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Meagan Parrish
Senior Editor

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Pharma Manufacturing™ (USPS number 023-188) (ISSN number 1550-6509) is published 10 times a year by Putman Media Inc. (also publishers of Food Processing, Smart Industry, Chemical Processing, Control, Control Design, Plant Services and The Journal), 1501 E. Woodfield Road, Suite 400N, Schaumburg, IL 60173 (Phone: 630-467-1300 Fax: 630-467-1120). Periodicals Postage Paid at Schaumburg, IL and additional mailing Offices. POSTMASTER: Please send change of address to Putman Media, PO Box 1888, Cedar Rapids IA 52406-1888. Phone: 1-800-553-8878 ext 5020. SUBSCRIPTIONS: To receive a complimentary subscription go to www.pharmamanufacturing.com. Subscription rate for non-qualified U.S. subscribers is $68/yr. Single copy rate is $15.00. Other international is $200/yr (airmail only). Canada Post International Publications Mail Product Sales Agreement No. 40028661. Canada Mail Distributor Information: Frontier/BWI, PO Box 1051, Fort Erie, Ontario, Canada L2A 5N8..

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

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

EDITORIAL TEAM

karen langhauser
Chief Content Director
klanghauser@putman.net

meagan parrish
Senior Editor
mparrish@putman.net

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

brian marz
Publisher
bmarz@putman.net

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DESIGN & PRODUCTION TEAM

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

michael annino
Associate Art Director
mannino@putman.net

rita fitzgerald
Production Manager
rfitzgerald@putman.net

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Karen Langhauser
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Mastering production

Pay attention to the manufacturer behind the curtain

I spent a good portion of my early childhood casually dressed up as the Wicked Witch of the West.

And while I probably looked a little odd pairing green face paint and a witch hat with a bathing suit in July, I've not regretted one moment from my Wizard of Oz-couture phase.

MGM's 1939 adaptation of L. Frank Baum's work is a movie full of moments. There's Dorothy tapping her heels together and returning home; Toto tugging back the curtain to reveal the true identity of the great and powerful Oz; the soggy witch dramatically melting to her death. And of course, the moment of all moments: When Dorothy slowly pulls open her front door and her sad sepia-filtered world magically transforms into a technicolor Munchkinland dream.

We all remember what this looked like on screen. Yet, I can't help but reflect on what it took, behind the camera, to bring these iconic scenes to life.

First, the camera technology itself. The trademarked process used to film "The Wizard of Oz" was the result of decades of tinkering with technology. The Technicolor Corporation was the first to get the tech on the market, and even after that, went through several iterations of the invention before it reached its full glory in the 1930s. The process, which involved a special camera recording the same scene through colored filters on three different strips of film, was a complex undertaking. Making a Technicolor film meant the studio had to lease the company's unique, modified movie cameras as well as rent a trained team of experts to help operate the complicated machines.

The cutting-edge film technology wasn't the only boundary pushed during the making of "The Wizard of Oz." Evidently, directors tried out some new ideas when it came to costume design and special effects, and hard lessons were learned along the way.

The original Tin Man actor almost died from an allergic reaction to his toxic aluminum makeup. The "snow" used during the poppy scene was apparently 100% industrial-grade asbestos. The actress who played the wicked witch suffered serious burns during pyrotechnics gone wrong. Even the winged monkeys weren't spared, crashing to the ground after their wires failed mid-monkey flap.

The final result? Arguably one of the most beloved, influential fantasy productions of all time.

While I've yet to witness the pharma industry break into song, the industry is certainly no stranger to this level of masterpiece. In just the last decade alone, pharma hits include: a cure for Hepatitis C, 3D printed body parts, reprogrammable T-cells to treat leukemia, gene therapies to cure sickle cell disease and blindness, gene editing through CRISPR, fecal transplants to cure C. diff — and of course, life-saving pandemic vaccines.

Each year as we embark on our Pharma Innovation Awards journey, we sort through dozens of new and unique technologies created to help enable these great advances in science. I'm continually impressed by all the behind-the-scenes work done by savvy equipment makers who play starring roles in bringing pharma innovations to the big screen.

So, to all the equipment and technology manufacturers toiling behind the curtains, the camera, the makeup: Thanks for having the brains, heart and nerve to help make patient dreams come true.

Meagan Parrish
Senior Editor

INTERPHEX in the time of COVID

Trade shows are back — but are they still worth it?

It's not uncommon for vendors and attendees at industry trade shows to casually ask each other how the experience is going. But this year at INTERPHEX, there was a more elevated sense of curiosity underlying the typical inquiry.

To be sure, INTERPHEX, one of pharma manufacturing's largest yearly trade shows, felt different this time around. Held at its usual location, The Javits Center in New York City, this October's show marked the first time the event had been held in person since before-COVID times — after being canceled last year and then postponed from its usual time slot this past spring. And for many of the vendors in attendance, it was their first venture back into a live trade show environment after spending a year and a half adjusting business practices to bolster connections and technology promotions with customers online.

Yet, one look around the trade show floor revealed that events for pharma manufacturers haven't completely rebounded. Although the space was full with its usual variety of exhibitors — from technology solutions providers to CMOs — INTERPHEX was clearly not as packed as it has been in years past.

In this new environment, the question of how it was going was now being asked in earnest as some vendors wondered if the investment of exhibiting in trade shows was still paying off in returns. Here's a look at what a handful of vendors had to say.

Kudos for safety

INTERPHEX went to great lengths to make the show safe for all in attendance by requiring proof of vaccination and strictly enforcing a mask mandate. Merrilee Whitney, head of BioContinuum Platform at MilliporeSigma, said she appreciated the measures.

> **INTERPHEX returns in the spring**
>
> Pharma manufacturing's renowned trade show will return to its usual time slot in the spring. The event is currently planned for **May 24-26**, 2022 at the Javits Center in NYC.

"They made it super easy and I appreciated that if we had to have this be our first major foray back into trade shows, I did not feel nervous because I thought they did an excellent job," she explained, adding that MilliporeSigma will be back to the next INTERPHEX in the spring.

Quality vs. quantity

Despite lower-than-usual attendance, there was a common refrain among many vendors about potential clients they were interacting with — quality over quantity.

"The traffic hasn't been what it usually is, but the leads have been high quality," Chris Casciato, sales manager at Entegris, which specializes in advanced materials for process solutions for the semiconductor and other high-tech industries, said. "It hasn't just been people grabbing pens."

Over at the sizable booth for CleanSpace, a vertically integrated cleanroom solutions provider, Jennifer Biro, vice president of sales, agreed.

"The show is a lot different than years past when people were shoulder to shoulder trying to get from one aisle to the next," she said. "However, people who are here are focused and decision-driven. So there may not be as much

networking going on…but people are coming who are already qualified."

Biro, who has been in the industry for 18 years, said that CleanSpace pivoted to networking online during the pandemic and heavily utilized LinkedIn to make connections throughout the industry. But she said that it can't replace the experience of INTERPHEX, the company's largest trade show.

"The human, face-to-face interaction is still the best way to do business," she said.

Some skepticism

Not everyone was convinced that the effort of attending was worth it.

Todd Grube, product manager of Heat and Control, which specializes in inspection systems, said that he's unsure if his company will be back to the next INTERPHEX, which is currently slated for May 2022.

"Several other vendors we know have said they are not coming back in six months because it is so slow," he explained. "It has been slower than we thought it would be."

And Grube said the jury is still out on whether or not his experience at INTERPHEX will impact the company's overall trade show strategy going forward.

"It's too soon to say," he explained. "Having not done trade shows for a year and now seeing less activity — not just for our company but for others — we may rethink our strategy for trade shows in general."

Plant machinery impacts many areas for pharma companies. When machines fail or underperform, productivity slows, workers become frustrated, delivery dates are missed, and supply chains suffer.

Our recent survey took a deep dive into the state of machine maintenance and reliability in pharma plants to uncover the true scope of failure and what that means for the industry.

Daniel Merriman, Strategic Marketing Manager, Thermo Fisher Scientific

A better way to measure critical attributes in bioreactors

The benefits of gas analysis for mass spectrometer applications

It's no secret that the pharma industry has been feeling the need for speed in the last few years. When the world asked for vaccines and therapeutics to be developed quicker than ever before, the industry responded and hundreds of potential vaccines and treatments were ushered into clinical trials within months.

But pharma companies couldn't just move fast — they had to be careful and accurate because the world was waiting.

To help meet all of those needs, Thermo Fisher Scientific offers a line of mass spectrometers for gas analysis and fermentation in bioreactors, which is critical for monitoring the health of the culture and measuring small changes to oxygen and carbon dioxide concentration at key phases of the process.

Whether a company is using continuous or batch fermentation for bacterial, microbial or mammalian cell culture expression, Thermo Fisher's gas analysis, mass spec product range, which includes its Prima BT and Prima PRO models provide precise off-gas analysis through every stage of fermentation, from the lab to the pilot plant to scale up. In addition, Thermo Fisher's mass spec products work quickly and provide significant process control improvements that can be achieved usually within just a few days.

To learn more about the Prima BT and Prima PRO models, Pharma Manufacturing recently spoke to Daniel Merriman, the Strategic Marketing Manager at Thermo Fisher.

Q: Let's start with some background on these technologies. Can you describe the relationship between gas analysis, mass spectrometry and process analytical technology as defined by the FDA?

A: The FDA itself supports the implementation of analytical technologies. When implementing PAT, users typically identify critical quality attributes that they wish to affect, usually attributes that might impact product yield or quality. The next step is to study critical process parameters that impact those quality attributes. And this is where online analysis comes in.

Gas analysis mass spec is one powerful tool for the study of these process parameters both directly by measurement of off-gas concentrations, such as oxygen or CO2, and then the utilization of that data to calculate parameters such as respiratory quotient. The goal is to use these process parameters to have better control of the process that ultimately yields better outcomes. And that's really what PAT is about as far as the FDA is concerned.

> "Operating costs of mass spec are very low, but the value of the measurements are very high.

Q: Could you tell me a little bit more about problems that pharma companies are trying to overcome when they're using this type of analyzer?

A: Implementation of online process monitoring of a fermenter or bioreactor is not a trivial matter. If the intention is to perform online automated liquid phase sampling, these can be complex systems. Whether the analysis is done online or offline, measurements at the fermenter often require high-value analyzers, which are costly to use from a consumable perspective.

The intention of online gas analysis though, particularly by mass spectrometry, is to make these measurements low-risk so that they should be fully automated and able to provide process data that can reduce the dependence on offline testing, but also to produce that data in real time, without the need for manual intervention. So, it turns it into an automated, online method.

Q: Are there simpler or cheaper methods for this?

A: For gas analysis there are, but they're not likely to facilitate the online measurements from a large number of fermenters. A mass spec could sample as many as 50 fermenters with a single system. And I should also note that the measurement precision of lower cost sensors is typically rather poor compared to mass spectrometry.

But another advantage of mass spec, which isn't available to other techniques, is that mass spec can measure more than just simple oxygen and CO2 components. For example, ethanol and methanol are routinely measured in fermentation processes by mass spec. And that doesn't add any cost to the solution.

Q: Speaking of costs, mass spec can be known to be a little bit more expensive, but is it a cost-effective solution in the long term?

A: Yes. A single mass spec could be utilized for many fermenters from a single analyzer. So, cost per point comes down very quickly. But as you said, it's not all about the initial cost. Operating costs of mass spec are very low, but the value of the measurements are very high.

Q: Let's talk about integrating mass spec if a company goes ahead and decides that they want to use this kind of system. You've described it as being relatively simple and low-risk. Can you elaborate on that a little bit more?

A: Measurements of sparge gas and vent gas from fermenters and bioreactors by mass spec require the mass spec to be entirely outside of the sterile environment. There's no interruption to the process or interference to the fermenter or bioreactor. These systems also provide a very reliable measurement method.

So, that's how they are a low-risk implementation.

Q: There are of course many different types of processes that are used in biopharma production. Can you tell me a little bit more about how this technology is suitable for those different types of processes?

A: Generally, it's been applied to microbial and mammalian cell cultures for the development and production of many types of products.

So, it's mainly used in the pharmaceutical industry, but it's also applicable to agricultural products, bio-materials and biofuels. And for the latter, there is a lot of interest in it.

Q: In biopharma, there's a lot of interest in mammalian cell culture. Tell me a little bit more about how this technology is used for this application.

