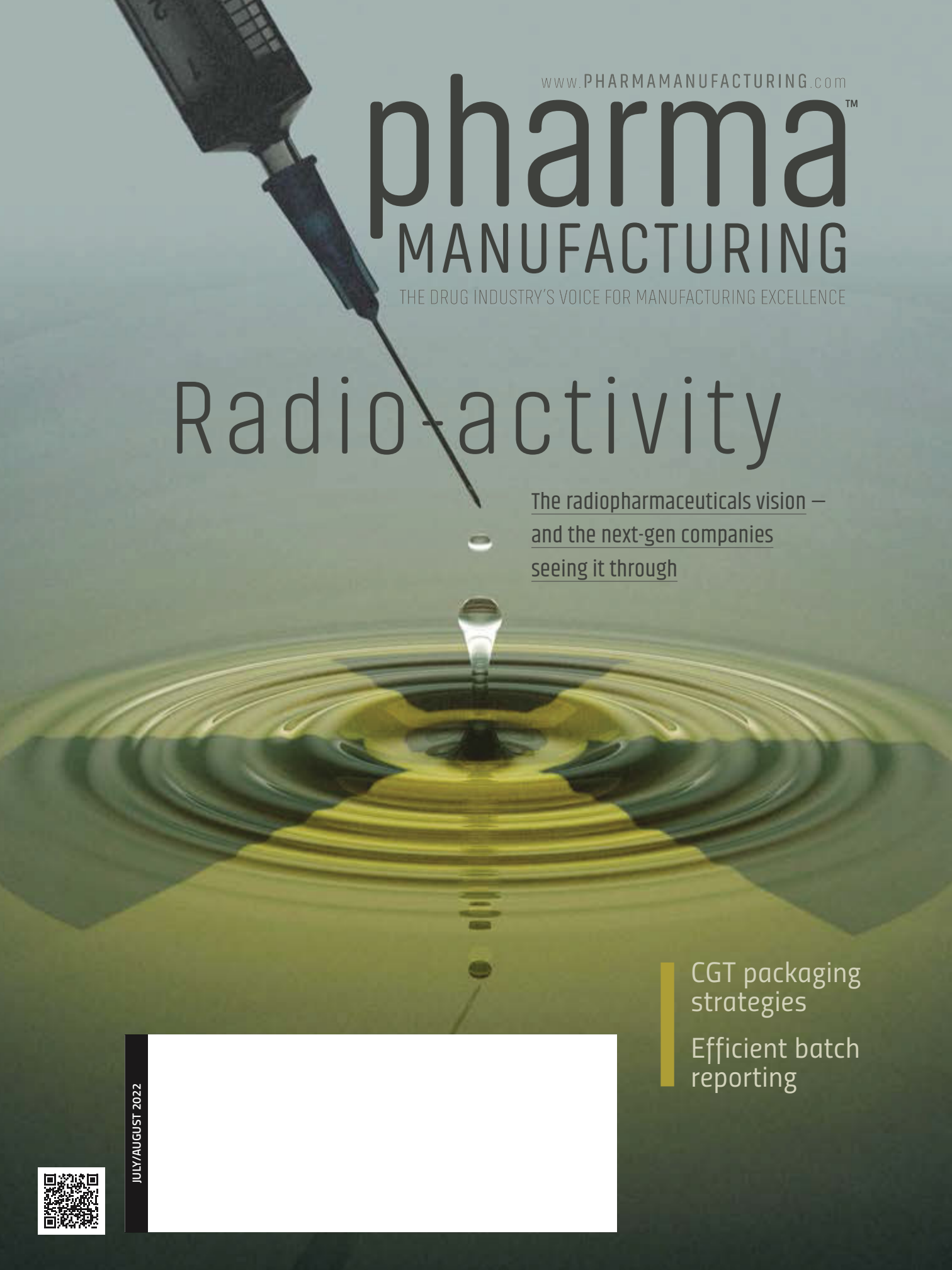

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Karen Langhauser
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The radiopharmaceuticals vision — and the next-gen companies seeing it through page 10

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Karen Langhauser
Chief Content Director

Filling in the gaps

Grit and experience give a promising sector teeth

One of the worst dental decisions I ever made involved brushing my teeth with an electric toothbrush and activated charcoal powder…in my white bathroom.

Dentistry fads are always tempting. From oil pulling to teeth whitening strips, even the savviest among us has fallen prey in our quest for a radiant smile. But there was a time in history when that desire was taken a little too literally.

If you were shopping for radioactive toothpaste in the 1920s, you had not one but two options. A German company was producing Doramad, a toothpaste with thorium as the active ingredient. Meanwhile, if combo radiation products were more your thing, a Paris-based radioactive cosmetics line called Tho-Radia was also offering toothpaste.

This all started in the late 19th century/early 20th century, when radioactivity and X-rays were discovered in parallel. Science was captivated by these new technologies, and it wasn't long before both found widespread application in medicine.

X-ray machines were put to use during World War I, to find embedded bullets and diagnose broken bones, and also used as a surface therapy for skin diseases. Science quickly recognized radium's potential in oncology through early experiments against various cancers of the throat, breast and skin.

But the outpouring of enthusiasm for these new 'medical miracles' — radium in particular — quickly leaked out of the mouth of the scientific community and dribbled down the chin of high society.

In addition to radium toothpaste, there were food products containing radium, including chocolate bars, water and bread. Some lucky consumers owned the bedside 'Revigator,' a ceramic water crock lined with uranium and radium. For the truly fearless, there were radium suppositories and even the 'Radiendocrinator'— a radium-coated card worn inside the underwear at night to treat impotence.

In the early 1920s, a NJ dentist began noticing an abundance of dental problems in young factory workers and rightfully became suspicious when a woman's jawbone broke off in his hand. The dentist discovered that his patients had all worked for the U.S. Radium Corp., painting watch dials with the company's 'Undark' luminous paint and licking their brushes to keep the bristles aligned.

By 1927, more than 50 of these now-famed 'radium girls' had died as a result of radium paint poisoning, as did the inventor of Undark paint. In 1932, a well-known amateur golfer died horrifically after becoming obsessed with drinking radium water, followed by the inventor of the Radiendocrinator, who died from bladder cancer. Radiation tragedy wasn't limited to those drinking the radiation flavored Kool-Aid, either — a staggering amount of scientists and their assistants also suffered the ills of radiation.

Undeterred, science continued to pursue the use of radiation in medical care, slowly filling in the large gaps in understanding.

As you will read in this month's cover story, when the first two antibody-directed radiotherapies — Zevalin and Bexxar — won FDA approval, it seemed like targeted radiation had finally cut its teeth in therapeutics. But the drugs failed on the market, leaving pharma manufacturers with a bitter taste in their mouths when it came to radiopharmaceuticals.

But today's pharma industry has finally worked through the aches of radiopharma past. Armed with a better understanding of manufacturing and logistics, the sector is filled with activity. As these experience-stacked companies bear down, we may soon see pharma's next crowning achievement in cancer care.

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Andrea Corona
Senior Editor

FDA decisions to watch

Four new drugs we could see in 2022

The second half of 2022 is gearing up to be a busy time for the U.S. FDA. With PDUFA dates and highly-anticipated regulatory filings looming in the near future, new drugs with blockbuster potential might not be far from market.

1. Bristol Myers Squibb's next-gen autoimmune drug

Psoriasis is a chronic, immune disorder that affects at least 100 million people around the world each year. Offering a new option for patients living with the illness, Bristol Myers Squibb's deucravacitinib works by selectively targeting TK2 and inhibiting the signaling of cytokines that play a role in pathogenesis of a range of immune diseases.

