approval when the concept of a multimodal facility is so new?
- **Partnership:** Should you invest in the necessary infrastructure to keep all your operations in-house, or find a CDMO to support some or all of your manufacturing and testing needs?
- **Supply chain:** Should you rely on a third-party supplier for your raw materials? What are the risks and potential payoffs of using your multimodal facility to manufacture plasmids, viral vectors and other necessary materials in-house?
- **Location:** Where should you put your multimodal facility? Near an urban center, where you're more likely to find top talent? Near a transport hub, which would simplify logistics? Next to a hospital or point-of-care facility?
- **Construction approach:** Traditional construction methods are falling out of favor as leaner, more flexible alternatives become available. What's the best option for your multimodal project? Should you take advantage of the speed of a prefab solution, despite its higher price tag? Or is the extremely popular approach of combining modular and stick-built systems best for your unique circumstances?

1. The multimodal revolution

Look for exponential growth in this area on the near horizon. Tasked with managing highly complex product pipelines and unsure of which modalities will move successfully through clinical testing, today's ATMP manufacturers are playing a numbers game by investing in diverse and complex product portfolios.

Nonetheless, almost 60 percent of survey respondents plan to adopt a multimodal solution within two years. We expect this number to dramatically increase over the next five years.

This revolution won't be easy. Shifting from a dedicated facility to a multimodal facility will challenge how owners, quality departments, regulators, facility designers and others in the industry perceive cell and gene therapy manufacturing. But with this challenge comes improved flexibility, ease of scalability and better cost control.

Like most revolutions, this one will arrive gradually and then all at once. The "gradual" chapter has been underway for some time, with ATMP platforms increasingly accepted in the mainstream clinical environment. This has prompted a recent explosion of mergers, expansions and new enterprises.

Multimodal biotech and ATMP manufacturing is about to take over. ATMP manufacturers who want to own their future by taking control of their present have a narrow window to make their move — but it's a move destined to pay off for years to come.

2. Gene therapy's rapid rise and emphasis on stable producer cells

Viral vector manufacturing is on the verge of an extraordinary leap forward. Experts predict that the field will grow by as much as 20 percent per year over the next five years, driven by a surge in regulatory approvals for in-demand cell and gene therapies.

More than 80 percent of survey respondents rely on transient transfection to manufacture viral vectors from packaging cells. Interestingly, however, the stable producer cell line is gaining momentum.

Fully 65 percent of survey respondents are developing (or intend to develop) this type of vector host cell, drawn by the potential for a less expensive, more scalable process. Stable producer cell lines, once an interesting aspiration of a few, are opening the door to compelling new operational models that will shape the future of viral vector production.

For example, what if manufacturers could propagate multiple batches of vector from a single stable producer cell culture? That would eclipse the productivity of the "terminal" triple transfection process and introduce all-new possibilities for the way manufacturers plan and qualify their facilities.

We don't quite know what the effect of new viral vector manufacturing approaches will be on the industry on the whole. What we do know is that the industry's innovators will keep finding compelling solutions to manufacture novel, life-sustaining genetic therapies for generations to come.

3. Focus on process and facility optimization

Everyone wants an optimized facility, but there are few clear instructions for getting it. So much depends on the complex science of cell and gene therapy manufacturing, but just as much, or more,

Optimization has now become mission critical and manufacturers know this.

depends on how well manufacturers translate that science into facility and process design.

Optimization has now become mission critical. Manufacturers know this. More than 77 percent of survey respondents ranked process development and optimization among their top three commercial manufacturing challenges across both cell and gene therapy platforms. These manufacturers also know that getting optimization right begins with the design of their new facility or manufacturing technology.

Manufacturers need a detailed map to guide them safely across that minefield. That's the big promise of optimization. It reveals the best possible path from high-level conceptual planning to construction and, finally, to commercial operations. Defining this path from the beginning matters. The further companies move along the path, the more they'll pay — in budget and in lost time — to accommodate changes and resolve unexpected challenges.

There's also the progressively higher risk of making a mistake and undermining a design's synergy late in the project's development, leading to inefficiencies in construction and in the facility's ultimate performance. To avoid these roadblocks, manufacturers need to begin with the end in mind, using a facility optimization approach from the start. This will avoid costly wrong turns and dead ends, ultimately delivering what nearly half of survey respondents consider their primary goal of optimization: lower capital and operational spending.

4. Growing interest in turnkey project delivery

Good, fast or affordable: Pick two. If you've been part of a traditional design-bid-build (DBB) project in the past, chances are you've faced that choice. This is a decade-old paradigm that has plagued a highly complex and technical industry where every project is considered unique. Meanwhile, other complex industries, such as health care, have been early adopters of integrated project delivery models which have proven successful.