A: There are already some excellent studies on the use of online mass spec for cell cultures. In general, the measurements are similar to microbial fermentation, but mass spec has a very impressive linear range for the gases that are required to be measured. And that's especially useful in cell culture because the concentrations of the sparge gas and vent gases can vary significantly.

Also, mass spec is very precise and again, in cell culture, the changes in CO2 and oxygen in the respiratory gas concentration changes can be very, very small. And mass spec is precise enough to measure those small changes reliably, whereas other techniques would not be able to.

Q: What kinds of advantages can companies realize by implementing this solution?

A: If I could summarize the advantages that have been gained given the things we've discussed so far, I'd say it's to have this real-time insight into cell metabolism that really enables the realization of PAT goals such as improving performance attributes. But it can also enable the prevention and minimization of poor process quality.

Q: But every process in biopharma production has its drawbacks and limitations as well. What are some of the limitations of mass spec?

A: One limitation, which is common to gas analyzers, is that they need a minimum sample gas flow. In some fermentation and cell culture processes, where the volume of the bioreactor is small, it's currently impractical to use online gas analysis to monitor them. So, there certainly are some limitations in that respect.

Q: Of course, vendors for pharma companies are always looking at ways they can innovate their solutions to make life easier for pharma manufacturers. So, what's next for gas analysis mass spec?

A: I think solving the above limitation would be a good start, but I think from where we are today, I do see an expected increase in the use of this technology for mammalian cell cultures, but also an extension of many other types of products, which are made by fermentation [and] are likely to use gas analysis mass spectrometry. Something, for example, like green energy such as biofuels and biomaterials.

So, I think that we will see a continued extension of different applications that have fermentation or cell culture.

2021

PHARMA INNOVATION AWARDS

Unveiling this year's winners

Meagan Parrish
Senior Editor

It's a cliché now, but when the curtain was tugged open at the end of "The Wizard of Oz" to reveal that the mighty Oz was really just a man pushing buttons and pulling levers, it marked one of the biggest surprises in cinematic history. And although the moment unveiled a shocking ruse, it also showcased the power technology can have when wielded in innovative ways.

Manufacturing vendors similarly play a vital role behind the curtain of the great and powerful pharma industry. Today, the gadgets are much more sophisticated than anything dreamed up in the land of Oz — with automation, robotics, remote monitoring and data analysis playing key roles in the innovations hitting the labs and plant floors of industry facilities.

The technologies also show that when it comes to getting drugs onto the market, manufacturing vendors are the true wizards of pharma.

For the ninth year, Pharma Manufacturing is paying homage to the equipment and solutions providers who help production in the industry hum along. This year in particular, the pressure has been on pharma to keep pace with the ongoing demand for pandemic products, while also meeting the needs of rapidly expanding areas of the industry, such as advanced therapeutics. Without innovations that boost speed and efficiency throughout the development process — from early drug creation to packaging and shipping — the industry would surely stumble on this journey.

Here, we proudly pull back the curtain on 19 recently launched or updated technologies selected by Pharma Manufacturing editors and reviewers for this year's Pharma Innovation Awards.

Bioprocessing

The biopharma sector often steals the spotlight in the industry — with updates about vaccines, monoclonal antibodies, and cell and gene therapies grabbing headlines nearly every day. Biopharma is also in the midst of a major manufacturing expansion. Between 2020 and 2027, the biopharma sector is forecasted to swell at a CAGR of about 7.3% to $535 billion.[1] The growth will be driven by an increase in the elderly population, a surge in chronic diseases as well as increased strategic collaboration between biopharma companies.

To stay in step with rising demand, our Pharma Innovation Award winners offer new and valuable tools to improve processes throughout the biopharma value chain.

Intensifying the process

Process intensification has emerged as a rising goal for biotech manufacturers in recent years because of how it can help a company shrink its facility footprint and lower costs. This year, **Univercells Technologies** introduced the **NevoLine Upstream platform**, an automated manufacturing solution for the high-performance production of viral vaccines, viral vectors and oncolytic viruses leveraging process intensification. Unlike large, stand-alone viral manufacturing units, the platform integrates, chains and automates production — from inoculation to midstream processing — into a compact module.

The three square-meter unit can be used in various configurations, offering flexibility in multi-product facilities. The chaining and continuous processing also allows end-to-end automation to deliver a concentrated, clarified bulk product. All told, the platform was designed to save space and reduce capital expenditures.

"The field needs this type of improvement," a member of the Pharma Manufacturing edit board said of the NevoLine Upstream platform.

Enhanced smart pharma tools

For all of the promise therapeutic proteins and viral vectors hold in pharma, several manufacturing challenges remain in their production. The growth in demand for viral vectors in particular, which is estimated to swell by about 20% per year for the next five years,[2] coupled with manufacturing bottlenecks and a slow supply, has led to shortages and long lead times throughout the industry.

Schreiner MediPharm
Smart Blister Packs and Smart Kit Boxes

With that challenge in mind, **Solentim's ICON** was developed to help streamline and accelerate a critical step in therapeutic protein and viral vector manufacturing: single-cell cloning.

The clonality stage of manufacturing ensures that the process has been brought down to a single cell to limit variability within the cell bank. Using low-volume measurements of critical quality attributes, such as IgG titer, confluency, cell volume and viability of cell density, the ICON system enables rapid stratification of leading cell candidates. Developed as what the company calls the "world's first" benchtop system that characterizes the high-productivity of clones in cell development, ICON works with Solentim's data management system, STADIUS. Leveraging data-driven insights, the system is designed to save resources and speed the development of new cell-based therapies.

For further downstream production, **Aizon's Bioreactor Application SaaS** combines almost all of what Pharma 4.0 has to offer — artificial intelligence, machine learning, cloud technologies, IIoT and other analytical tools — into what the company calls "the industry's first predictive analytics and deep knowledge management application targeting bioreactors in GxP environments."

Applicable to both batch and continuous operations, the turnkey application offers a wide range of insights for operators — from process discovery and batch comparison tools to real-time monitoring and yield prediction capabilities. Using the tools and dashboards within the app, operators are able to quickly analyze and visualize a number of process parameters in different batches and see how those parameters interact with each other.

With the help of digital tools that enable data-driven decision making, companies are able to use the Bioreactor Application to optimize processing.

Research and development

There's a lot riding on the extensive R&D process in pharma. From identifying potential drugs to assessing their viability to ushering winning candidates into clinical trials, the R&D phase is time-consuming and critical to a drug's eventual success.

Tools or solutions that streamline any of the steps in this long and arduous process — such as this year's winners in the R&D category — can be a major boon for drug developers.

Accelerating drug discovery

Although ion mobility (IM) techniques have long been used in pharma research, ion loss and resolution limitations remain an ongoing hurdle with the method. Using high resolution ion mobility (HRIM), **MOBIILion Systems' MOBIE** mass spectrometer overcomes these challenges with separations that are achieved on 13-meter path lengths — 12 times higher than other technologies, according to the company — realized with serpentine electrode patterns on standard printed circuit board (PCB) technology. MOBIILion says that the beauty of this approach to digitizing separations on PCBs is that it allows for virtually limitless path lengths, resulting in superior separation with molecules of interest.

The driving technology of MOBIE — Structures for Lossless Ion Manipulation (SLIM) — has become instrumental in allowing researchers to separate and identify molecular structures that wouldn't be detected with many other established techniques. And with easy push-button software, MOBIE is designed to simplify workflows with faster separations of challenging analyte classes — an innovation that will accelerate the characterization of biotherapeutics, and biomarker identification and validation.

"[This technology] is a good method to focus analysis and save time," a member of Pharma Manufacturing's edit board said of MOBIE.

Enabling faster drug discovery was also the driving goal behind the development of **Araceli Biosciences' Endeavor** high content analysis (HCA) platform. Combining advanced scanning hardware and AI software, the platform has the ability to generate high-resolution full-well results in 10 minutes and preliminary data in as little as 30 seconds — a feat the company says is "ground breaking," exceeding the speed of any other HCA system on the market by six-fold.

The platform performs complicated work as it helps scientists quickly identify and potentially discard a range of drug candidate compounds — including small molecules or RNAi — based on their phenotypic effect at the cellular level. But with its Voyager software, Endeavor was also designed to be user-friendly, with a touchscreen and intuitive workflow. All together, Endeavor was developed to shrink the gap between discovery and commercialization by allowing faster decision-making in research.

Smarter clinical trials

Ensuring medication adherence is vital to the success of a clinical trial — and patients who fail to comply can undermine the results of the study. With so much at stake, it's no surprise that all experts who provided feedback to Pharma Manufacturing on this year's candidates voted unanimously to include a solution to this issue — **Schreiner MediPharm's Smart Blister Packs and Smart Kit Boxes** — among the Pharma Innovation Awards.

With the help of AARDEX Group, an expert in digital medication adherence, Schreiner MediPharm developed the solution to bolster and ensure better compliance in clinical trials. Using sensor technology and smart medicine packaging, the technology provides real-time data when doses are taken (Smart Blister Packs are used for tablets and capsules, and Smart Kit Boxes for vials and syringes). The information is then automatically stored and sent to a database through an app that can be used on a smartphone.

In addition to enhancing confidence in clinical trial results, the solution also alerts users to structural deficiencies in the packs and generates critical information about patient behavior.

"Nicely done. These types of systems are the future in compliance for clinical dosage regimens," a Pharma Manufacturing edit board member said of the Smart Blister Packs and Smart Kit Boxes.

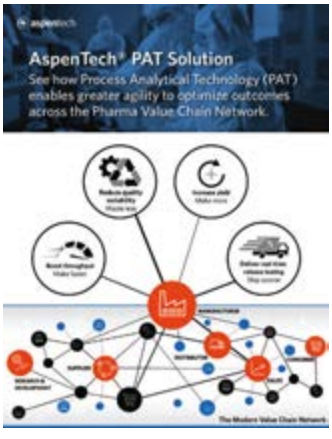
Plant operations

Once manufacturing begins, the pressure is on to ensure consistent results through the various stages of processing — a challenge that is growing more predominant as the industry pivots towards a wider array of batch sizes and products.

With demand rising for a growing number of diverse pharma products, this year's winners offer new ways to increase efficiency and lower costs while helping manufacturers stay nimble on their feet.

Boosting efficiency through automation

With the goal of improving batch consistency and quality in pharma processing, **Aspen Technology's PAT portfolio** now combines several technologies for product and process modeling, analysis and optimization — Aspen Unscrambler, Aspen Process Pulse and Aspen ProMV. The newly combined suite uses the best of these technologies



Aspen Technology
PAT portfolio

to create a powerful continuous improvement suite that can be used in large-scale production for a number of pharma products, including small molecules and biopharmaceuticals.

The benefits of the suite include real-time product and process quality monitoring that combines information from traditional process sensors and advanced spectroscopic sensors; accurate batch end-point determination; batch-to-batch quality and yield trend analysis and optimization; and in-line quality testing to enable real-time release.

With these various functions under a single suite, the PAT portfolio is designed to automate workflows, enhance diagnostics capabilities and optimize outcomes for operations personnel. This drives more consistent in-spec production, higher yields and greater throughput, all helping to alleviate supply chain pressures by delivering more saleable product every day.

Combining capabilities is also a key feature of **BEA Technologies' MAGNEXFLO**, a fully automated filtration unit. By pooling three filtration stages into one skid unit, the solution saves space while maintaining efficiency for many demanding products, such as raw gelatins and viscous fluids, that need to be clarified.

MAGNEXFLO leverages the company's MAGNEX filter element, which can retain a large amount of impurities and colloidal particles. The new unit is customizable with several options for filtration elements available to meet different production needs. It also provides direct filtration, without the need to recirculate products.

Ultimately, the company says that the system lowers cost compared to other options on the market.

Next-gen tableting

Avoiding contamination is a major priority in tablet production, especially when manufacturers are working with multiple products. Thus, containment remains a chief concern when assessing tablet presses.

Fette Compacting's new **F30i** double rotary tablet press satisfies containment concerns — while operating at high speeds. Released this year as a follow-up to the company's F10i single rotary press for small batches, the F30i is designed for large-scale production with the ability to crank out 1.6 million tablets per hour. The unit's dust-tight design also protects operators from contamination by keeping dust from being released from the machine. And despite its updates, the unit's cross-generation system capability also allows die and turret rotors to be adopted from earlier models.

In addition, the unit comes with various Pharma 4.0 bells and whistles including open interfaces that comply with automation standards and can be integrated with IoT and manufacturing execution systems.