The potential first-in-class TYK2 inhibitor is currently in trials against indications in psoriasis, psoriatic arthritis, inflammatory bowel disease and a common type of lupus. Recently, BMS reported positive data from its POETYK PSO trial — which evaluated the drug in comparison to a placebo and Amgen's Otezla — sharing that after a year, 58.7% of patients reported having clear or almost clear skin.

When the company announced the FDA's acceptance of their New Drug Application last year, BMS' senior vice president of Immunology, Jonathan Sadeh, touted the drug as a potential game-changer. "Findings from the pivotal POETYK-PSO trials demonstrate the potential of deucravacitinib to elevate the oral standard of care for individuals who are candidates for systemic therapy," said Sadeh.

If approved on its PDUFA date of September 10, the drug would enter the market with only Otzelta as a competitor. BMS estimated that deucravacitinib has the potential to reach $4 billion sales if approved for multiple inflammatory disease indications. BMS is also expecting EMA approval later this year.

If approved, deucravacitinib would become the first tyrosine kinase 2 inhibitor approved for the treatment of any disease.

2. Mirati's lung cancer drug

This past February, Mirati Therapeutics announced that the FDA had accepted its NDA for adagrasib, its drug candidate meant to treat patients with non-small cell lung cancer (NSCLC).

Adagrasib works by sustaining target inhibition, an attribute that could help treat cancers with KRAS mutation, as the protein regenerates every 24-28 hours. It's being evaluated by itself and in combination with other cancer therapies for patients with not only KRAS G12C mutated solid tumors, but colorectal and pancreatic cancer as well.

Recently, Mirati reported that the disease control rate was 100% across a subset of 27 patients participating in the phase 2 KRYSTAL-1 study, which included patients suffering from gastrointestinal cancers.

Adagrasib is also being reviewed under the FDA's Real-Time Oncology Review pilot program, which helps streamline revolutionizing treatments to get them to patients as early as possible.

If approved on its PDUFA date of December 14, potential sales could reach $1.7 billion by 2026, giving adagrasib blockbuster status.

3. bluebird bio's rare disease gene therapy

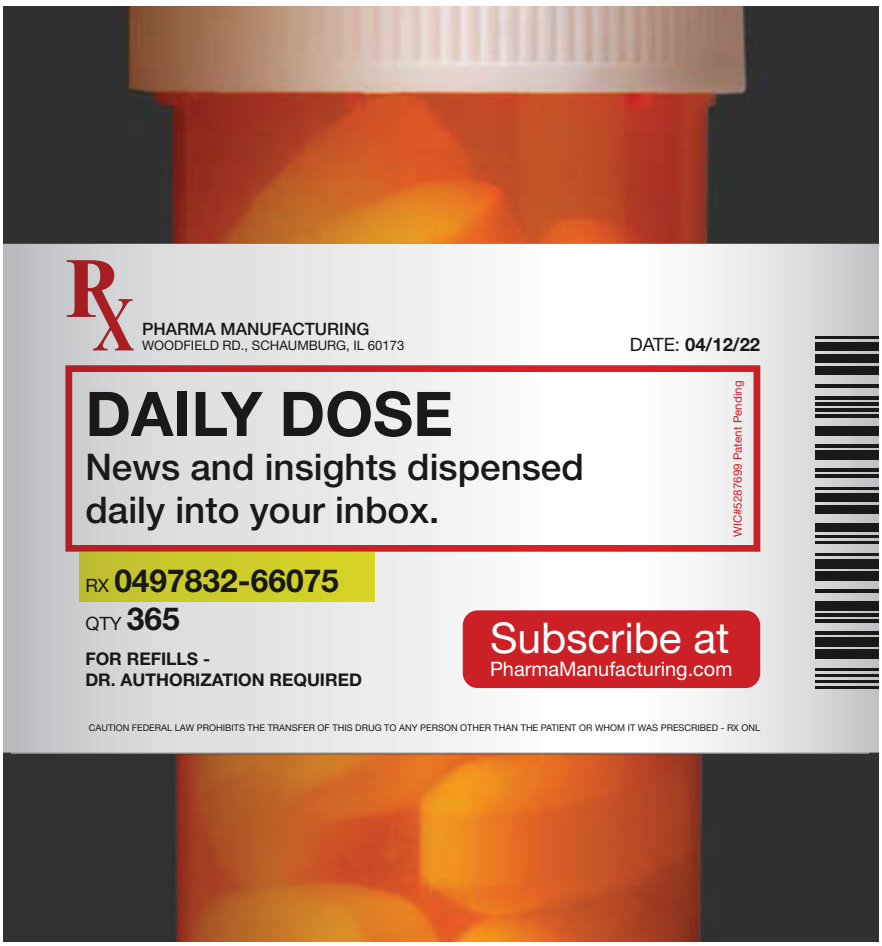
If approved, bluebird bio's beti-cel has the potential to not only be the first one-time gene therapy treatment for people with beta-thalassemia, but also the first ex vivo lentiviral vector gene therapy offered in the U.S.

Beta-thalassemia is a rare genetic blood disease caused by mutations in the beta-globin gene which can result in significantly reduced or absent adult hemoglobin production. Patients living with the most severe form often rely on blood transfusions for the duration of their lives, a process they have to undergo every 2-5 weeks.

Beti-cel is designed to add functional copies of a modified form of the B-globin gene into the patients' hematopoietic stem cells. But the promise made by cell and gene therapies is complicated to keep.

"Gene therapies are complex, potentially transformative treatment options for those living with severe genetic diseases," said Andrew Obenshain, CEO of bluebird, back in January when the company announced that the FDA had extended beti-cel's review period.

With the PDUFA date approaching on August 19, the company announced workforce reductions and general restructuring to prioritize investments towards near-terms wins, including the approval of beti-cel and a therapy targeting cerebral adrenoleukodystrophy.



4. Roche's Alzheimer's disease treatment

Alzheimer's drugs run the risk of not living up to their hype, with Aduhelm being the perfect example.

Roche's gantenerumab, however, has garnered positive momentum after being put on the shelf for a few years. The company brought its phase 3 study back in 2018, with the hope that giving patients a higher dose would yield different results.

The drug is an IgG1 antibody developed to bind to aggregated forms of beta-amyloid and remove the plaques, which are believed to cause the neurodegenerative effects on the brain that characterize Alzheimer's disease. Given as a subcutaneous injection, the drug has proven to lower amyloid plaque presence.

The number of Alzheimer's cases is expected to rise to 78 million worldwide by the end of this decade. It's the most common form of dementia, and effective treatments are scarce.

Gantenerumab received FDA Breakthrough Therapy designation in October 2021.

"This Breakthrough Therapy designation reinforces our confidence in gantenerumab, which would be the first subcutaneous medicine for the treatment of Alzheimer's disease with the potential for at-home administration," said Levi Garraway, Roche's chief medical officer and Global Product Development head.

Gantenerumab is currently being investigated in eight clinical trials, including a phase 3 secondary prevention trial in participants at risk for or at the earliest stages of Alzheimer's, and two phase 3 studies investigating gantenerumab versus placebo in participants who have early Alzheimer's over 27 months. The latter two trials are nearing conclusion, which would allow Roche to seek FDA approval.

Gantenerumab is believed to have the potential to reach blockbuster status, with Evaluate Vantage estimating sales of $2.5 billion by 2026.