This impractical choice has persisted for as long as traditional project delivery has been around — and it hasn't aged well. Not long ago, 100 percent of survey respondents might have been using DBB. Today, that number has fallen to just 28 percent, while the rest search for more integrative alternatives.

We're not surprised to see ATMP manufacturers leading this overall migration towards modern and more efficient project delivery methods. They've already moved the goalposts in pharmaceutical manufacturing, and now they're accelerating the adoption of the non-traditional project delivery methods that make those manufacturing goals achievable.

Over the next few years, ATMP manufacturers will continue to propel our industry into a promising era of holistic, turnkey project delivery. The majority of our survey respondents say they would consider turnkey for their next project. We expect this trend to rise dramatically over the coming years.

Of course, not everyone is ready for this evolution. More than a third of our survey respondents say they would not consider a turnkey approach. Keep in mind, however, that a turnkey facility — with a project team that understands your objectives and can balance standardized design with customization — provides exactly what some fear they may be giving up: flexibility and control, simplicity, speed and predictability.

5. Continued reliance on a model which leverages CDMOs and in-house manufacturing

A majority of respondents are uncertain whether they will switch to gene-modifying technology in the near term. Overall, 15 percent of respondents anticipate a technology switch within the next three years.

In the interim, nearly three-quarters of survey respondents work with a CMO or CDMO in some capacity, most often as part of a hybrid in-house/CMO model. This gives manufacturers an opportunity to own the development of their process without huge capital outlay on dedicated facilities and manufacturing talent. It also enables them to completely outsource specific components such as plasmid production.

Partnering has its own costs, though. Despite a recent surge in facility construction and expansion, it's not unusual for manufacturers to wait a year or more for an opening with a qualified CMO. This accounts for the 27 percent of survey respondents who have chosen to pursue only in-house viral vector manufacturing.

Rather than wait for the industry to catch up with demand, this smaller percentage of respondents are initiating their own solutions and accepting the risks — and potential rewards — that come with going it alone.

6. Regulatory compliance strategies for closed processing

Most ATMP manufacturers surveyed (78 percent) are making products destined for human or veterinary use. Because progress in discovery, developing and evolving therapeutic applications among manufacturers has almost always moved faster than regulation, look for a surge in the development of regulatory compliance strategies — particularly in the area of closed processing and patient specific therapies.

Top challenges facing the ATMP sector

- Lack of commercial GMP manufacturing capacity to meet current and future demand
- A need to automate and optimize processes
- Open and manual operations are difficult to scale, driving the need for closed, automated processing at the commercial scale
- A transition from adherent cell culture to suspension cell culture to maximize scalability
- Lack of skilled and available expertise to manage and operate new process equipment

In many cases, regulators are familiar with ATMP technologies. In others, the emerging technologies and process platforms for ATMP production are so novel that they may not be fully compatible with current GMP regulations. Making a wrong decision — or a decision that works for small-batch production but will not scale to commercial-volume GMP production — could result in significant regulatory delays. With so much depending on speed-to-market, avoiding these risks is paramount.

ATMP manufacturers who want to own their future by taking control of their present have a narrow window to make a move — but it's a move destined to pay off.

In 2013, the International Society of Pharmaceutical Engineers (ISPE) introduced the concept of closed bioprocessing, laying out the rationale and criteria for what is closed and what is not. Soon after, regulators began recommending the use of closed bioprocessing. They saw it as the safest way to make biologics with the least risk of contamination, including for vaccines and therapeutic proteins. These concepts must now continue to be implemented for novel therapies. For manufacturers, this translates into lower cost to patients, lower operating costs, lower facility costs, and a smaller overall footprint.

To take advantage of these benefits, therefore, pharmaceutical manufacturers need a regulatory strategy. This means understanding ATMP regulations, communicating with regulatory agencies and industry peers and embracing closed bioprocessing.

A sound regulatory strategy will help with the initial design of the bioprocess used during commercial production, and in turn will reduce contamination risk and operating costs, ensure reliable production and smooth the regulatory approval process.

Preparing for the future

The pharma manufacturing industry is poised for some large-scale changes as early as the coming year. In some cases it may have been prompted by facing the hard realities of drug development and discovery in the COVID era; in others it's simply an extension of the groundwork laid over past years of diligent effort.

Regardless of what has motivated these changes, the next five years will be interesting. Companies that acknowledge these trends will be best prepared for a sound and successful future.

Gary Hutchinson
President, Modality Solutions

Solving the cold chain conundrum

A well-designed transport validation approach can mitigate potential distribution hazards

The pharma cold chain has never been more crucial or complex.