BEA Technologies
MAGNEXFLO

Fette Compacting
F30i

Monitoring and analytical devices

Failing to accurately monitor the many variables at play during pharma processing can result in costly problems such as contamination. Ideally, monitoring devices should work easily, quickly and effectively to help companies stay on top of conditions inside manufacturing environments.

This year's Pharma Innovation Awards winners represent impactful step changes in the field for monitoring and analytical devices.

A better CO2 sensor

Dissolved carbon-dioxide (DCO2) in biopharma applications is traditionally monitored by means of indirect pH measurement (Severinghaus technology) — requiring operators to wrestle with product calibration, maintenance and multiple sources of drift. On top of that, the embedded pH sensor has to be replaced quite often. To simplify the process, **Hamilton Bonaduz AG's CO2NTROL** solid-state sensor directly identifies DCO2 levels using a novel optical approach. Once CO2 molecules are diffused into a gas permeable membrane, the instrument measures the absorption of CO2-specific mid-infrared region wavelengths, which directly correlates to the partial pressure of CO2 in the sample (liquid or gas).

The result is a measurement that is more accurate and

maintenance-free — no replacement parts — than traditional sensors, enabling real-time, automated control of CO2. The improvements also ensure batch-to-batch reproducibility, lower costs and increase consistency throughout processing — from R&D to large-scale production.

"A more reliable CO2 sensor is welcome. This seems like a real step forward," a Pharma Manufacturing edit board member noted.

Enhanced particulate measurements

The regulatory requirements for operating cleanroom environments are continuously becoming more strict. To stay compliant, drugmakers need the most up-to-date monitoring technologies.

Particle Measuring Systems' IsoAir Pro-E Remote Particle Counter was developed to provide a superior level of continuous particle measurement in environmentally controlled spaces. With its 316L stainless steel enclosure design, the particle counter incorporates several leading-edge monitoring technologies into a single instrument.

According to the company, the instrument is the first ever with a built-in vacuum designed for use with the vaporized hydrogen peroxide process. In addition, it is powered by Power over Ethernet and features an internal blower that minimizes the need for external connections and supporting equipment. By integrating into a variety of software systems and featuring a quick release mounting bracket that stores essential sensor data, the instrument also provides enhanced data management.

Put together, the instrument ensures a more complete particle measurement solution for small- or large-scale pharmaceutical and biomanufacturing environments.

Particle Measuring Systems
IsoAir Pro-E

Quality control

From a patient's point of view, the quality of pharma products should be a given, and drugs should only serve to improve health — never to harm it. From a manufacturer's viewpoint, achieving high quality is the result of painstaking processes that ensure the safety, consistency and compliance of products.

But when done right, quality-related innovations, such as this year's winners, can go beyond regulatory compliance to improve commercial performance while helping companies achieve other critical business goals.

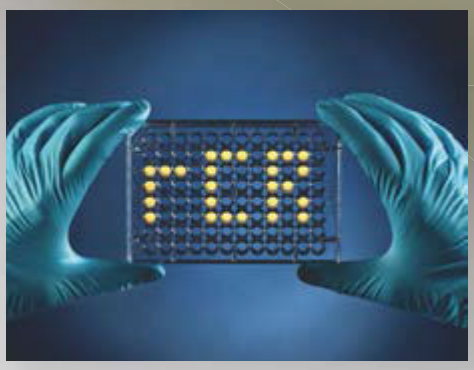
Holistic quality management

A quality-by-design approach to manufacturing goes hand-in-hand with strategic business practices. **Optimal Industrial Technologies' synTQ 5.5** provides both regulatory quality compliance and business insights, from R&D through to manufacturing.

A vendor-agnostic, PAT knowledge management and quality-centric software suite, the company says that the synTQ was the "first product of its type on the marketplace."

By providing a holistic and data-driven overview of various phases of manufacturing, the solution utilizes interconnected tools, sensors and systems to provide real-time insights on quality parameters. The solution thus offers full visibility and control over manufacturing to address current and future production needs.

Hamilton Bonaduz AG
CO2NTROL



Associates of Cape Cod
PyroSmart NextGen

The latest version of the system also integrates orchestration digital twin functionalities for partial or complete PAT methods virtually, which allows companies to create and test process data flows before applying new manufacturing activities in real-world settings.

Animal-free BET testing

Horseshoe crabs have long been an integral part of creating the bacterial endotoxins test (BET) — also known as limulus amebocyte lysate (LAL) tests — that are required for injectable drugs like vaccines. But the process of making the test involves bleeding horseshoe crabs, which is an unsustainable method for the long term.

Now the **Associates of Cape Cod's PyroSmart NextGen** provides a recombinant LAL reagent that is sustainable and animal-free. Designed for end-product testing of human and animal injectable drugs and medical devices, the PyroSmart NextGen uses the same enzymatic cascade pathway as traditional methods and provides results that are just as consistent and high quality. It can directly replace naturally sourced reagents without the need to purchase new equipment or instruments.

The reagent can be used for a variety of endotoxin tests — from water sampling to studies that require high sensitivity, such as intrathecal products or those requiring high dilutions to overcome interference. It also provides a number of other benefits over competing animal-free options, including single step reconstitution and the ability to perform kinetic assays.

Packaging

With the pandemic ramping up demand throughout pharma, the pressure has been on to ensure that bottlenecks don't slow down progress. On the packaging line that means that systems have to work quickly and accurately. It's no simple task — the pipeline for pharma products is becoming ever-more complex as newer and smaller batches of advanced therapies make their way through production lines. Thus, packaging systems have to also be flexible.

This year's winners showcase packaging innovations that balance speed and complexity to help deliver critical medicines to patients.

Faster checkweighing

Across the industry, the leading checkweigher systems operate at about 700 ppm when working with lightweight blister packs. But this year, **Mettler-Toledo's FlashCell** load cell for Mettler-Toledo checkweighers moved the goal on what's possible with a checkweigher system by hitting 800 ppm.

FlashCell allows the checkweighers to reach these new speeds without sacrificing accuracy. According to Mettler-Toledo, the checkweigher works with regulation-compliant precision. In fact, its weigher is so sensitive that it can detect if even one drug leaflet or filled syringe is missing from a load.

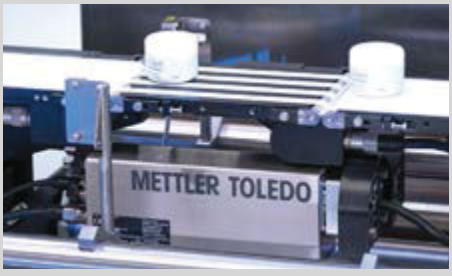
As an added bonus, Mettler-Toledo checkweighers with FlashCell load cells also have a smaller footprint. Because the unit works with shorter measuring times at high speeds, the weighing conveyor can be reduced in length. This shorter conveyor also moves slower, which boosts product handling stability, and feeds into a shorter product collection area. Overall, these reductions in conveyor length can shrink the size of the unit by 24%.

Dual shipping capabilities

An increasing number of pharma products that require ultracold storage are entering the market, adding new challenges to shipping. This year, **Packaging Technology Group's TRUEtemp Naturals Dual Temperature Packaging Solution** emerged as an innovative new option to handling different therapies in one shipment.

With its thermal design, drug products that need to be stored at different temperatures — often one is frozen while the other is

Mettler-Toledo
FlashCell



Stevanato Group
Vision Robot Inspection Machine

refrigerated — can be shipped in the same container. The shipper could be particularly useful for shipments of immunotherapies for certain cancers and other illnesses.

On top of that, the shippers are made with 100% curbside recyclable and repulpable materials. With sustainability as a top priority for many companies, the shippers were designed to help drugmakers meet corporate sustainability goals while simplifying shipping.

Robotic inspections

In factories of the future, robots will largely take over many of the more menial and redundant tasks. The goal, however, isn't to simply replace humans — it's to combine human-like flexibility with machine learning capabilities.

Stevanato Group's Vision Robot Unit Inspection Machine achieves both as a fully automated, highly accurate and flexible inspection system with AI technology. Capable of handling a variety of high-value pharma products — including mAbs, vaccines and lyophilized drugs — the unit can react quickly to changing product characteristics even throughout a single batch. It also learns continuously from both product and operator stimuli, resulting in a system that ultimately reduces the number of false rejects and false positives.

The system is also modular and can be customized for different environments — from labs to small scale production. Its customizability also ensures that the system is optimized for a company's specific production needs, which enhances efficiency and speed.

Labs

With the market for advanced therapies swelling and demand in pharma ramped up due to the pandemic, the life sciences sector is undergoing a major boom. This growth has triggered spiking demand for lab space. In 2020, the industry was set to deliver 4.5 million square feet of new life sciences space — more than double the prior five-year average.[3]

As the pressure mounts to develop increasingly complex therapies at a fast clip in expanding lab spaces, innovative solutions that were once focused on the plant floor — such as lean operations, robotics and automation — are now making their way into labs as well.

A fully integrated lab

In many pharma companies, lab operations have often been performed in isolated sub-units or clusters. But with the growing emphasis on the importance of lab success, a need has emerged for an open, flexible layout with operations that are more fully transparent throughout the company.

To meet this need, **Integrated Project Services** launched **iLAB - Intelligent Lean Lab**, a fully digital process dashboard that seeks to break down the silos of lab work. Based on the concepts of lean, flexible and process-based operations, the software platform is unique in its ability to integrate personnel, space, bench, equipment and project schedules into one solution.

After implementation, the solution offers a data-driven view of lab operations that allows for easy monitoring throughout the company. It also allows various lab professionals to develop supply chain mapping under a digital umbrella that includes orders for a host of essential lab products such as raw materials, equipment and more. It uses lean tools for lab programming, educates lab staff on lean and automation principles, and leverages process mapping at the facility and individual lab level.

Overall, the company says that iLAB offers a holistic view of lab operations to improve efficiency.

Precise robotic tips for liquid handling

Minimizing downtime and ensuring reliable results are essential for lab operations. At research workstations, automated robotics can help minimize stumbles in workflow — as long as the components function efficiently.

J.T.Baker Robotic Tips from **Avantor** are designed with precision in mind. Engineered to help scientists move from discovery to delivery faster, the robotic tips feature a straighter tip for low rejection and less breakage when used in robotic liquid handling systems.

The tips are ideal for a range of applications — from genomics and cell biology to proteomic workflows — and are able to accurately dose small volumes.

In addition, the robotic tips are manufactured for compliance in even the strictest environments. According to the company, the tips are produced on a fully automated line under cleanroom conditions, and are untouched by human hands.

The transparency feature of the tips also enables easier visual

Integrated Project Services
iLab - Intelligent Lean Lab

inspection while delivering reliable results for dynamic lab needs.

Automated sample prep

Sample preparations are one of the largest potential bottlenecks in the lab and the process eats up a large amount of time for lab techs. Now, **accroma labtec's SamplePrep** has transformed this longstanding challenge into a fully automated and precisely documented process.

According to the company, the new system automates full sample preparation for solid samples — from weighing to the transfer into high-performance liquid chromatography. The result is a simple, sample in/answer out system that reduces the time spent on the process.

The system can also prepare samples for different workflows at the same time, while allowing users unlimited possibilities for combining different steps including weighing, shaking, dispensing, pipetting, filtering and more.

By automating the process, the system reduces data variability, personnel costs and quality control concerns.

And that's it for the 2021 Pharma Innovation Award winners — impactful technologies that were unveiled this year for pharma manufacturing. Thank you so much to all of the companies that submitted entries to this year's awards. And thank you to all the vendors that work tirelessly towards the goal of making pharma a better industry.

Avantor
J.T.Baker Robotic Tips

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Karen Langhauser
Chief Content DIrector

Focus on: Lithuania

A small country looking to make big moves in pharma

There's an interesting anecdote about Lithuania that is often shared among basketball aficionados.

During the time the Soviet Union occupied Lithuania, the U.S.S.R.'s national basketball team won golds in two Olympics, three FIBA World Cups, and 13 EuroBasket Championships — and players from Lithuania had a starring role in this dominance. But after the Republic of Lithuania restored its independence from the U.S.S.R. in March 1990, Lithuania found itself in need of some financial support to fund the basketball team's trip to the 1992 Olympics.

The U.S. rock band The Grateful Dead — famed fans of freedom — decided to kick in some funds as well as provide the basketball team with the band's iconic style tie-dyed shirts, designed in Lithuania's national colors. The shirts became wildly-sought after Olympic souvenirs, and sales raised money for basketball and other Lithuanian charities.* But more importantly, the Lithuanian national team beat Russia to take home the bronze — reminding the world that the small country of Lithuania was determined to come up big on the boards.