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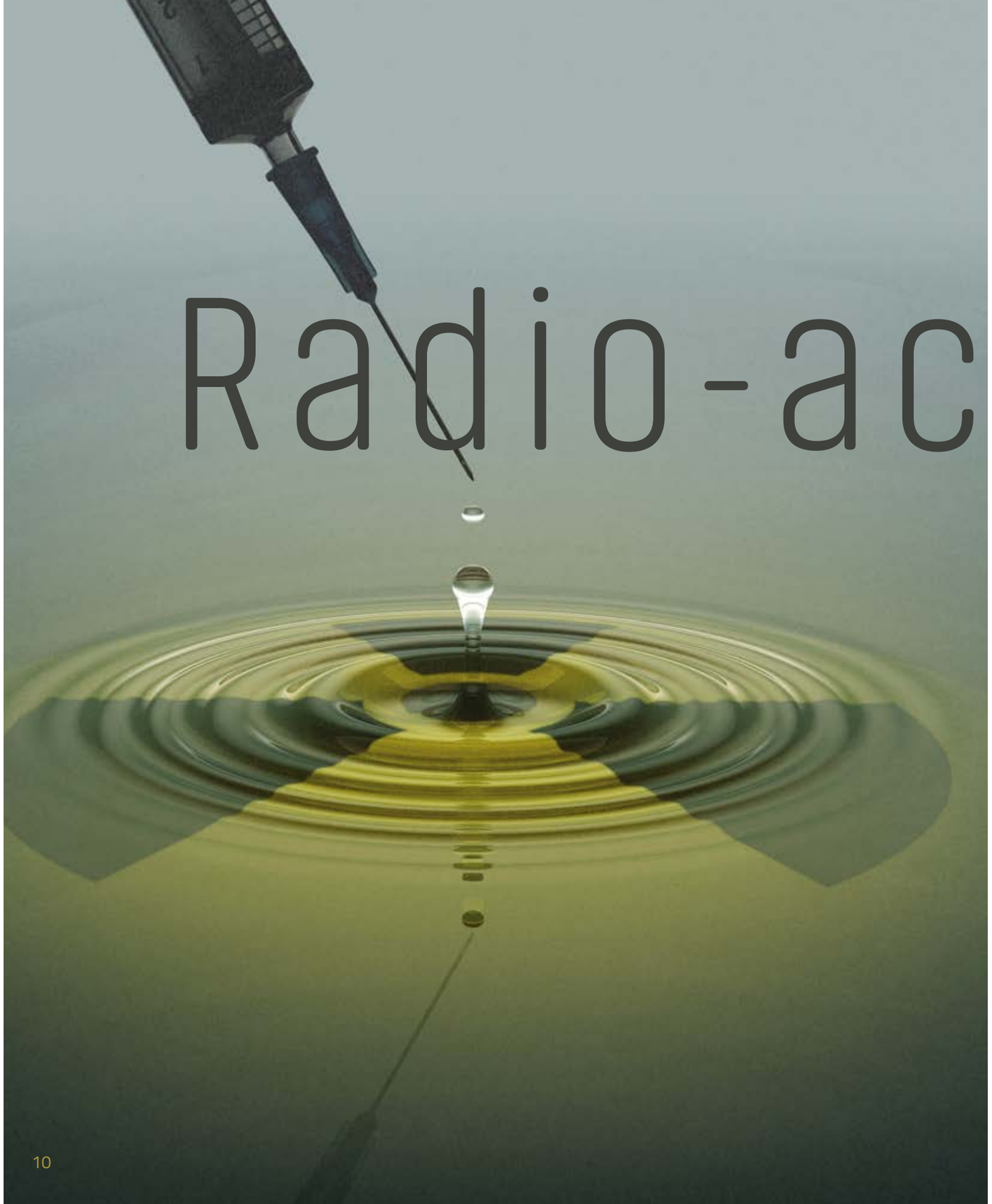


Radio-activity

Karen Langhauser
Chief Content Director

The radiopharmaceuticals vision — and the next-gen companies seeing it through

For 125 years, the phenomena of radioactivity has captured the attention of the scientific community, illuminating a seemingly endless world of medical possibility.

Spurred by the discovery and subsequent widespread X-ray experimentation craze in the late 19th century, famous names in science, including Henri Becquerel and Pierre and Marie Curie, ushered in an era of radioactive exploration.

Shortly after the Curie duo isolated and named radium, science recognized its potential in cancer treatment. Once the radium floodgates opened, it was difficult to contain the outpouring of enthusiasm for the new 'medical miracle' and radium was examined as treatment for everything from diabetes to pneumonia to impotence.

But a ride on the radium bandwagon came with a steep ticket price. While scientists were quick to realize the medical benefits, they were slower to comprehend radiation's serious and sometimes fatal effects. Both Curies endured radiation sickness, and Marie's death from aplastic anemia was attributed to radiation exposure. Becquerel died suddenly of 'unknown causes' not long after his discovery of radioactivity, with severe radiation burns on his skin.

Yet the half-life of science's love for radioactivity proved robust, and rather than abandon the dream, the world found safer ways to source, handle and utilize radiation.

In the early '90s, drug developers were busy pursuing the promise of precision medicine through monoclonal antibodies. At this point, radiopharmaceuticals were mostly relegated to imaging and diagnostic tools, but a handful of drug developers began exploring a niche area of cancer treatment by linking mAbs to radioisotopes — using the mAb to deliver radiation treatment directly to cancer cells.

By 2003, the first two antibody-directed radiotherapies — IDEC Pharmaceuticals' Zevalin and Corixa Pharma's Bexxar — had won Food and Drug Administration approval. Although clinically effective against non-Hodgkin's lymphoma, the drugs struggled with regulatory delays, manufacturing issues and general infrastructure challenges. Corixa, laden with debt and unable

Radiopharmaceutical production line at the Evergreen Thergnostics facility in Springfield, New Jersey.

to recover from Bexxar's market flop, sold the company to GSK, who ultimately yanked Bexxar from the U.S. market.[1] Zevalin changed hands several times and after sales plummeted to just a few hundred patients per year, it was Spectrum Pharmaceuticals that pulled the plug.[2]

These early therapies became cautionary tales in a nascent radiopharmaceuticals space. While the learning curve for therapeutic radiopharmaceuticals was far less fatal than it was for radiation a century ago, it was no less treacherous. And yet, the allure of these treatments continued to burn bright in cancer care.

"When we entered this space in 2019, we understood the potential challenges of entering into the radiopharmaceutical ring, and yet we also were completely entranced by the promise of being able go into a brave new world of cancer treatment — and this commitment has been justified as the field is now massive with an explosion of interest," says Thomas Harding, executive vice president and chief scientific officer at Clovis Oncology.

With a market estimated to exceed $13 billion by 2030 and a space lit up with acquisitions, new company launches and clinical trials, therapeutic radiopharmaceuticals have gone mainstream.[3] And this new generation of radiopharmaceutical companies is stacked with experienced experts who are laser-focused on correcting the missteps and misfortunes of earlier pioneers.

Now, by tackling the uniquely complex development, manufacturing and supply chain concerns, players in the therapeutic radiopharmaceutical space are positioning themselves to revolutionize the future of oncology.

Going mainstream

Clovis Oncology's journey into radiopharmaceuticals started with 'the one that got away.'

The Colorado-based company was founded in 2009 with a focus on precision cancer treatment, initially through poly (ADP-ribose) polymerase (PARP) inhibitors. Five years ago, Clovis bid on an early-stage drug, PSMA-617, that, while being studied as a diagnostic tool for prostate cancer, had accumulated ample compassionate use data demonstrating its efficacy as a therapeutic.

"It was a diamond in the rough," recalls Harding. "Most traditional pharma companies had completely overlooked it. And that's probably because it lived in a unique space."

But a lot was about to change for PSMA-617 and for therapeutic radiopharmaceuticals in general.

Ultimately, it was Endocyte that put up the winning bid for the asset in October of 2017, obtaining the rights to develop and commercialize the injectable drug that targets diseased cells with the beta-emitting radioisotope, lutetium-177.