As the nature of the modalities in the product pipeline evolve, the logistics challenges escalate. Consider that an ever-increasing percentage of new pharmaceuticals are vaccines, cell and gene therapies, and other biologics — drugs with stringent temperature and transportation requirements. The FDA approved a record 22 new biologics in 2019, and 21 of them have cold chain requirements.[1]

For pharma manufacturers with environmentally sensitive drugs like these in their portfolios, the cold chain is both a priority and a challenge. While regulatory compliance is always a key objective, protecting against environmental hazards throughout the distribution network is crucial to ensuring drug safety and efficacy and staying competitive. And with billions spent annually on pharma logistics — including transportation, specialized packaging, monitoring and controls — the financial stakes are high.

Current Good Distribution Practices (cGDPs) for the pharma supply chain are always a formidable task due to the distributed nature of modern controlled environment networks and the third-party contractor relationships involved. When developing a transportation plan for environmentally sensitive drugs, the task is further complicated by five potential hazards: temperature, shock, vibration, pressure and humidity. Together these hazards create a pharma cold chain conundrum, but one that can be solved with the right approach.

It starts with the right testing

When transporting pharma products that are based on proteins, tissues, genes or cells, the inevitable variations in equipment, material handling, personnel skills and experience make it difficult to validate the controlled environment logistics network to a high degree of confidence. In turn, careful consideration must be given to in-transit monitoring, procedural controls, visual indicators and stability testing. These areas have an increasing focus with technology advances making it possible to dynamically test the cumulative and significant hazards that can occur during transport.

Temperature variation is one hazard of particular concern for environmentally sensitive drugs. Even temporarily storing a thermal packaging system in a forced-air refrigeration cooler within the qualification time period can cause low temperatures and potential freezing of the drug product. In protein-based drugs, that raises the risk that the protein will degrade, become inactive, or suffer other issues that could impact safety or efficacy.

But it's not only temperature shifts that can create problems. Vibration and shock events are inherent in the logistics network, often occur concurrently with temperature fluctuations, and are particularly troublesome for solution formulations of certain large proteins. Large molecules — like those used in many modern therapies (including many for COVID-19) — are susceptible to damage that can alter the protein chemically or physically.

Traditional testing approaches — essentially shipping the drug out in the real world — don't allow for testing such hazards concurrently and at worst-case levels, leaving gaps in a manufacturer's understanding of the cumulative effects. Dynamic transport simulations testing is an effective approach to closing those gaps, especially for drugs with cold chain requirements.

A well-designed transport validation approach starts with assessing the risks for each environmental hazard to each specific drug in your expected commercial supply chain, the expected shipping durations, and the expected range of variances that could occur, including temperature exposure. Then advanced simulation technology is used to test multiple hazards simultaneously, at the worst-case edges of the intended operating space, and assess their interaction in a controlled environment.

The data gleaned from dynamic transport validation testing is invaluable — enabling pharma manufacturers to confidently define the shipping conditions, handling procedures, and specialized packaging required to protect a drug's integrity in transit. By making informed decisions about how to best design the cold chain for a particular drug, manufacturers can reduce the compliance, quality and financial risks associated with transportation and ensure the safety and efficacy of the final product.

1 | *Shelley, Suzanne. Today's pharma cold chain is going cryogenic. Pharmaceutical Commerce. Sept. 25, 2020.*

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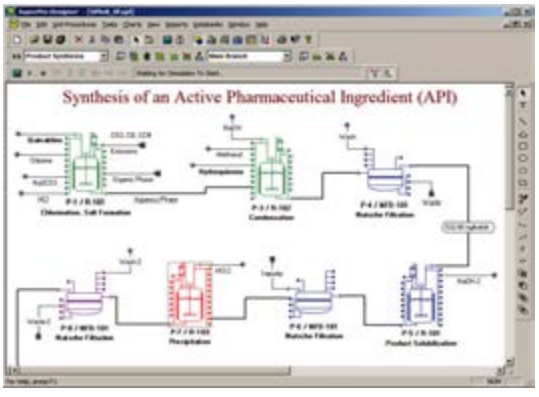

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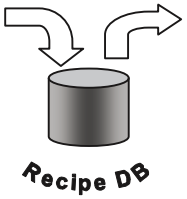

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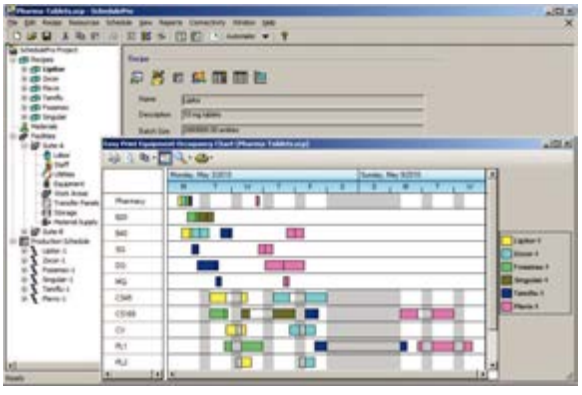