As Lithuanian basketball approaches its centenary, hoops aren't the only thing hitting a milestone anniversary. This year, the country is celebrating 50 years since the start of its biotechnology industry.

The Vilnius, Lithuania enzyme manufacturing factory — one of five facilities built by the Soviet Union's government — began operating in 1971 and shortly after, a research center was opened in the factory. The research center became the foundation of the renowned Institute of Applied Enzymology in the Soviet Union. After Lithuania broke from the U.S.S.R., many of the scientists once working at the large institute stayed in Lithuania and set up spin-off companies that still exist today. The institute was renamed the Institute of Biotechnology and is now part of the Life Science Centre at Vilnius University.

It was this 1971 research and manufacturing facility that launched the Lithuanian biotech sector, which, after a temporary lull in the 90s, resumed its steady incline, with a particular focus on R&D of reagents and enzymes, as well as more broadly across the life sciences. Today, according to the Lithuanian Biotechnology Association, the biotechnology and life sciences sector is one of the most productive sectors of the country's economy — and the fastest growing in the European Union.

Backed by a rich scientific heritage and ongoing government support, Lithuania's dynamic pharma industry is hungry for an even bigger spot on the world stage.

*The shirts, featuring a slam-dunking skeleton, were designed by New York artist Greg Speirs. Even after the shirts were given to the players, sales continued and the artist donated the remaining profits to the team and Lithuanian children's charities.

Full court press

Over the last two decades, the Lithuanian life sciences industry (which includes pharma, med-tech and biotech) has skyrocketed. According to Enterprise Lithuania, a nonprofit government agency focused on business development, the biotech and pharma sectors grew by 62% last year, stimulated by the pandemic.

"The whole world has seen the consequences that change can have on human health and the breakthrough that united science and business can achieve in their decision to solve a problem," says Enterprise Lithuania's Managing Director, Daina Kleponė. "The pandemic brought all private and public sector attention to this area, and last year it accounted for approximately 2.8% of Lithuania's GDP."

And the Lithuanian government is focused on making sure this momentum isn't lost. Long-term investments in life sciences are seen as both a key part of the national strategy for economic recovery from COVID, as well as for future growth. Back in 2018, the government laid out a strategy to increase the GDP contribution of the life sciences industry to 5% by 2030.

According to Kleponė, it's an ambitious, but attainable goal.

"Lithuania has a strong foundation in life sciences. We have famous scientists and enough talent and modern infrastructure. We've seen a sharp increase in the willingness to invest into life sciences startups, which is stimulating the birth of [many] businesses in this area. Last, but not the least, our government's economic promotion program provides special attention to this sector," says Kleponė.

The government's playbook

The Lithuanian government is backing its ambitious expectations with a strong set of financial incentives.

The Vilnius City Innovation Industrial Park is dedicated to companies that want to build research centers, labs or factories, as well as to business and science collaboration.

The Lithuanian parliament recently adopted a new package of laws, which came into force at the start of 2021. According to Invest Lithuania, the official government agency for foreign direct investment and business development, the new legislative package offers significant tax incentives and dramatically cuts red tape, making it quicker and easier for international businesses to establish and grow large-scale operations in Lithuania.

Specifically, large-scale projects (LSPs) that meet the requirements — spending 20 million euros in capital expenditures and creating 150 new full-time jobs — will enjoy 0% corporate income tax for up to 20 years. All LSPs will be given the status of "Project of State Importance" ensuring additional state support for territorial planning and environment assessment procedures. Other perks include: faster decision-making from public authorities, streamlined immigration process for employees, and simplified project planning requirements.

There are also favorable tax incentives for investments into R&D, including triple deduction — meaning expenses incurred by companies while carrying out R&D can be deducted from taxable income three times. Additionally, investments into substantial technology improvements can entitle companies to reduce taxable profits by 50%.

At the recent Life Sciences Baltics event, panelist Karolina Karl, head of the Life Sciences team at Invest Lithuania, pointed out that the government is "hungry and eager to make sure companies that invest are successful." Life sciences is high on the political agenda, and this brings advantage for companies in the sector.

"The government ensures that all decisions companies require are fast, and that all companies have [the] opportunity to get the most benefits the country can offer," said Karl.

Attracting multinational investments

Several prominent multinational pharma companies are already taking advantage of the financial benefits and have a well-established presence in Lithuania. Two of the biggest and most successful life sciences companies currently in the country began as Lithuanian companies — and then were acquired by large multinationals.

Among them is the country's largest pharma manufacturer, Teva Baltics. Israeli giant Teva Pharmaceutical Industries acquired the Lithuanian company, Sicor Biotech, in 2006 forming Teva Baltics. Since setting up in Lithuania, the company has continued to expand operational capabilities, investing more than $80 million, building new labs and installing new manufacturing lines. A number of new technologies have since been developed in Lithuania including Teva's biosimilar to Amgen's blockbuster cancer drug, Neupogen, which won FDA approval in 2012.

Another well-known multinational name in the country is Thermo Fisher Scientific. The U.S. company came to Lithuania in 2010, after acquiring Lithuanian biotech company Fermentas. Now, the Thermo Fisher Scientific Baltics site, located in Vilnius, boasts world-class capabilities in manufacturing molecular, protein, and cellular biology products, and has one of the largest private R&D centers in the Baltic region. Back in January the company announced plans to open a new production building in Vilnius — a project that has already been completed — in order to produce more reagents for developers of vaccines and therapy products, including COVID-19 vaccines.

Last year, the country's new recruit, Biogen, established a subsidiary in Lithuania — the first part of what the U.S. biotech calls a "long-term commitment" to Lithuania. Biogen has said the company plans to carry out clinical trials and develop innovative medicines with Lithuanian partners.

Karl attributes Lithuania's attractiveness to international companies to the country's business-friendly environment and good quality-to-cost ratio.

"Lithuania is constantly improving and adjusting the business environment to grant companies business opportunities, which allows them to maximize their investments," said Karl.

of all Lithuanian life sciences production is exported to more than 100 countries.

—Enterprise Lithuania

Building a dream team

Two key strengths that are enabling Lithuania to continue to come out on top as a life sciences and biotech destination are the country's talent and infrastructure.

The labor force in Lithuania is often described as young, skilled and enthusiastic. The country, with a population of just 2.8 million (roughly that of Chicago), boasts 15,000 scientists working on life sciences projects. Close to 600 life sciences companies call Lithuania home, employing over 7,500 people.

And the country is looking to keep growing this number through its educational infrastructure. There are six universities and seven colleges offering studies in life sciences fields. In 2016, Vilnius University, located in the country's capital, opened a state-of-the-art Life Sciences Centre. The Centre offers education and training in life sciences, together with advanced research in biochemistry and related fields, providing world-class facilities for around 1,000 students. Enterprise Lithuania estimates that 23% of the country's students are enrolled in programs related to life sciences.

This large talent pool combined with the solid life sciences infrastructure has contributed to a thriving startup scene, says Kleponė.

"Talented people can do a lot in a good infrastructure and make the discoveries that attract the attention of investors," says Kleponė.

Investments in Lithuanian life sciences startups have been increasing. According to Invest Lithuania, there are currently more than 1,000 startups in Lithuania, and more than 60 of them are in life sciences.

The capital city of Vilnius in particular has been a hot spot for startups, driven by fintech companies. But life sciences isn't far behind. Recently, Vilnius University's Life Sciences Centre partnered with the Vilnius City Innovation Industrial Park, which has been operational since August 2018, to launch a specialized life sciences incubator in the park. The goal is to create an enabling environment for young, promising companies developing projects in the life sciences and related fields.

The incubator will be equipped with a GLP-compliant molecular biotechnology laboratory complex, specialized for work with microorganisms, viruses and bacteria, and a complex and open access center focused on bioinformatics, a subdiscipline of biology and computer science focused on DNA and amino acid sequences.

As Lithuania pushes to grow its life sciences ecosystem, efforts like these that enable R&D and foster collaboration between innovative startups and mature investors will be key.

Already successful, yet still eager, the life sciences community in Lithuania has access to both support and resources — and that opens the door to a lot of opportunity for growth.

"The community plays a huge role — the network is tight and all the decisions are fast," said Karl.

Clifford Rossi, Ph.D.
Professor-of-the-Practice and Executive-in-Residence,
Robert H. Smith School of Business, University of Maryland

Continuous versus batch: Weighing the choices

New research compares the financial risks and rewards of investing in each manufacturing path

Continuous manufacturing has generated buzz in the pharma industry for years. Some large pharmaceutical manufacturers have even piloted continuous manufacturing (CM) under the U.S. Food and Drug Administration's Emerging Technology Program (ETP).

But beyond the small number of companies testing the waters on CM, the industry has yet to fully embrace this advanced technology as a replacement for the tried-and-true decades-old batch processing of pharmaceutical products. Aside from the regulatory risks of implementing and validating a new process in a pharma facilities, companies may also be squeamish about making large investments in technologies that have yet to prove their worth across the industry. CM sounds good in theory — but is it really the best bet for a company's bottom line?

This year, I spearheaded a research effort at the University of Maryland's Robert H. Smith School of Business to answer that question. Using a simulation-type of analysis comparing the net present value (NPV) of investing in CM versus batch technology in the U.S. or abroad, the study gathered hard data to determine whether or not CM provides more economic benefits over batch for oral solid dose (OSD) products made in new facilities.

The conclusion? CM appears to win handily over batch processing in the U.S. and even provides an economic advantage over batch processing abroad. This analysis suggests that domestic manufacturing may well be worth a closer look, and the use of advanced manufacturing technologies such as CM could pave the way to reshaping pharmaceutical supply chains and reducing product shortages and recalls.

What's at stake

Factors at play in determining whether to manufacture pharmaceutical products in the U.S. or abroad include corporate taxes, differential labor and manufacturing costs, regulatory and environmental costs, and foreign exchange hedging expenses. Differential costs of production have been widely referenced as a primary reason for the loss of U.S. manufacturing over the last several decades.

The ascendancy of China as a major manufacturing hub over the years was accomplished in large measure by much lower labor, land and capital costs as well as more relaxed environmental regulations than in the U.S. Recent studies, however, indicate that wage and cost pressures over time have reduced the China cost advantage to a slim 4% lower cost of manufacturing compared to the U.S.[1]

Deciding whether to adopt a new technology comes with a number of financial and nonfinancial considerations, tradeoffs and uncertainties. And any switch to a new technology comes with both cost and regulatory uncertainty.

Batch processing has a well-established track record in the industry, which reduces both capital and operating cost uncertainty in any investment analysis. Although CM technology has been in place for decades in other industries such as commodity chemicals and food processing, there has been limited experience with it in the pharma industry. As a result, significant uncertainty over the all-in lifetime costs of this technology for specific applications, products and manufacturing scale remains.

Batch vs CM in theory

The use of advanced manufacturing technologies could help reduce regulatory risk for pharma companies. Under a standard batch manufacturing process, hold times, additional touch points and off-line testing before moving to the next step can extend overall processing time, and this can adversely affect intermediate substances such as powder segregation or lead to increased risk of contamination.

Conversely, a CM process is more automated and thus less susceptible to these potential batch processing issues. Pharmaceutical products already in place using batch manufacturing processes would require regulatory validation by the company if they were to replace the batch process with a new process such as CM. While regulatory uncertainties may be a factor that reduces interest in developing CM capabilities, the FDA has signaled its strong interest and support to industry in adopting advanced manufacturing technologies.

One of the touted advantages of CM over batch processing is a more seamless and efficient processing of inputs and materials that can reduce manual touchpoints during production runs as well as reduce processing time, upfront investment costs due to smaller facility and land requirements, and operating costs over time. There is also the potential for greater flexibility to adjust batch size as well.

How the study was designed

To assess the economics of investing in a new batch versus CM OSD manufacturing facility in the U.S. or abroad, I conducted a simulation of the net present value over a 20-year investment horizon of batch and CM technology options for brand- and generic-focused companies. Engineering cost estimates from a seminal cost study comparing batch and CM technology used in producing 2,000 tons of tablets per year were used in the analysis along with other actual industry information on revenues and non-manufacturing costs.