Most know how this story ends: A year later, Novartis inked a $2.1 billion deal to acquire Endocyte and the phase 3-ready therapy. The drug, now blockbuster-hopeful Pluvicto, was approved by the FDA to treat metastatic castration-resistant prostate cancer (mCRPC) this past March.

Clovis found its opening in radiopharmaceuticals a year later, entering into a collaboration with German biotech, 3B Pharmaceuticals. The deal gave Clovis the rights to an IND-ready fibroblast activation protein (FAP)-targeted radiopharmaceutical therapy, as well as a discovery program for additional targets.

"I think what you have witnessed in the last few years is companies bringing these kinds of drugs into more mainstream clinical development — and working through the rough edges," says Harding. "The field has gotten enormous and it's great to be at the front of this emerging wave of therapeutics."

Many market analysts point to the move Novartis made just prior to snatching up Pluvicto — a $3.9 billion deal to buy Advanced Accelerator Applications and its peptide receptor radionuclide therapy branded as Lutathera — as the watershed moment for modern therapeutic radiopharmaceuticals. When Lutathera was given the go-ahead by the FDA in 2018 for the treatment of neuroendocrine tumors affecting the pancreas or gastrointestinal tract, the approval highlighted the broad potential of radioisotopes to target solid tumors.

"Recent promising trial results reporting remarkable tumor shrinkage without significant side effects is leading to the beginning of a new major class of cancer treatments," says Renu Bala, senior analyst at Citeline. "The number of positive trials, added to the broader commercialization of radiopharmaceuticals, are providing a precedent for others to follow."

According to Bala, more radiopharmaceutical trials were initiated in 2021 (80) than ever before — a upward trend that has been consistent since the beginning of the last decade. As of March 2022, Citeline's Trialtrove database identified 1,104 trials that involve radiopharmaceutical-based treatments. According to the Pharmaprojects R&D database, the pharma industry has ~60 investigational radiopharmaceutical therapies in various stages of development.[4]

As these new drugs race towards commercialization, industry eyes are watching closely to see if modern radiopharmaceutical companies can work through the kinks of therapies past and advance what many are viewing as the next pillar in oncology.

Don't decay

While time is typically a factor in pharma manufacturing, speed becomes a non-negotiable need when working with radioactive substances.

In a quest for stability, atoms with an unstable nucleus shed excess energy in the form of radiation. This shedding process — radioactive decay — is measured in a time period known as half-life. A radioisotope's half-life is the time it takes one-half of its atoms to decay. While this time can range from less than a second to billions of years, most of the radioactive isotopes used in pharma have a half-life of just a few days. Two commonly used isotopes, lutetium-177 and actinium-225, have half-lives of 6.7 days and 9.92 days, respectively.

"They are like melting ice cubes — time is of the essence," says Kevin Staton, vice president, CDMO Project Management, Evergreen Theragnostics. "Once the isotopes are in hand, it's a well-defined quick series of processes that have to happen."

A New Jersey-based specialty CDMO, Evergreen opened the doors to its 14,000-square-foot facility this past fall, in anticipation of the

Recent FDA approvals

ZEVALIN, 2002

IDEC Pharmaceuticals

yttrium-90 ibritumomab tiuxetan
Non-Hodgkin's lymphoma

BEXXAR, 2003

Corixa Pharma *(now GSK)*

iodine-131 tositumomab
Non-Hodgkin's lymphoma

XOFIGO 2013

Bayer Pharmaceuticals

radium-223 dichloride
mCRPC

LUTATHERA, 2018

Novartis

lutetium-177 dotatate
Gastroenteropancreatic neuroendocrine tumors

AZEDRA, 2018

Progenics Pharmaceuticals
(now Lantheus Holdings)

Iobenguane iodine-131
Rare adrenal gland tumors

PLUVICTO, 2022

Novartis

lutetium-177 vipivotide tetraxetan
PSMA-positive mCRPC

pharma industry's expanding unmet need for these types of radio-friendly facilities.

While working on early-stage clinical projects at his previous position at Memorial Sloan Kettering, Staton had witnessed the industry's need for dedicated manufacturing facilities.

"While at MSK, we heard of numerous issues when companies we partnered with tried to work with radiopharma CDMOs after working with us. These issues spanned from technical limitation to a general unwillingness to adapt the process," says Staton. "Evergreen and other CDMOs in the space have gained experience since those days to help ease these types of issues."

A radiopharma manufacturing facility and its workflow must be designed to accommodate not just a rushed timetable, but also a host of other unique considerations that come with radioactive substances. Meeting all these expectations for Evergreen's cGMP-compliant facility was no small task, but Staton credits close collaboration between the design and engineering firm, contractors and the Evergreen team — all of which had radiopharma facility experience.

In addition to meeting the FDA's cGMP requirements, facilities that manufacture radioactive drugs or materials must be certified by the U.S. Nuclear Regulatory Commission (NRC). In most states, like New Jersey, NRC's authority is transferred to the state's department of environmental protection. In Staton's experience, this Radioactive Materials (RAM) license application process usually takes anywhere from 6 months to a year.

And the process is ongoing — after the initial site inspection, facilities can be audited, unannounced, at any time.

Facilities require specialized equipment — much of Evergreen's equipment is custom designed and shipped from a radiopharmaceutical equipment supplier in Italy. Isolator technology is utilized to prevent accidental contact, inhalation or ingestion. Most of the equipment is encased behind lead to minimize operator exposure, and the added weight makes it difficult to move and warrants a sturdy concrete support system underneath.

Most importantly, because both speed and safety are paramount, the relationship between spaces and equipment, as well as the flow and containment in the facility must be carefully considered from the start.

Locking down the supply chain

All these special considerations of course come at a cost — which means that for many drug developers, in-house manufacturing of radiopharmaceuticals is impractical from both a business and strategic standpoint.

"If you look at the cost of setting up your own manufacturing facility, I think there will always be aspects of the process that we will outsource," says Harding. "Because of the amount of complexity involved, our preference is to partner with CDMOs who have fully committed to the radiopharma space."

Clovis has outsourcing agreements with Evergreen as well as with Ontario-based Centre for Probe Development and Commercialization (CPDC) for its pipeline of targeted radionuclide therapies — both CDMOs specialize exclusively in radiopharmaceuticals.

Currently, the radiopharma CDMO market is somewhat fledgling, but new companies — like Evergreen — are beginning to pop up. When it comes to North American CDMOs who can handle end-to-end (pre-clinical through commercialization) radiopharmaceutical work, Staton estimates there are less than half a dozen options at present.

While the industry is currently not experiencing capacity restraints, for some companies, the potential future shortage of CDMOs in the space is a risk not worth taking.

Indianapolis-based POINT Biopharma was launched in 2019 with the mission of making lifesaving radiopharmaceutical treatments available to more patients by solving the historical challenges that blunted the success of earlier therapeutics.

As of March 2022, there were 21 ongoing or planned industry-sponsored phase 3 trials involving radiopharmaceutical-based treatments.

— Citeline Trialtrove database

The next-generation company is led by a management team packed with radiopharmaceutical veterans with firsthand experience of past supply chain constraints. POINT's strategy for success in radiopharmaceuticals involves internalizing as many steps in the supply chain as possible.

"Reliability is in our DNA," says Joe McCann, chief executive officer of POINT Biopharma. "POINT's platform was designed from inception with a focus of ensuring the reliable delivery of next-generation radiopharmaceuticals."

POINT, whose lead candidate is currently in phase 3 trials for metastatic castration-resistant prostate cancer, has its own 80,000-square-foot facility currently supplying doses for clinical trials and equipped to handle large commercial volumes when the time comes.

The volatile nature of radiopharmaceutical therapies means that a single glitch can send the entire supply chain into a tailspin — which can end with patients not getting the lifesaving treatments that were made-to-order for them specifically.