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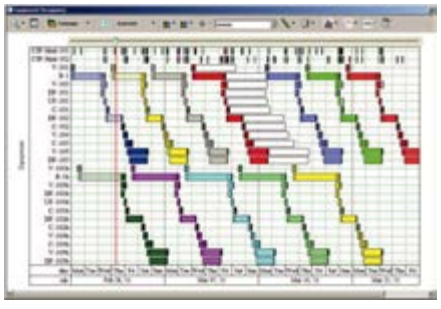

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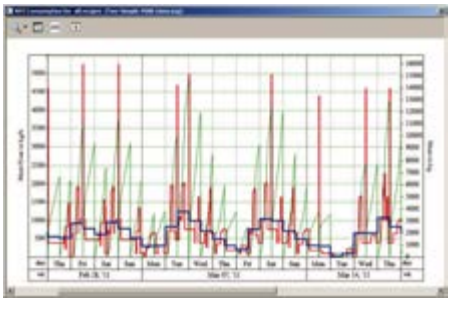
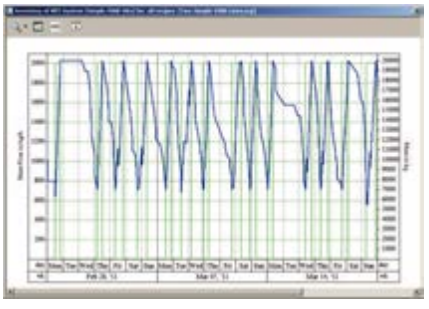


Tracking demand for resources (e.g., labor, materials, utilities, etc.)



Managing inventories for input, intermediate, and output materials

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

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

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Why digital systems are vital

The UK Excel blunder was a stark warning for pharma manufacturers

The response to the coronavirus pandemic by the international scientific community has been extraordinary. There are more than 140 separate teams of researchers working on a vaccine and five candidates already in large-scale efficacy trials, not to mention large-scale testing programs established across the world. All this, just one year after the emergence of a novel virus which has impacted all eight billion human lives on the planet.

Considering the magnitude of this global effort, the 16,000 COVID-19 test results lost by Public Health England should serve as a stark warning for pharma manufacturers. The error, caused by the use of outdated XLS file formats which could only handle around 65,000 rows of data rather than the one-million rows Excel is actually capable of, had a huge impact on public trust in the UK's testing system at a time when cases were on the rise.

Spreadsheet limitations

With logs produced by commercial firms analyzing swabs, the results were filed through text based lists on CSV files. An automatic process pulling this data into Excel templates was designed to upload the data onto a central system available for analysis by the National Health Service Test and Trace team and other government departments.

The use of the old XLS file format and the fact that each test result created several rows of data meant that each template was limited to just 1,400 cases. When that total was reached, further cases were simply left off. The XLSX file format, which superseded XLS in 2007, would have handled 16 times the number of cases.

For those skilled in working with vast amounts of data, particularly in the pharma manufacturing sector, this is hardly a surprising revelation.

As the world seeks to ramp up vaccine manufacturing capacity, consideration must be given to how modern planning and scheduling systems can ensure this is done in the most efficient manner to rapidly manufacture a vaccine en masse.

Reliable processes

As vaccine trials continue around the world, I'd argue that having the right technology and systems in place to ensure the best manufacturing process will be as important as having the means of production on standby.

The use of an advanced planning and scheduling (APS) system will be critical in creating a single real-time plan to reduce lead times and optimize resources. The granularity of data far exceeds that of spreadsheets and users are able to use this to model scenarios based on resources, constraints and process time in order to make more effective decisions.

Spreadsheets are complex, inconsistent, prone to errors and out-of-date — not to mention time-consuming. With no visibility over processes, they are unable to show where there is capacity. Having a single source of data to base decisions on means no time lag and the assurance of a standardized dataset, leading to one single version of the truth.

> **Spreadsheets will not be the platform that provides the planning and scheduling of the COVID-19 vaccine or vaccines for future pandemics.**

This will be key to ramping up vaccine production quickly. After all, without a reliable basis of evidence, how can managers make informed decisions that ultimately drive performance? This will save all important time and reduce the likelihood of planning mistakes and delays — setbacks we can ill-afford.

Far from simply an embarrassing mistake, the UK government's Excel blunder may have put lives at risk at a critical time for public health and pharma manufacturers must heed this warning. Spreadsheets will not be the platform that provides the planning and scheduling of the COVID-19 vaccine or vaccines for future pandemics. Having the right technology in place is critical to optimize resources, reduce lead times and create a single plan to get the world back to some form of normality.

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