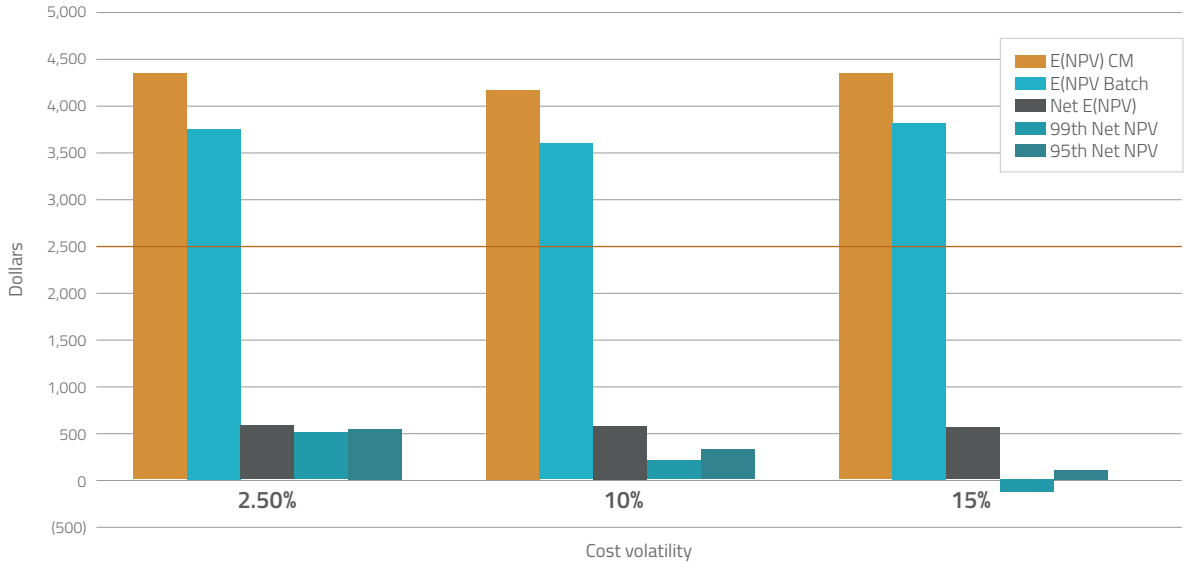
The significance of this analysis is that it represents the first comprehensive investment study of pharmaceutical industry manufacturing investment choices in the U.S. and abroad as well as between current and CM technology.

In order to capture the uncertainty of costs related to CM, several scenarios were included that applied different cost factors to the CM capital and operating cost estimates used in the study. In addition, differences in brand and generic company revenues reflected actual industry historical data where brand companies in aggregate show higher and more stable profit margins compared to generic companies. Further, over the 20-year project time horizon, it was assumed based on other studies that the loss of exclusivity for brand drugs ended at year 12. Other considerations in the analysis included differences in country manufacturing productivity and corporate tax rates, and hedging costs for foreign-made products.

EXHIBIT 1

U.S. site technology NPV comparisons by cost volatility (generic companies)

For all CM cost volatility scenarios, CM maintains a positive net E(NPV) over batch processing technology.



Let your voice be heard about CM guidelines

Long-awaited ICH continuous manufacturing guidance is available for public comment

The International Council for Harmonization (ICH) Q13 draft guidance on continuous manufacturing describes scientific and regulatory considerations for the development, implementation, operation and life cycle management of continuous manufacturing in pharma operations.

Building on existing ICH Quality guidelines, this document provides clarification on CM concepts and describes scientific approaches and regulatory considerations specific to CM of drug substances and drug products.

Draft guidance is available for comment on the FDA website.

Submit comments by Dec. 13, 2021

The study investigated several investment strategies for brand and generic companies:

- One strategy was whether investing in CM produced higher NPV than batch processing in the U.S.
- A second strategy examined whether investing in batch processing facilities in the U.S. generated higher NPVs than investing in batch processing facilities in China, India or Ireland.
- Lastly, a set of scenarios were generated to compare investment in CM-based U.S. facilities to batch processing operations in those other countries.

A total of 156 different combinations of country, company type (i.e., brand or generic), costs and profit margin volatility assumptions were examined.

Rather than rely on a single NPV result for each of these scenarios, 10,000 different NPVs were simulated to permit evaluation of a wide range of investment outcomes.

What the analysis found

An investment in CM pays off: When looking at investments in either CM or batch for a new U.S. facility, the results showed that the lower costs of CM led to higher NPV for both brand and generic companies over investing in batch technology — even when taking into account the greater cost uncertainty of CM.

For brand and generic companies, the incremental contribution of CM over batch to the project's lifetime expected net present value ranges between $490-$560 million, and $550-$590 million, respectively, assuming the current corporate tax rates of 21%.

The tax environment affects domestic manufacturing: Under current U.S. tax rates, investing in batch or CM in the U.S. resulted in higher NPVs than investing in batch in China or India. For example, for brand companies investing in U.S.-based CM facilities, the additional NPV benefit over investing in batch technology in China ranges between $780-$990 million. In the case of Ireland, however, their significantly lower corporate tax rate of 12.5% contributed to a higher after-tax NPV of investment in batch facilities over batch or CM facilities in the U.S.

Further, when U.S. tax rates were raised to 28%, investing in U.S. batch facilities was no longer viable compared to investing in batch facilities in China and it reduced the attractiveness of investing in U.S. CM-based facilities compared to batch processing in China or India.

The bottom line

While the results strongly suggest that investment in U.S. manufacturing of OSD is financially viable, the industry has mostly been reluctant to make investments in CM.

Several factors explain the industry's limited investment in advanced manufacturing in the U.S.: cost and regulatory uncertainty associated with new technologies and deeply entrenched supply chains are high on the list. The pandemic underscored the tenuous nature of global supply chains and the dependency of pharma on this complex system. While reconfiguring supply chains will take time and expense, the financial viability of domestic manufacturing leveraging CM technology may make this an important strategic initiative for pharmaceutical manufacturing going forward.

This project was supported by the FDA and HHS as part of a financial assistance award [U01FD005946] totaling $285,000 with 100% funded by FDA/HHS. The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by FDA/HHS, or the U.S. government.

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MedPharm

Professor Marc Brown
Co-Founder & Chair of Scientific Committee

Dr. Jon Lenn
Chief Scientific Officer

Dr. Jon Volmer
Senior Director, Research Biology and Innovations

Assessing the nasal drug delivery landscape

New high-throughput screening models provide clinically reproducible and translatable results

Intranasal delivery is an exciting target for drug delivery as it allows for both systemic and topical drug absorption due to its large surface area, extensive blood vessels and the possibility of direct access to the central nervous system (CNS).

However, any promising treatments can only advance as fast as the models that are used to evaluate them. Here, the latest advancement in the modeling of intranasal delivery — the reconstituted nasal epithelium (RNE) model — is summarized along with the long-standing traditional techniques that have helped pharma companies de-risk and expedite the delivery of intranasal drugs.

An intro to the nose

Delivery into the nose is relatively painless, the onset of drug action can be rapid, and formulations can be administered in emergency situations, such as with Narcan intranasal spray for opioid overdose.

A major contributor to the potential of the nose as a drug delivery route is the structure of the epithelial surfaces, which can be divided into several general regions. The largest of these is the nasal cavity, which has a convoluted surface to slow incoming air and promote particulate deposition on the nasal mucosa. It consists of three rigid shell-like protrusions known as turbinates. These bony structures have a high density of blood vessels to provide warmth and moisture, which serves to condition the air for optimal gas exchange. As such, the nasal cavity makes an excellent target for drug delivery because droplets from sprays or particulates from powders, which encounter the turbinates, adhere to the mucosal surface and thereby gain access to the vasculature.

One limitation is the protective layer of mucus on the epithelium and ciliated epithelial cells, which can rapidly capture and sweep drugs to the oropharynx where they are cleared by swallowing. To avoid this, formulations need to be designed to allow for optimum drug release and absorption.

Another target for drug delivery within the nose is the olfactory mucosa, a specialized region situated above the nasal cavity. The olfactory neurons and supporting sustentacular cells in this region provide direct access to the CNS, bypassing the blood-brain barrier and making it possible to deliver a drug within seconds. The mechanism by which this happens is still a subject of differing opinion but is likely to involve drug transport through the paracellular space between olfactory axons, or via the conduit-like lamina propria in which they are bundled.[1]

Traditional intranasal screening models

Numerous models have been developed for testing intranasal formulations. Among the earliest of these were differentiation of airway epithelium in air-liquid interface (ALI) cultures, which first appeared in literature in the early 1980s.[2] However, such models have historically been highly complex and difficult to reproduce, and reliable sources of primary cells are hard to obtain.

Another traditionally successful screening technique involves excised nasal animal mucosa (e.g. sheep) mounted in a static diffusion cell. In this model, formulations are applied to the apical side of the tissue, and receptor solution is sampled from the basolateral side to assess the performance of the formulation.

Such models have assisted in the development of nasal drug formulations for decades. However, although the passive barriers such as basement membrane and matrix binding remain intact, the active components such as tight junctions, mucus production, cilia and other cellular activities do not, and thus, these models do not provide a true representation of nasal drug absorption.

Improvements to traditional models

To build on these models, a reconstituted nasal epithelial model has been developed.

In this model, nasal epithelial cells are harvested from a donor using a nasal swab and suspended in a gentle proteolytic media bath. The epithelial cells are then isolated from resident immune cells and fibroblasts. Subsequently, they are

seeded onto porous membranes and expanded in monolayer culture using a proprietary epithelial growth media. Over the course of about a week, the cells expand and become fully confluent, beginning the differentiation process. At this point, the proprietary media is changed, and the apical surface is kept dry to promote full differentiation, which occurs over the span of three or four further weeks. Over this time, the epithelial cells adopt a pseudostratified columnar compound epithelial layer. These cells exhibit mucus production, ciliary activity and tight junctions, and this architecture typically persists for approximately four weeks.

An important aspect in determining the success of this model is the development of tight junctions present in the nasal cavity, which form an electrochemical barrier between the basolateral and apical chambers. Thus, the existence of these tight junctions can be determined from trans-epithelial electrical resistance (TEER), a measurement of resistance across a cellular layer. TEER can be measured immediately prior to administering a formulation to the RNE model, to ensure that only intact and well-differentiated constructs are used in analysis.

Current studies suggest that tight junctions can develop to a stable state over about three weeks while differentiation media is present (Exhibit 1).

Testing an RNE model

Several clinical studies have compared intranasal to IV administration of oxycodone and buprenorphine.[3] To determine if the same qualitative trends translate from such studies to the RNE model, researchers prepared buprenorphine and oxycodone formulations that closely mimicked the formulations used in these clinical studies.

Clinically, the oxycodone formulation was reported to have a several-fold higher maximum active pharmaceutical ingredient (API) concentration (Cmax) than the buprenorphine formulation. It was also found that the RNE model produced similar results to the clinical studies, with only minor differences in the magnitude of differentiation (Exhibit 2).

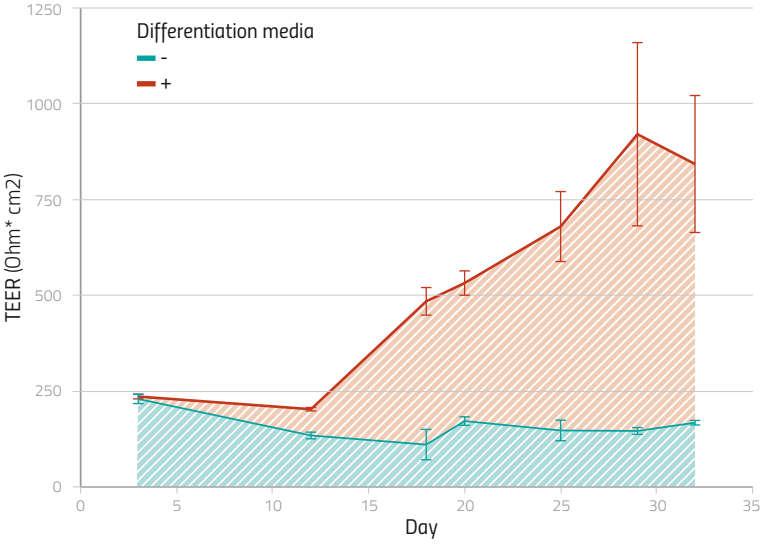
To further determine formulation discrimination in the RNE model, dose-response for the oxycodone formulation was evaluated. Four concentrations of oxycodone formulation were prepared and administered apically to RNE constructs (n=5). At designated intervals, basolateral media was sampled and replenished to constant volume. At each time point, the total cumulative amount of API was calculated. The total cumulative amount at all time points past two minutes showed a linear response to formulation concentration (R2 > 0.90) and thus a dose-response for the oxycodone formulations was observed.