"Radioactivity is being lost by the second — a dose made on Tuesday may need to be injected on Wednesday — the process can't afford even the slightest delay," says Staton.

One needs to look no further than the recent Novartis shutdowns to illustrate that even pharma giants with their own in-house manufacturing are not impervious to the complexities of radiopharmaceuticals.

Back in May, Novartis suspended production of Lutathera as well as freshly-approved Pluvicto at two of its radioligand therapy production sites — one in Italy and one in New Jersey. For almost two months, the "potential quality issues identified in its manufacturing processes" stopped Novartis' deliveries in the U.S. and Canada as well as brought clinical trials to a screeching halt.[5] Novartis later announced the expansion of both facilities, as well as a plan to build a new radioligand manufacturing plant in Indiana that will be operational in 2023.

Both small and large companies in the space have realized that the single most important aspect in the supply chain is redundancy.

"You need to have your supply chain complexity completely locked down to do this properly. The name of the game is redundancy — you need systems in place in case anything fails," says Harding.

Sourcing the power

Medical isotopes, the source of radiopharmaceuticals' tumor-destroying power, are a vital piece of the supply chain.

In order to create these modern therapeutics — which McCann aptly describes as 'cancer-seeking missiles' — radioisotopes are linked to a cell-targeting molecule, such as a monoclonal antibody, small molecule or peptide. When injected into the body, the radioisotopes are delivered to the tumor, emitting high-energy particles that damage the tumor cells' DNA, killing the cells.

While there are thousands of known radioisotopes, not all of them are suited for therapeutics — and choosing the right isotope is key to the success of the radiopharmaceutical drug.

"Utilizing the best isotope for the job is a core philosophy at POINT," says McCann.

According to McCann, there is a narrow group of characteristics — referred to as 'goldilocks properties' — which makes a radioisotope valid for use in therapeutics. The isotopes must: be commercially available, have a medically useful half-life, have an emission type that is suitable for treatment, and demonstrate appropriate energy transfer — meaning the energy associated with particles being released from the nucleus will damage tumor cells.[6]

Drug developers are left with a short list of isotopes — about half a dozen — ideal for therapeutic use.

Lutetium-177 — which is a beta emitter, meaning it emits radiation in the form of negatively charged beta particles — currently has the lion's share of presence in clinical trials. Both of Novartis' approved drugs,

Market happenings

OCT. 2017 Novartis enters into a $3.9 billion deal to buy France-based Advanced Accelerator Applications, adding add Lutathera, a first-in-class radiopharmaeutical to its portfolio. The FDA approved Lutathera in Jan. 2018.

OCT. 2018 Novartis pays $2.1 billion to acquire Endocyte. The deal gave Novartis 177Lu-PSMA-617, which was approved as Pluvicto in March 2022.

SEPT. 2019 U.S-based POINT Biopharma is established, creating a precision oncology company focused on radiopharmaceutical drug development and commercialization.

OCT. 2020 U.S. radiopharma startup RayzeBio launches, with a pipeline of targeted therapies against validated oncology targets, and a focus on actinium-225.

NOV. 2020 Canada-based Fusion Pharma and AstraZeneca sign a deal to develop and commercialize alpha-emitting radiopharmaceuticals and combination therapies for cancer, giving AstraZeneca an entry point into radiopharmaceuticals.

JUNE 2021 Bayer acquires Noria Therapeutics and PSMA Therapeutics, giving Bayer rights to a alpha radionuclide therapy based on actinium-225 and a small molecule targeting PSMA.

SEPT. 2021 Australia-based Radiopharm Theranostics launches to develop a platform of radiopharmaceutical assets for both diagnostic and therapeutic uses.

SEPT. 2021 CDMO Evergreen Theragnostics opens the doors to its cGMP radiopharmaceutical manufacturing facility in Springfield, NJ.

OCT. 2021 Radionetics Oncology launches as a spinout of Crinetics Pharmaceuticals, with a focus on targeted, nonpeptide radiopharmaceuticals.

Lutathera and Pluvicto, also rely on lutetium. But lutetium isn't the only game in town — the therapeutic efficacy of actinium-225, an alpha-emitter, is attracting clinical attention as well.

These more modern isotopes are safer to work with and easier to deliver to patients, primarily because they emit lower levels of gamma radiation. During the process of natural radioactive decay, in addition to alpha and/or beta particles, some isotopes also emit gamma rays. Gamma radiation is the most penetrative type of energy currently known — and because it can pass right through the human body — arguably the most dangerous. To their detriment, early radioactivity pioneers, including Becquerel and the Curies, worked with high levels of gamma radiation with no protective measures in place.

Most radioisotopes used in therapeutics today are produced using neutron activation in nuclear reactors. Radioisotope suppliers source their isotopes from a few nuclear reactors around the world. According to the World Nuclear Association, most of these reactors are over 50 years old, which means there is an ongoing risk that they could break down and temporarily be taken offline.[7]

The growing popularity of certain isotopes combined with the limited number of nuclear reactors, as well as the ultra-rare input materials and complex purification processes needed to make radioisotopes, means that isotope supply has been and remains top of mind for those in the radiopharma space.

"The supply chain is different for each isotope. Currently, actinium-225 is in high demand but supply has not been able to keep up. A number of companies are working on expanding supply, but they are still 2-3 years away from making a substantial dent in this demand/supply gap," says Staton.

The medical isotope industry has sprung into action, and efforts are underway to develop more efficient production methods, as well as improved reactor and purification technology. New suppliers, such as Isogen — a Canadian joint venture between Framatome and Kinectrics — are launching to strengthen the supply.

"Everyone has realized this is a major limitation, so you have all these new isotope supply companies coming online to meet those demands," says Harding. "If you look at the projections, I think the industry will solve the lutetium and actinium supply issues within the next five years."

The radioisotope for GSK's Bexxar, iodine-131, came from Canadian supplier, MDS Nordion. Nordion was relying on an aging nuclear reactor in Ontario, which at one point was shut down for over a year.[8] To make matters worse, on more than one occasion, Bexxar's isotope supply was disrupted by snowstorms.[1]

Keeping these past glitches in mind, POINT is unwilling to risk an isotope shortage and has extended its self-reliant philosophy to its isotope supply chain. The company is in the process of building capabilities to make lutetium-177 in-house, to not only ensure supply resiliency but also lessen isotope loss due to decay during transport.

A targeted future

While the dream of radiopharmaceuticals is much broader, at present, applications for therapeutics are limited to certain types of cancer.

In the U.S., marketed products target two popular indications: neuroendocrine tumors (Progenics' Azedra and Novartis' Lutathera) and metastatic castration-resistant prostate cancer (Bayer's Xofigo and Novartis' Pluvicto). Zevalin and Bexxar, which are no longer available in the U.S., were both approved for non-Hodgkin's lymphoma — another area where radiopharmaceuticals have seen success.

Bala, citing recent Trialtrove data, points out that 19 of the top 20 most studied indications for radiopharmaceuticals are in oncology (the one exception being pain relief in central nervous system disorders). The majority of trials are focusing on non-Hodgkin's lymphoma and prostate cancer.[4]

Prostate cancer has been a popular target because its cancer cells have high prostate-specific membrane antigen (PSMA) levels. About 95% of this protein rests on the surface of the prostate cells. The external location of PSMA and the fact that it is over-expressed in the vast majority of prostate cancers, but very limited on normal tissues, makes it ideal for treatment by radiopharma therapeutics.[9]

Prostate cancer is the second most common cancer among men, with an estimated 1.4 million people diagnosed globally each year.[10] If radiopharmaceuticals were to become the standard of care, the potential market is extensive.

Therapeutic radiopharmaceuticals accounted for just 6% of the total global nuclear medicine market in 2013, jumping to 20% of the market by 2019.

— MEDraysintell

Approved drugs, such as Pluvicto, are currently used after a patient's prostate cancer has failed to respond to other anticancer treatments, such as chemotherapy. The future hope is to also be able to apply radiopharmaceuticals earlier in the disease cycle, perhaps before the prostate cancer has metastasized — and trials testing this are already underway.

Although prostate cancer is currently a popular indication, theoretically, these targeted therapeutics could be applied to almost any malignancy — and several companies have set out to prove the technology's pan-cancer potential.

Pan-cancer clinical trials, such as POINT's FRONTIER trial and Clovis' LuMIERE trial, could provide the breakthrough that brings radiopharmaceuticals to a variety of high-volume indications — both as a monotherapy or in combination with other treatments.

"Drug candidates like PNT6555 from POINT's FRONTIER trial could exponentially increase the number of patients which could benefit from radiopharmaceuticals," says McCann.

Both POINT and Clovis are investigating treatments that target fibroblast activation protein (FAP). FAP is highly expressed in the cancer-associated fibroblasts found in the majority of cancer types, making it a suitable target across a wide range of tumors.

POINT's phase 1 FRONTIER trial, which began this summer, will evaluate pipeline therapy [Lu-177]-PNT6555 in patients across five FAP-avid cancer indications: colorectal, pancreatic, esophageal, melanoma, and soft tissue sarcoma.

In a world where more than 10 million people die of cancer each year, therapeutic radiopharmaceuticals are poised to offer another powerful option in the arsenal of treatments for common cancers, as well as new hope in cancers that have historically been resistant to other types of treatment — and given the surge of activity in the reinvigorated space, this realization may not be far off.

"For most of their existence, therapeutic radiopharmaceuticals have been limited to small, orphan indications," says McCann. "The capability of delivering radiation directly to a wide variety of cancers could revolutionize cancer treatment paradigms."

References

1. *Timmerman, Luke. (2013). Why Good Drugs Sometimes Fail: The Bexxar Story. Xconomy.*
2. *Reno, Jamie. (2016). An effective treatment for a common cancer in the US may vanish from the market. yahoo!finance.*
3. *P&S Intelligence. (June 2022). Radioligand Therapy Market Size & Share Analysis by Indication.*
4. *Bala, Renu. (2022). Radiopharmaceuticals: A New Approach to Cancer Treatment. Informa Pharma Intelligence.*
5. *Novartis. (June 2022). Novartis resumes production & delivery of radioligand therapy medicines ahead of schedule.*
6. *Investor education. (Dec. 2021). The First Principles of Radiopharmaceuticals. Point Biopharma.*
7. *Radioisotopes in Medicine. (April 2022). World Nuclear Association.*
8. *SEC Filing (6-K) from the SEC Edgar Database. (2014). 2013 Annual Information Form. Nordion.*
9. *Stallard, Jim. (2017). PSMA: A New Target for Prostate Cancer Treatment. Memorial Sloan Kettering.*
10. *Prostate Cancer: Statistics. (2022). Cancer.net.*

Avantor

Ger Brophy
Executive Vice President, Biopharma Production

Nandu Deorkar
Vice President, R&D, Biopharma

Toward a collaborative ecosystem

A new biomanufacturing era demands that suppliers and manufacturers partner to efficiently bring new therapies to market

Traditional biologic therapies like monoclonal antibodies (mAbs) and recombinant proteins have been positively impacting human health outcomes for decades. As of 2022, more than 100 mAb therapies have been approved by the FDA.[1]

Along with the ongoing success of traditional biotherapies, the biopharmaceutical industry has seen a sea change in workflow types and speeds since the start of the COVID-19 pandemic. New and exciting therapeutic areas have been opened, and researchers, suppliers and manufacturers alike will have to be flexible to meet rapidly growing needs. An urgent demand for new treatments and the introduction of new modalities such as mRNA vaccines and therapies have led to a surge both in speed of development and speed to market. At the same time, supply chain disruptions and material shortages have challenged the industry's ability to meet these newly shortened timelines.

These combined challenges present a heightened need for new efficiencies, which can be developed through collaboration between raw material suppliers and manufacturers. Solutions to problems of scale-up, quality and regulatory considerations, and commercialization timelines will need to address cost, throughput and material availability.

Specifically, current challenges can be addressed through the provision of globally sourced, cGMP process materials for in vitro transcription and capping steps, and the identification of more effective chromatography technologies.

Efficiency challenges

Availability of high-quality raw materials

One of the most important factors in the production of consistent, high-quality pharmaceuticals is the availability of raw materials that are consistent, high quality and reliably sourced. This challenge is especially relevant when it comes to emerging modalities such as mRNA vaccines and therapies, which demand large quantities of high-quality plasmid DNA (pDNA) to serve as a template for the desired mRNA sequences. Currently, pDNA demand is massively outpacing supply.[2]

Issues in the pDNA supply chain have led to difficulties in scale-up and regulatory hurdles. The first of these issues is the long lead times and high expense of outsourcing the production to contract manufacturing organizations (CMOs). CMOs that can produce high-quality pDNA usually have long waiting lists, which often prioritize larger companies and those with which the relevant CMO has an existing relationship. When these roadblocks are coupled with a high potential for batch failure, it becomes clear why pDNA is the primary bottleneck in the development of not only mRNA vaccines and therapeutics but in a variety of cell and gene therapies and nucleic acid products.[2]

A similar inefficiency occurs with capping enzymes used in the in vitro transcription phase of mRNA workflows. Capping must occur either during or after transcription to limit the degradation of an mRNA strand. Some capping reagents are expensive and should be used in ideal conditions to avoid material waste.[3] On top of this, a precise ratio of enzymes to plasmids is necessary to ensure that the resulting mRNA is capped and transcription is not limited. This process is sensitive to

Ways to improve downstream process chromatography of mAbs

Reducing the number of chromatography steps:
If manufacturers can reduce steps by using a selective resin or a resin washing mechanism, this will immediately reduce complexity. For example, downstream purification of mAbs often includes the use of a protein A chromatographic resin for affinity chromatography. Since this step has been shown to provide good purification, typically only one or two standardized polishing steps (such as cationic exchange followed by ion exchange) are needed after protein A.

Utilizing a single-use system:
A single-use system for buffer preparation and media preparation eliminates time-consuming and costly cleaning steps, making these processes available on-demand to improve overall efficiency.

Using a continuous downstream process:
The current standard workflow involves eluting the material from a first column, then storing it in a holding tank before it is prepared and loaded into a second column. This process is not truly continuous because of the holding step. It is possible for some molecules to elute directly from the first column into the second column, without the intermediate storage step in a tank.

buffer conditions, time and temperature, so minor mistakes leading to batch failure could drastically increase the expense of this stage of mRNA workflows.

Downstream purification
Downstream process chromatography is a late-stage step of many workflows (from traditional biologics to nucleic acid products) but it is considered a major bottleneck in mAb workflows. Since mAbs constitute more than 50% of biologics currently on the market and downstream processing accounts for as much as 80% of the cost of producing mAbs, improving downstream process chromatography could significantly impact the finances and time a manufacturer must dedicate to a product.[4]

Even though chromatography has long been a part of biopharma workflows, the processes used will need to be significantly refined and improved to yield more efficient and economical outcomes for manufacturers. One inefficiency in chromatographic processes is related to the increased safety features required to account for variations in upstream processes, some of which might result from inconsistencies in raw material supplies.

Chromatographic processes themselves also feature complexities that can give rise to inefficiencies. Different drug substances react differently to chromatographic resins, meaning that desired products and impurities might coelute. This necessitates more chromatographic cycles, potentially with a variety of resin types and methodologies. Improvements to the specificity and dynamic binding capacity of resins, such as the protein A chromatographic resins used in affinity chromatography, can offer solutions to downstream bottlenecks in mAb workflows.