It is always desirable to develop the next, more useful model to advance drug discovery and formulation.

Taking the RNE model forward

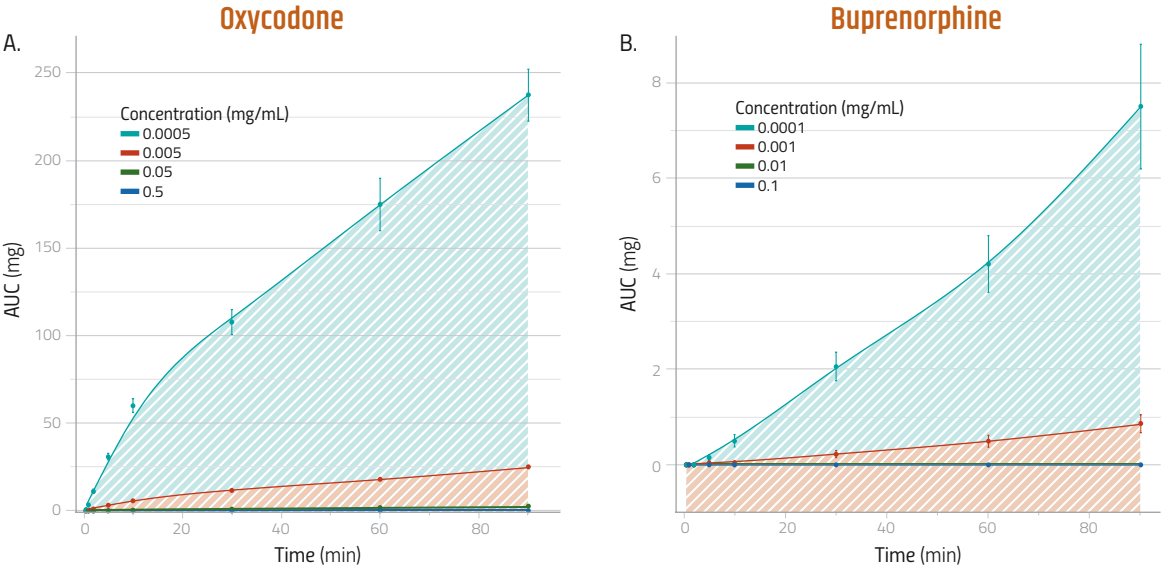
It is always desirable to develop the next, more useful model to advance drug discovery and formulation development. The development of an RNE model has increased the range and potential of available models for testing intranasal

EXHIBIT 1



Primary human nasal epithelial cells were seeded onto a permeable membrane suspended in media. The cells were allowed to grow until confluent (approximately 10 days), at which point they were switched to an air-liquid interface and provided with differentiation or growth media. The figure shows transepithelial/transendothelial electrical resistance plotted vs time for cells treated with growth media (light blue) or differentiation media (red). Error bars are standard error of the mean (SEM), n=5.

EXHIBIT 2



10 µL of Oxycodone (A) or Buprenorphine (B) in saline solution was applied to the apical side of well-differentiated RNE cells. At the indicated times, the basolateral media was collected and replaced it with an equal volume of fresh, pre-warmed media. Total permeated quantity at each timepoint (AUC) was calculated and plotted vs time. Error bars are standard error of the mean (SEM), n=5.

formulations. In addition to more closely resembling the nasal mucosal barrier than traditional animal tissue models, RNE cultures allow for additional analyses that are not possible using ex vivo tissue.

These additional analyses include modeling; the impact of the mucosal epithelium, which contain influx/efflux pumps that transport drugs through the cell layer; the effects of metabolic enzymes on drug permeation; the impact of tight junctions; and the type and quantity of nasal mucus. The model can also be used to monitor the direct effects of drugs targeting nasal epithelium, as well as local toxicity or irritation.

In addition, the RNE model can be adapted for bronchial epithelium, allowing for the testing of a host of new formulation types, such as those for the treatment of asthma, COPD, bronchiectasis and cystic fibrosis. In the case of cystic fibrosis (and other genetic diseases), epithelial constructs can be grown from cells collected from the affected patient population during routine medical care.

Another application of RNE models is co-culturing RNE and other airway epithelium. One example is co-culturing RNE with inflammatory cells in invasion assays to compare the performance of anti-inflammatory and antibiotic drugs. Reconstructed airway tissue can also be co-cultured with airway smooth muscle to compare the efficacy of drugs treating airway hyperresponsiveness in asthma. Due to the long-term viability of such RNE constructs, they can also be used to model the effects of irritants, such as smoke, diesel exhaust particles and other environmental particulate, and the recovery of the airways from injury.

Finally, RNE models can be used to monitor nasal infection. The COVID-19 pandemic has highlighted the importance of good models of infection and pathology, and the role of the nasal epithelium in infection and viral propagation. Models of coronavirus infection in the nasal epithelium using reconstituted nasal epithelium have also been developed.

Modeling infection in RNE bypasses many well-known shortcomings of cell lines (such as HBE4 and A549), as well-differentiated primary cells more closely mimic in vitro physiology, cell signaling and architecture. Although RNE models don't eliminate artificial selection due to conditions in the host cell (such as protease and receptor expression), they reduce this effect.

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Khanh Ngo Courtney, Ph.D.
Senior Director of Biologics, Avomeen

Leave no CMC stone unturned

Building a CMC strategy for biologics is a critical, multistep process

The journey begins when a new biologic entity shows promise in the lab. From there, a pharmaceutical company must seek permission to continue its investigation of the drug's therapeutic potential in humans. At this critical stage, the company must navigate a complex regulatory landscape which includes filing an Investigational New Drug Application (IND) and subsequent Biologic License Application (BLA).

Each application will include a chemistry, manufacturing and controls (CMC) section to ensure drug products are consistently effective, safe and high quality for consumers when they are manufactured. To maximize the chances of gaining regulatory approval, companies must provide CMC plans and meticulously collected data that align with U.S. Food and Drug Administration (FDA) expectations.

Developing a CMC strategy

A CMC strategy is an approach to providing the FDA with scientific data characterizing the therapeutic molecule, its stability and formulation, the manufacturing process, and how the manufacturer is planning to ensure consistency and control of the product throughout the product life cycle. The tricky part about a CMC strategy is the fact that it may not be a straight path to market, especially if the biologic is granted FDA fast-track designation. These strategies would consist of pursuing multiple paths to get to market as soon as possible, while still ensuring a controlled product. The CMC strategies to produce a chemical or biologic should be established early on and used throughout the drug development process to provide continuity between clinical trial results and commercial use.

The manufacturer communicates the CMC strategy to the FDA by providing a robust CMC package that outlines a biomanufacturer's process for testing, scaling and optimizing a biologic; it must be efficient, reliable and consistent, and it must meet regulatory expectations to lay the groundwork for commercial production. It should describe core characteristics about the biologic including its ingredients and their purpose, its molecular, chemical and physical characteristics — particularly stability — as well as evidence that the biologic produces the intended biological effect.

A CMC strategy must provide evidence of a detailed manufacturing plan to produce the biologic, as well as anticipated administration methods. Additionally, the CMC strategy must provide a robust and reliable testing protocol for conducting quality control and safety assessments, such as forced degradation and stability testing. Finally, the strategy must describe the facilities where the biologic and all other relevant components will be manufactured, including how they are designed, maintained and operated as well as their qualifications to ensure high-quality production.

A complex process, accelerated

The development process for biologics is often granted fast track designation after IND application approval, meaning that later processes, such as the compilation of data for the BLA application, may proceed on shorter timelines (Table 1). The FDA grants fast track designation to drugs and biologics that meet an unmet need to treat a serious condition. The designation expedites the development process by rendering the pharmaceutical company eligible for priority review and accelerated approval of documents. It also entitles the company to more communication with the FDA to discuss the biologic's development, ensuring all necessary data are being collected to support approval, and to further discuss clinical trial design.

When a biologic has been granted fast track designation, its accompanying regulatory applications are eligible to be assessed under the rolling review policy, by which a company may submit portions of its BLA to the FDA as they are produced, rather than having to assemble a complete application to submit.

The fast track designation is a great boon to the development of a new biologic because it enables manufacturers to bring products that address substantial, unmet medical needs to market as fast as possible. At the same time, there is not much leeway when it comes to developing a robust CMC strategy that ensures the safety and efficacy of a biologic on such a tight schedule. Therefore, manufacturers should initiate the development of a CMC strategy as early in development as possible, in addition to meeting their other expedited timelines, to get a head start on conducting CMC for their novel biologic.

Because assembling a complete CMC package is an incredibly time- and labor-intensive process,

an additional strategy that pharmaceutical companies use to hit the ground running is to pre-design broad CMC strategies that are applicable to multiple product pipelines. These pre-designed strategies function as a starting point, but because every drug is different, each must be tailored to the mode of delivery (e.g., inhalant, injectable, controlled release, solid dose, topical, oral) and the platform technology of any new drug. Biologics, having been designed for personalized medicine approaches or to target a rare disease, tend to be more functionally and molecularly diverse than other kinds of drugs on the spectrum. So, while the system of starting with a pre-designed template does speed the process up, CMC strategies for biologics still require significant revision.

Building a case

While meticulously collecting data to go into a CMC package, a manufacturer must carefully consider how each piece of information meets FDA expectations and builds a cohesive case for the biologic it is developing. The CMC strategy must provide scientific evidence and irrefutable rationale to support the design of the workflow that outlines how each step will eliminate risk during manufacturing and will maximize the production of a high-quality product. Then, during development, manufacturers should reflect on instances when production of the biologic is being put to practice to identify risks in the process and predict potential pitfalls — and this should also be detailed in the CMC strategy.

In short, to produce an exemplary CMC strategy, no stone may go unturned. Therefore, manufacturers should take every opportunity to work with the FDA to ensure that they are building a body of data that provides the necessary level of detail to illustrate that a biologic molecule and its indication are scientifically understood and that its formulation and manufacturing are optimized. Companies should not underestimate the complexity of the process and should strive to be thorough, particularly when identifying potential sources of risk. By doing so, they can then optimize product development by systematically removing sources of risk from underlying processes, and only decide to take risks that can be justified by sound scientific reasoning. Otherwise, taking shortcuts

TABLE 1

CMC processes (BLA)	Description
Formulation	Develop a target product profile to formulate a safe and effective biologic candidate
Method development and validation	Test defined characteristics of the components of the biologic against standard criteria
Stability testing	Evaluate the quality of a biologic over time and in response to environmental factors such as humidity, temperature and light exposure, and identify degradants
Raw material release testing	Evaluate each raw material's identity, purity and quality prior to use
Extractables and leachables (E&L) studies	Identify and quantify harmful impurities derived from manufacturing, packaging and storage
Elemental impurity analysis	Reduce the risk of contamination and test for contaminants, impurities and residuals in products
Finished product batch release testing	Assess each batch of a compound and finished product to confirm if it matches its registered safety and efficacy specifications
Compendial testing	Evaluate if raw materials and finished protocols meet standardized specifications, such as in the US Pharmacopoeia-National Formulary, the European Pharmacopoeia, the Japanese Parmacopoeia or the British Pharmacopoeia
Reference standard characterization and management	Development, characterization and management of reference standards
Cleaning validation support	Establish a plan to clean lines before manufacturing a product of a different formulation; validate the cleaning process, parameters and limits

Taking shortcuts may lead to expensive and nonproductive studies or leave critical gaps in the CMC strategy.

may lead to expensive and nonproductive studies or leave critical gaps in the CMC strategy.

Manufacturers should anticipate feedback from the FDA and build additional time into their development schedules to respond and provide revisions. In some cases, revisions requested will be extensive; however, the company must do all additional work that is required to satisfy the FDA's expectations. Failing to do so risks reducing the quality of the biologic and therefore its eligibility to reach the market. If at any point the FDA finds that a company is not meeting its expectations surrounding CMC, it may fine the company, pause production or even withdraw the market authorization of the biologic.

Consistency is key

Manufacturers do not just have to compile an extensive and detailed body of data. To the best of their ability, they must ensure that manufacturing processes and product specifications will remain consistent over time. This can be particularly challenging when operating under the expedited timeline of fast track designation. In these cases, it is not uncommon during development to find that the process underlying production is ill-defined, the molecule or disease pathways are not fully understood, or the formulation requires improvement — any of which may trigger the FDA to halt product development in its tracks. Therefore, developing an FDA-compliant CMC strategy is critical to reducing the risks involved with biologic product development.