Solutions

Raw material suppliers are uniquely positioned within the biopharma industry to alleviate inefficiencies across workflows for their biomanufacturing customers. From scale-up and regulatory considerations to commercialization, issues of reliable, safe sourcing and efficient downstream chromatography processes provide opportunities for suppliers to alleviate pain points in the workflows that produce both traditional and emerging drug substances.

Provision of reliably sourced cGMP process materials
As high costs and low supply cause delays for biologics manufacturers, raw material suppliers must step in to help fill gaps. A globally integrated supply chain with built-in redundancies is the best way to ensure that slowdowns in the receipt of necessary materials are kept to a minimum. A close relationship between suppliers and biologics manufacturers will be crucial to the efficacy of this solution, as it will be necessary for suppliers to continually assess the evolving needs of their customers. Likewise, this relationship would allow drug manufacturers to work with their suppliers to maintain a reliable supply of necessary materials, including those like pDNA that are difficult to secure in large quantities, and secure new nonstandard raw materials.

The supplier-manufacturer relationship will also allow the development of a shared characterization of critical quality attributes for raw materials. Ultimately, a consistent supply of high-quality materials will not only reduce the slowdowns caused by delays in the receipt of raw materials but also improve product consistency entering the downstream phase.

Downstream chromatography
There are two primary ways in which the supplier-manufacturer relationship can drive improvements in downstream chromatography processes. First, because

EXHIBIT 1

Suppliers can help address scale-up and commercialization challenges

SCALE-UP	TECHNOLOGY TRANSFER	REGULATORY CONSIDERATIONS	COMMERCIALIZATION
Challenges	**Challenges**	**Challenges**	**Challenges**
▪ Raw material availability ▪ Design new SU assemblies ▪ New non-standard raw materials	▪ Design conversion to scalable format for commercial manufacturing ▪ Sourcing of starting acceptable raw materials ▪ Visibility/understanding of control over product quality	▪ Quality systems for demonstrating consistency ▪ Quality system for process reagents ▪ Unclear global regulatory standards/expectations	▪ Supply with forecasted needs and timing ▪ Effective capacity management ▪ Low volume and uncertainty

chromatographic processes are sensitive to buffer conditions, suppliers can suggest workflow improvements and supply the necessary raw materials in a convenient form. A complete, curated portfolio for downstream chromatography process needs ensures that suppliers can deliver buffers, resins and other materials that meet the specific needs of a customer's process and product.

Suppliers can also support customers in the selection of an appropriate resin that will help to alleviate many of the pain points discussed earlier. Though chromatography resins have existed for decades, they are still being improved upon through the use of additives to achieve specific conditions or the development of new ligands that have an increased dynamic binding capacity (DBC).

For example, protein A resins are the most widely used resins in the first purification step of mAbs. This is largely due to protein A resin's ease of implementation, high specificity and strong regulatory track record.[5] Despite the resin's advantages, the cost of the protein A capture step is significant and leaves room for improvement. While the optimization of buffer preparation goes a long way toward improving the performance of a protein A resin, resins themselves can be enhanced to reduce time and cost while increasing yield.

A resin with a higher DBC improves the productivity of the capture step without necessitating a larger equipment footprint, saving manufacturers money on equipment. The increased efficiency resulting from a higher DBC also means that fewer cycles are required to capture the desired material, meaning that overall downstream processing time is reduced. This leads to lower operational risk, decreased labor and consumables cost, and potentially a smaller equipment footprint as lower buffer consumption enables smaller buffer tank sizes.[6]

This example demonstrates the cost savings and reduced barriers to scale-up and time-to-market that result from more efficient downstream chromatography processes. Similar innovations are taking place with other chromatographic resins and technologies, and optimization in this phase will lead to improved downstream efficiency overall. While

protein A resins are used in affinity chromatography for mAbs, other resins and methods are used for other modalities. For example, high-pressure liquid chromatography (HPLC) can be improved for increased purification efficiency of mRNA products.

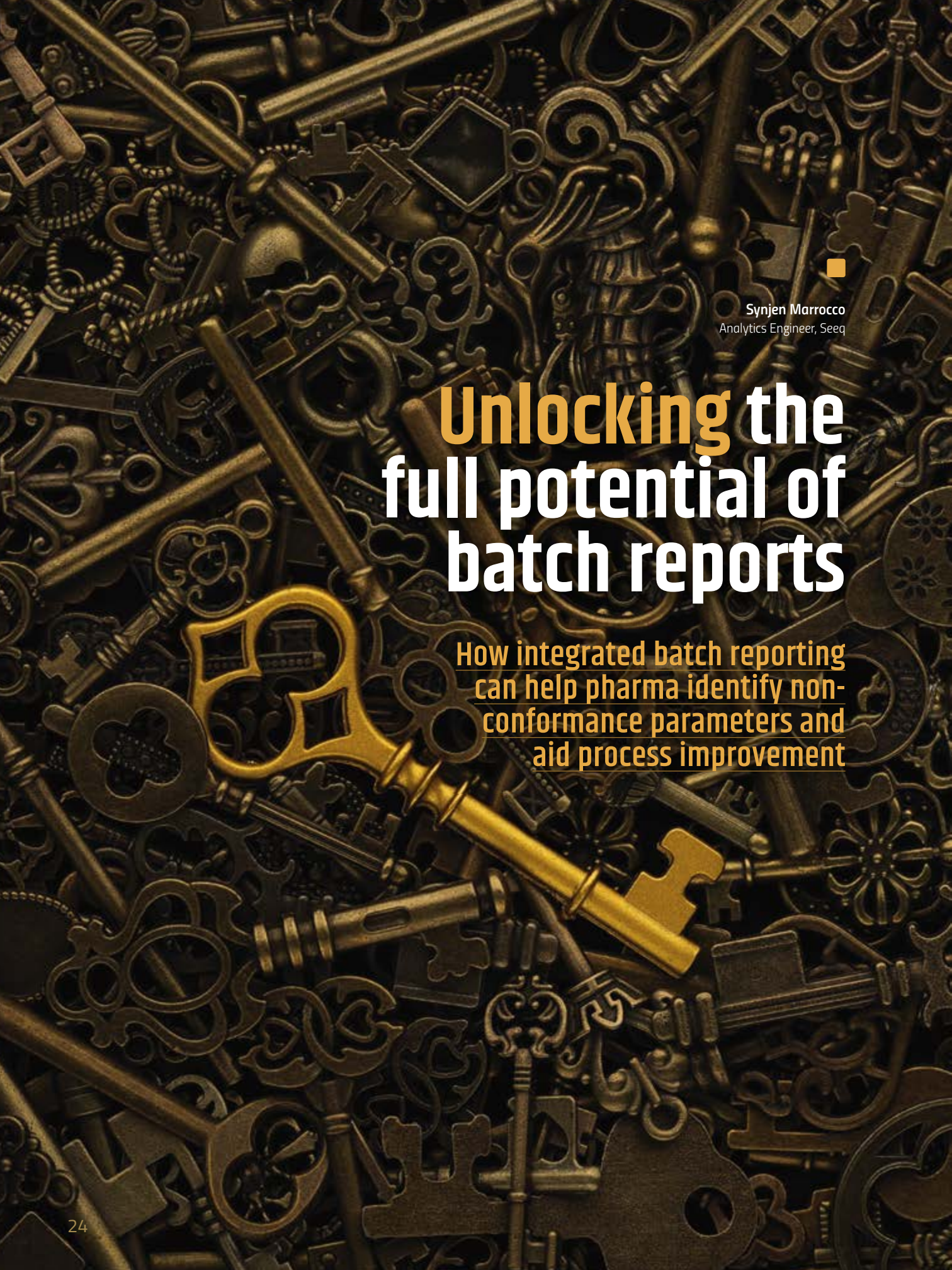
Transformation through collaboration

While it's a remarkable time for the biopharma industry, it is important to acknowledge that emerging opportunities come with new challenges. The evolution of new modalities and therapeutic areas — from mRNA vaccines against COVID-19 to cell and gene therapies for challenging diseases — has led to an emphasis on biomanufacturing innovations because products like cell and gene therapies require efficiency and flexibility in the supply chain as well as in manufacturing processes. The explosiveness of this growth means that efficiency and flexibility must be developed rapidly and alongside new and nonstandard processes and materials.