To ensure that the final CMC strategy is optimized, manufacturers should begin thinking about CMC during target development, and continue to hone the strategy during preclinical formulation and clinical research. Pragmatic companies will consider several CMC strategies in parallel and evaluate these based on several parameters: A CMC strategy should maximize the safety and efficacy of a biologic while at the same time ensuring availability to patients and satisfying regulatory requirements; it should be practical to carry out based on the manufacturer's needs. By performing continuous improvement of the plan, and adapting the strategy should new information emerge during development, companies will streamline the process of establishing the optimal strategy for their biologic and can circumvent unexpected roadblocks that would otherwise derail development and commercial release onto the market.

Streamlining CMC with a CDMO

While large pharma companies have abundant in-house resources and experience to plan, optimize and implement a CMC strategy, smaller biopharma companies with fewer resources may face challenges in this arena. For instance, larger companies have infrastructure set up to test their biomolecules, refine their manufacturing protocols and validate their methods. Smaller biopharma companies do not have these capabilities on hand.

Increasingly, smaller companies are carrying out a larger proportion of early drug development activities. Because they do not have sufficient resources or experience to craft a CMC strategy, they will often partner with a CDMO to advise them. As a manufacturer takes a biologic candidate into the Current Good Manufacturing Practice (cGMP) and CMC phases of development, a CDMO's advice can be instrumental in streamlining the process.

A CDMO partner will make its resources and experience available to a biopharma company as it is preparing to submit its new biologic for review. The regulatory, quality and technical expertise that CDMOs can offer, as well as the consulting services, can be key to the preparation of an optimal CMC strategy. Furthermore, a CDMO can offer a wealth of scientific knowledge to justify all elements of the CMC plan. Because an experienced CDMO knows the many different approaches that manufacturers take to CMC design and how the FDA responds to those strategies, they are well-equipped to guide manufacturers through the application process.

Enlisting the help of a CDMO can also be a good option for small companies who would like help managing the cost of CMC development. Cost can become prohibitive if companies try to undergo CMC without cost controls. On the other hand, a CDMO can work within a CMC budget and anticipate how the various steps and decisions will affect it throughout product development.

In sum, CMC is a segment of all INDs and BLAs that is critical if a biologic is to reach the market. Developing a satisfactory CMC strategy is a massive, expensive undertaking. Large companies might feel that they have resources and expertise to manage the CMC design independently, but small companies may appreciate drawing on the experience and resources of a CDMO, particularly if they are developing their first product.

Either way, companies need to develop a comprehensive, reliable CMC strategy to achieve regulatory and commercial success and finally bring a new treatment to patients with few other options.

James Klingelhoefer
Director of Sales, Americas, Peli BioThermal

Solving the packaging puzzle

Evolving considerations when choosing between single-use or reusable temperature-controlled packaging

When it comes to manufacturing health-giving and life-saving pharmaceutical products, the No. 1 goal is to protect valuable payloads. The right thermal packaging solution is critical to maintain the efficacy of temperature-sensitive vaccines, biologics, blood supplies, tissues and more. But choosing the right temperature-controlled packaging is more complex than payload size and temperature requirements. The ever-changing nature of the supply chain plays an important role.

Over the past two years, COVID-19 and its impacts on transportation significantly disrupted supply chains. Companies were forced to reassess nearly everything, including their cold chain logistics. One area of focus: choosing between single-use packaging or reusable temperature-controlled packaging.

Based on best practices and today's economic environment, here are the criteria companies should consider when deciding which type of packaging is best.

Performance

Historically, single-use thermal packaging was made with extruded polystyrene (EPS) or polyurethane (PUR) insulation and gel pack heat sinks that provided temperature control for shorter durations and decreased payload space. Pharma companies with high-value products and long shipping durations would choose reusable packaging for its ability to maintain temperature control and for volumetric efficiency.

But today's single-use packaging now includes phase change material (PCM) and vacuum insulated panels (VIPs) like reusable systems, so there is less of a performance difference between the two types of packaging.

Companies that do evaluate packaging based on performance typically look at durability and the ability to monitor temperatures in transit. Reusable packaging is more sturdy and able to withstand rugged conditions. It also allows companies to use reusable data loggers or temperature recording devices with high-value products or on challenging shipping lanes. Some companies also select reusable packaging for longer shipping durations, though some single-use shippers can provide comparable performance.

Questions to consider:

- Is your payload fragile or high-value?
- Is it important to use a temperature monitoring device or data logger?
- Are any of your shipping lanes challenging with a significant risk for temperature excursions?
- Does the company you're working with have quality processes for refurbishment and conditioning of

reusable packaging? Do they follow Good Manufacturing Practices and have necessary certifications?

Cost

The hypercompetitive and unforgiving biopharma landscape demands that organizations achieve consistency and control without eating into margins. Increasing cost pressures lead organizations to take a closer look at defining total cost in their logistics and supply chain operations.

At the most basic level, pharma companies compare the price of single-use shippers and the per-use cost of a reusable shipper. However, other factors impact total cost. For single-use shippers, companies must consider real estate required to store inventory. This cost could also include housing, running and maintaining conditioning equipment, as well as staff and training expenses.

One large biopharma company customer was experiencing extensive labor in conditioning and assembly of single-use solutions, which resulted in limited payload performance protection from excursions. The company used active systems for longer international lanes and emerging markets, and the rental costs had a significant financial impact on product and distribution budgets.

The customer switched to a reusable pallet-accepting shipper to eliminate onsite conditioning and assembly labor, which provided significant cost savings. The most notable key performance indicators were an increase in warehouse real estate by eliminating dedicated space for conditioning or warehousing of components, and reduction in labor times for assembly and pack out.

Cold chain companies recently began offering pre-conditioning and just-in-time packaging for reusable temperature-controlled packaging. Although not available from all cold chain packaging companies, some

The hypercompetitive and unforgiving biopharma landscape demands that organizations achieve consistency and control.

now also offer the same service for single-use packaging to help pharma companies conserve valuable real estate and eliminate barriers to picking the right packaging option for their business. Additionally, these services set the stage for pharma companies to fully outsource their cold chain operations — a growing trend in the pharma industry.

Another factor to consider for reusable packaging is the cost to buy versus pay-per-use. Buying shares similar advantages and disadvantages to single-use shippers, specifically inventory storage, staffing and training. Pay-per-use can alleviate all three of these requirements by allowing companies to fully outsource their cold chain operations.

When using reusable shippers, reverse logistics is also critical. There are costs associated with returning a shipper, and inventory not returned is money lost on the unreturned product and an additional cost to purchase a new shipper.

Questions to consider:

- How frequently do you ship products that require a similar size shipper?
- What is the cost of a single-use shipper vs. the per-use cost of a reusable shipper? How many trips would it take to make a reusable shipper cost less per trip?
- What is the cost of reverse logistics for your shipping lanes? Are your receiving locations set up to return shippers?
- Do you have warehouse space to store owned reusable packages? Do you have trained staff dedicated to cold chain logistics?

Transport

In today's economic environment, transportation has a more pronounced impact on the decision about which type of temperature-controlled packaging to use. In early October 2021, a record number of container ships were sitting off the West Coast of the United States waiting to dock. Each ship carries thousands of containers — space that is currently unavailable for moving other products around the world.

In the early days of the COVID-19 pandemic, pharma companies began switching from reusable to single-use packaging out of sanitization concerns. Now many companies use single-use packaging as a risk-mitigation strategy. While companies ship high-value pharmaceutical products by air freight, reusable packaging often returns by less costly sea freight internationally and ground freight domestically. Today that process could take months, leaving companies without reusable inventory when they need it most.

Additionally, the backup of shipping containers and lack of truck drivers means demand for shipping space is higher than supply, causing an increase in shipping costs. Although reverse logistics is slightly easier domestically, moving packaging internationally is challenging and expensive.

Outside of the pandemic, shipping lanes can impact the decision on which type of thermal packaging to use. Some countries have onerous import and export requirements or customs challenges that impact reverse logistics. This is particularly true for some countries in the Middle East and Latin America. Single-use packaging could also make sense when the frequency of shipments to a location is low.

Questions to consider:

- Are current shipping challenges impacting your ability to receive shipments?
- Does the current cost of shipping change the per-use cost of a reusable shipper? How does that compare to the cost of a single-use shipper?
- Are the countries you ship to set up to accommodate reverse logistics?
- How frequently do you ship to the same location?
- Does your cold chain company have service centers in locations near your departure and destination locations?

Sustainability

According to the Peli BioThermal 2020 Biopharma Cold Chain Logistics Sustainability Survey, the biopharma industry is increasing its pace to prioritize sustainability in business and operational strategies. Nearly half of all respondents say that they always factor sustainability into cold chain purchasing decisions, and 53% indicate that it is very important to choose cold chain packaging options that advance their organization's sustainability goals.

Recyclability and lower emissions matter to pharma companies. Greater focus is being put on how cold chain packaging is constructed, with increasingly high value placed on cold chain packaging that is recyclable or can more easily enter the waste stream. Likewise, the industry leans toward lighter, more energy efficient shippers that reduce carbon emissions for temperature-sensitive pharma products being shipped by air.

Traditionally, companies have used single-use thermal containers made with EPS or PUR insulation and gel pack heat sinks to ship temperature-sensitive pharmaceuticals. Over the course of a two-year clinical trial, companies would make an average of 30,000 individual package shipments and emit 1,122 tons of CO2e with this approach.

A two-year clinical trial using a reusable product in this example would require only 772 units and 241 tons of CO2e. This is a 78% difference in global warming potential between the single-use and reusable approaches.

Similar differences exist in other impact categories with the reusable approach including 56% less human

toxicity potential and 95% less post-consumer waste. The cradle-to-gate emissions of a single-use container is the overwhelming cause of its high environmental burden since it requires manufacturing and using more units. Additionally, the reusable container in this example is about half the weight of the average single-use container, which lowers its transportation impact below the single-use approach emissions despite an extra leg of travel needed to return reusable containers.[1]

The same biopharma company mentioned earlier also saw an impact on its sustainability goals by moving from single-use to reusable shippers. Consignees were no longer burdened with disposal challenges, and the elimination of waste in the landfill made a significant impact on the environment.

The environmental break-even point between the two logistical approaches occurs after as few as six shipments. This outcome suggests that a reusable approach is environmentally preferable for any organization that utilizes large shipping volumes that require thermal control.

Questions to consider:

- What are your sustainability goals?
- What impact do your cold chain operations have on these goals?
- Do you ship a high volume of temperature-sensitive products?
- Do your end users have set sustainability goals or expectations for their suppliers?
- Does your cold chain company use recyclable materials and have stated sustainability goals?

Choosing the right thermal packaging is not a one-size-fits-all approach. Both single-use and reusable packaging are necessary — the real goal is to have the right tool in the toolbelt at the right time.

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Kate Coleman
Senior Director/Principal Consultant, Pharmalex

Optimizing the facility design phase

Early planning will ensure pharma facilities meet requirements

Participation in a project team embarking on the design and construction of a new pharma facility is both challenging and rewarding in equal measure. There are endless opportunities for innovation, learning and improvement but at the same time, a balance between innovation, cost and compliance must be maintained — and this often leads to challenging cross-functional discussions and tough decisions.

The design phase for a new facility is critical as it's the only opportunity for all stakeholders and end users to significantly influence the facility design and ensure it meets their requirements for optimum process layout in addition to including the critical design elements required for efficiency, contamination control and containment.

Build a diverse team

The SME group involved in the facility design should be cross-functional. In addition to architects and engineers, the team should include end users such as operations and quality personnel who can represent the requirements of their functions but also maintain a pragmatic approach to project time and budget. The goal should be the delivery of a final facility design that meets the expectations of regulatory guidelines and incorporates features to fully support the manufacturing of safe, efficacious drugs. Also, the design should satisfy end-user requirements and provide appropriate conditions for facility personnel.

The EU regulatory guidelines presented in Eudralex, chapter 3, "Premises and Equipment," provide guidance on the general requirements for heating, ventilation, drains and other systems and features that are necessary for the provision of a controlled manufacturing environment that is suitable for medicinal product production. A 2015 revision included guidance relating to the application of appropriate facility design in the prevention of cross-contamination.

The FDA Code of Federal Regulations (CFR) Part 211 also outlines the minimum good manufacturing practices for building and facilities in subpart C. This section outlines requirements for design and construction features, lighting, ventilation, air filtration, air heating and cooling, plumbing, sewage and refuse, sanitization and maintenance. All of these must be considered during facility design if seeking FDA approval. Although the FDA doesn't include a requirement for a contamination control strategy as outlined in the EU guidance, the control of contamination is an inherent FDA requirement for multi-product facilities.

To get maximum benefit from the facility design process, the road map for design approval should be defined at the beginning of the process, providing structure to the review process and allowing time for cross-functional meetings where all stakeholders and end users can walk through the layout drawings and highlight areas of concern. The SME group must be given the opportunity to review, challenge and assess the design for usability and operability, as well as its ability to provide protection to the drugs being manufactured.

Keep quality in mind

From a quality perspective, specific emphasis should be placed on the proposed flow of people, equipment, materials, product and waste through the facility, providing a design that will minimize cross contamination and offer adequate product protection and the appropriate level of containment. Quality risk management is essential for providing a structured approach to facility design review as it provides a mechanism for documenting risks and actions identified during the review and provides justification, based on risk, for any changes required in the design.

Newer technologies such as building information modeling and virtual reality can be useful tools to communicate and display the facility design to help end users and stakeholders gain a better understanding of how the facility will look and feel post construction. These technologies can display the design in a more tangible way than traditional 2D drawings and although more costly to implement, may provide savings later in the process.

Collaborative approaches to pharma facility design provide the design team with an opportunity to receive cross-functional end-user feedback, and identify cross-contamination risks and design weaknesses before construction has even started. This way, changes that will enhance operability, usability and compliance can be made when the cost of change is much lower.

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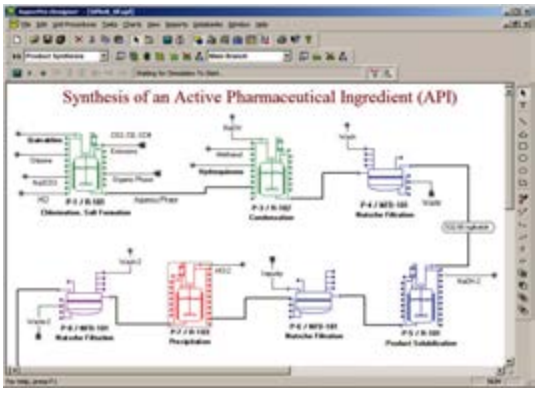

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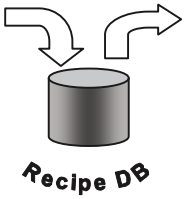

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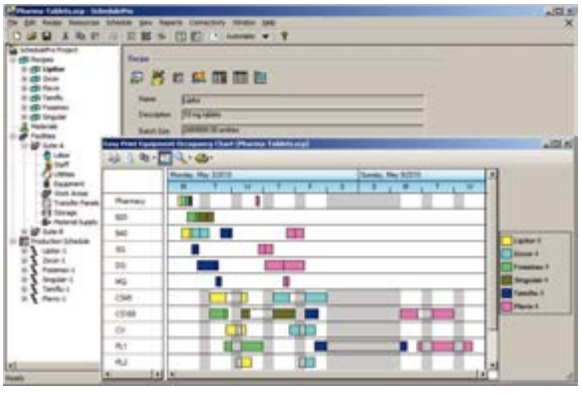

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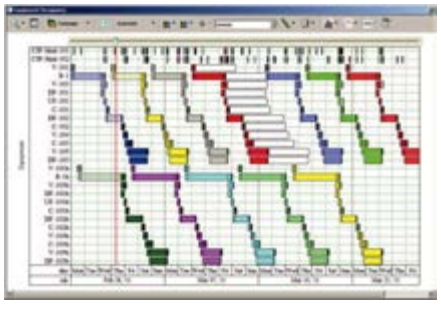
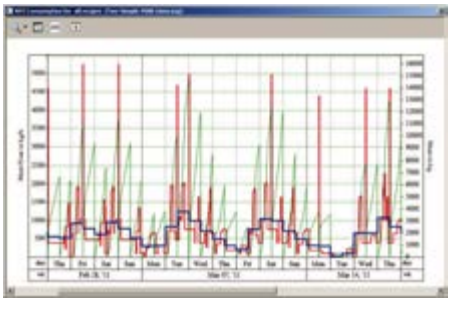
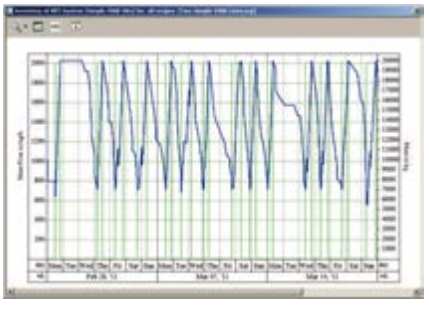


Easy production tracking, conflict resolution and rescheduling



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



Managing inventories for input, intermediate, and output materials

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

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Tel: (908) 654-0088 • Fax: (908) 654-3866
Email: info@intelligen.com • Website: www.intelligen.com
Intelligen also has offices in Europe and representatives in countries around the world

United States Postal Service Statement of Ownership, Management, and Circulation
(Requester Publications Only)

1. Publication Title: **Pharmaceutical Manufacturing**
2. Publication Number: **023-188**
3. Filing Date: **10/1/21**
4. Issue Frequency: **Monthly** (excluding Jan. & Aug.)
5. Number of Issues Published Annually: **10**
6. Annual Subscription Price: **$68.00**
7. Complete Mailing Address of Known Office of Publication (Not printer) (Street, city, county, state, and ZIP +4®):
Putman Media, Inc., 1501 E. Woodfield Road, Suite 400N, Schaumburg IL 60173-6053;
Contact person: **Kim Leonard,** Telephone: **(319) 861-5011**
8. Complete Mailing Address of Headquarters or General Business Office of Publisher (Not printer):
Putman Media, Inc., 1501 E. Woodfield Road, Suite 400N, Schaumburg IL 60173-6053
9. Full Name and Complete Mailing Address of Publisher, Editor, and Managing Editor (Do not leave blank) Publisher (Name and complete mailing address): **Brian Marz, 1501 E. Woodfield Road, Suite 400N, Schaumburg IL 60173-6053**; Editor (Name and complete mailing address): **Karen Langhauser, 1501 E. Woodfield Road, Suite 400N, Schaumburg IL 60173-6053**; Managing Editor: **Meagan Parrish, 1501 E. Woodfield Road, Suite 400N, Schaumburg IL 60173-6053**
10. Owner (Do not leave blank. If the publication is owned by a corporation, give the name and address of the corporation immediately followed by the names and addresses of all stockholders owning or holding 1 percent or more of the total amount of stock. If not owned by a corporation, give the names and addresses of the individual owners. If owned by a partnership or other unincorporated firm, give its name and address as well as those of each individual owner. If the publication is published by a nonprofit organization, give its name and address.)

Putman Media, Inc.	**1501 E. Woodfield Road, Suite 400N, Schaumburg IL 60173-6053**
John M. Cappelletti	**1501 E. Woodfield Road, Suite 400N, Schaumburg IL 60173-6053**
Jenny G. Cappelletti	**1501 E. Woodfield Road, Suite 400N, Schaumburg IL 60173-6053**
Nicholas G. Cappelletti	**1501 E. Woodfield Road, Suite 400N, Schaumburg IL 60173-6053**
Melody L. Cappelletti	**1501 E. Woodfield Road, Suite 400N, Schaumburg IL 60173-6053**

11. Known Bondholders, Mortgagees, and Other Security Holders Owning or Holding 1 Percent or More of Total Amount of Bonds, Mortgagees, or Other Securities. If none, check box ☒ **None**
12. Tax Status (For completion by nonprofit organizations authorized to mail at nonprofit rates((Check one)
The purpose, function, and nonprofit status of this organization and the exempt status for federal income tax purposes: ☒ **Has Not Changed During Preceding 12 Months**
13. Publication Title: **Pharmaceutical Manufacturing**
14. Issue Date for Circulation Data Below: **September 2021**

15. Extent and Nature of Circulation:			No.copies 12 months	No.copies single issue
a.	Total number of copies (net press run)		**20,915**	**21,200**
b.	Legitimate paid and/or requested distribution	1. Outside-county paid/requested mail subscriptions stated on PS form 3541.	**12,668**	**12,678**
		2. In-county paid/requested subscriptions stated on PS form 3541		
		3. Sales through dealers and carriers, street vendors, counter sales, and other paid/requested distribution outside USPS®		
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c.	Total paid and/or requested circulation		**12,668**	**12,678**
d.	Non-Requested Distribution	1. Outside-county non-requested copies stated on PS form 3541	**7,771**	**7,771**
		2. In-county non-requested copies stated on PS form 3541		
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f.	Total distribution		**20,439**	**20,699**
g.	Copies not distributed		**476**	**501**
h.	Total		**20,915**	**21,200**
i.	Percent paid and/or requested circulation		**62%**	**61%**

16. Electronic copy circulation		No.copies 12 months	No.copies single issue
a.	Requested and paid electronic copies	**5,019**	**5,020**
b.	Total requested and paid print copies (line 15c) +requested/paid electronic copies (line 16a)	**17,687**	**17,698**
c.	Total requested copy distribution (line 15f) +requested/paid electronic copies (line 16a)	**25,457**	**25,719**
d.	Percent paid and/or requested circulation (both print & electronic copies) (16b divided by 16c i 100)	**69.5%**	**68.8%**
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17. Publication of Statement of Ownership for a Requester Publication is required and will be printed in the **November 2021** issue of this publication.
18. Signature and Title of Editor, Publisher, Business Manager, or Owner
Brian Marz, Publisher, Date: **09/29/2021**

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Chris Eccles
Chief Executive Officer, Chargepoint Technology

Adapting to Brexit

Exploring the impact of Brexit on UK pharma industry supply chains

Since leaving the European Union on Jan. 1, 2021, UK companies across every sector have been preparing for the profound changes the exit will bring, on top of those brought by the global pandemic.

But what has this meant for the pharmaceutical industry so far?

While the UK is no longer subject to regulation by the EU's European Medicines Agency (EMA), the Medicines and Healthcare products Regulatory Agency (MHRA) — the UK's regulator — remains aligned with the EMA for the time being in a number of areas, including the list of approved drug products. This means that UK pharma companies can continue to supply medicines to the EU and vice versa without significant cost or loss of market access. How long this alignment will continue remains to be seen.

Preemptive measures

While the current alignment supports continued trade of finished medicines, there is now new friction at the UK-EU border that companies on both sides of the Channel have to contend with. This is particularly the case when sourcing raw ingredients and commodities, such as primary packaging and single-use (SU) production line components. Many pharma companies and their suppliers put measures in place well in advance of Brexit to mitigate against this issue. These steps included:

- The onshoring of production of APIs, raw materials and commodities, such as packaging and line components.
- The diversification of supply chains to reduce reliance on European and UK-only suppliers, as around 80% of pharma's raw materials are sourced from the UK or EU.
- The stockpiling of raw ingredients, primary packaging and SU components in order to mitigate against the impact of the new friction at the UK-EU border on established just-in-time (JIT) supply chains.

These preparations stood pharma companies and their suppliers on both sides of the new border in good stead to mitigate against the disruption experienced by companies in other sectors when the new trading rules came into force in January 2021. For example, many suppliers based in the UK now hold six weeks of inventory on-site, especially when sourcing from overseas. Not only are suppliers of APIs and intermediates holding stores of raw ingredients, but manufacturers of split butterfly valves and other SU equipment are stockpiling materials to produce their finished components as well.

Many line equipment suppliers are also working with EU customers to build their own on-site inventories of manufactured SU components. This can ensure they too have adequate access to vital parts when they need it, without the risk of supplies being delayed at the border.

Supply chain adaptations

In the future, we can expect these preparations by both suppliers and their customers to become an established feature of the UK and EU pharmaceutical landscape. We can expect more companies to nurture supply chains composed of a mix of local and international suppliers — ensuring that they are less reliant on partners in specific countries to mitigate against future shortages and adapting their supply chains away from pre-Brexit JIT approaches.

> It is likely that buffers such as the stockpiling of material and finished commodities, as well as supply chain onshoring, will continue.

It is likely that buffers such as the stockpiling of material and finished commodities, as well as supply chain onshoring, will continue. Research has found that up to $31.5 billion worth of trade could be onshored over the coming 12 months as firms continue to mitigate against new border frictions.

We can also expect suppliers to boost collaboration with pharma companies to help them continue to build stockpiles of essential ingredients, packaging and SU components to further mitigate against the impact of the friction on established supply chains.

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