A strong supplier-manufacturer relationship can ensure that biologics manufacturers have what they need when they need it, even as those needs are rapidly evolving. Both parties must make an effort to create a fruitful relationship, however suppliers are limited by their knowledge of their customers' needs. By involving suppliers early in a process, manufacturers can reduce cost and speed-to-market, leading to a collaborative biopharma ecosystem that may help safely and quickly deliver therapies to the people who need them. The future of biopharma is a complex and rapidly evolving topic, but it is clear that collaboration is set to transform the industry.

References

1. *Baldo, B. (2022). Immune- and Non-Immune-Mediated Adverse Effects of Monoclonal Antibody Therapy: A Survey of 110 Approved Antibodies. Antibodies, 11, 17.*
2. *Ohlson, J. (2020). Plasmid manufacture is the bottleneck of the genetic medicine revolution. Drug Discovery Today, 25(11), 1891–1893.*
3. *Kostelec, T., Sekirnik, R., Celjar, A. M., Nemec, K. S., Livk, A. G., Gagnon, P., & Strancar, A. (2021). Eliminating the analytical bottleneck in production and purification of mRNA. BioProcess International.*
4. *Deorkar, N. (2021). Much needed advances in biopharma chromatography. Pharma Manufacturing, 20(1), 22–23.*
5. *Liu, H. F., Ma, J., Winter, C., & Bayer, R. (2010). Recovery and purification process development for monoclonal antibody production. mAbs, 2(5), 480–499.*
6. *Oh, J., Vengsarkar, P., Fura, J., & Deorkar, N. (2021). Removing bottlenecks from mAB purification. Pharma Manufacturing, 20(1), 24–28.*



Synjen Marrocco
Analytics Engineer, Seeq

Unlocking the full potential of batch reports

How integrated batch reporting can help pharma identify non-conformance parameters and aid process improvement

Batch reporting is a critical component of the pharma manufacturing process because it provides the complete manufacturing history of a given product. This includes proof that good manufacturing practice was adhered to throughout production, and that all critical process parameters (CPPs) and critical quality attributes (CQAs) were met as prescribed in a drug's regulatory filings.

To provide patients with the best drug quality possible, this comprehensive reporting procedure has traditionally required weeks to months following the completion of a batch. Once compiled, batch reports would often span hundreds of pages in length, each of which would require a quality review to ensure compliance and identify errors prior to a product's release.

Data integrity, integration, contextualization, analytics and other qualities are essential for ensuring effective and efficient reporting, and ultimately for safeguarding the public — but existing procedures make it difficult to meet these and other requirements. By leveraging new analytics tools to create integrated and automated reports, pharma manufacturers can expedite the batch record generation and review process.

Procedural shortcomings

Time is by far the greatest limitation in batch reporting procedures today, with manufacturers expected to meet strict production and distribution schedules. Because batch reporting can be cumbersome and time-consuming, it limits the time process engineers and data analysts have available to improve batching process efficiency, increase overall product throughput, and reduce production costs.

Batch reports are typically a manual collection of smaller reports, test results and investigations, each of which is used collectively to verify product safety and quality prior to its release to patients. The data making up these reports can span multiple platforms, such as manufacturing execution systems, process historians, laboratory information management systems and computer maintenance management systems. Generating batch records and reviewing the reports is often very labor-intensive, even when using electronic batch records. While these records provide reduced post-process review latency, real-time review and monitoring capabilities are limited.

Despite the inclusive nature of batch reports, traditional reporting fails to take advantage of the significant opportunity to gain insights into processes, increase throughput and shorten time to market. Instead, many pharma manufacturers today treat manually-assembled batch reports as standalone quality records, leaving unharnessed potential on the table.

Leveraging integrated and automated reports

To enhance process efficiency, expedite reporting procedures and improve data centralization, pharma manufacturers are increasingly using advanced analytics applications to connect and examine their data in new and more efficient ways. These applications empower pharma manufacturers to automate and further integrate the assembly of batch reports, freeing up valuable time for engineering teams to extract process insights for improving overall production outcomes.

Equipped with live data connections, advanced analytics applications interconnect data in a central location from all the steps of a batch process and provide built-in visualization options, enabling subject matter experts (SMEs) to hone in on time periods of interest. This empowers multidisciplinary teams to collaborate and analyze processes using all available data in near-real time.

In addition to automatically generating reports and real-time dashboards, which can be displayed graphically or tabularly, these applications provide rapid report filtering and exception-based reporting. These built-in analytics tools can be further leveraged to expedite the typically tedious review process for CPPs, CQAs, major deviations investigations and subsequent root cause analyses (RCA).

These capabilities enable pharma manufacturers to leverage existing data streams, tools and SMEs to create integrated batch reports, providing a quick return on investment by reducing batch release times and generating near real-time CPP

metrics. Advanced analytics applications can even be used to deploy machine learning (ML) models using the data, and like other software applications leveraged throughout the pharma industry, it is CFR 21 Part 11 compliant with cybersecurity built in, including audit trails.

Spotlighting benefits

By leveraging tools within advanced analytics applications, SMEs can perform calculations to identify and prioritize areas for operational improvement. These activities include finding process bottlenecks, calculating overall equipment effectiveness metrics, performing cycle time analysis, identifying equipment and instrument drift, implementing predictive maintenance, and qualitatively tying all analyses to business needs and priorities.

This novel approach takes advantage of an organization's existing data systems, including integrations with business intelligence (BI) platforms. Highly integrated batch reports reduce rework, and they provide additional value to the organization's original investments in data historians, analytics and BI tools. Implementing fully integrated reports is the first step of the journey toward automating report generation and review processes, and it also provides further insights with data-rich reports.

The following case studies spotlight the benefits companies can leverage by automating batch reports within advanced analytics applications.

Exception-based report and review

Working with integrated batch reports built on advanced analytics applications provides the additional benefit of automatically-generated, exception-based sub-reports. By configuring the application to call out noncompliant items, SMEs and process experts can quickly devote their attention to the associated data and

EXHIBIT 1

A multi-national organization used an advanced analytics application to build reports and to identify anomalies by leveraging proprietary ML algorithms.

information required to investigate further. A high-level overview within reports provides a quick status update across batches, including pre-generated trends and reports, along with other relevant information to pinpoint deviations.

This approach significantly reduces the required batch record review time because quality reviewers and the accompanying team are provided with a clear indication of where to focus their investigation to complete the report and release the associated batch. Sub-reports can be configured with varying granularity. For example, at a high level, a sub-report may only highlight items requiring review prior to closing out the record. At a more granular level, sub-reports may identify operating conditions, equipment sensors and measurements showing signs of degradation, along with improvement opportunities. The latter can be achieved by integrating ML or multivariate models with the reports, and it can be leveraged to improve overall process performance and reduce future deviations.

Although this example is not from the pharma industry, it is instructive because it shows how one company is currently leveraging an advanced analytics application to deploy exception-based reports. The example shows how a multi-national energy provider built reports and identified anomalies across hundreds of assets and thousands of signals by leveraging proprietary ML algorithms (Exhibit 1).

The associated automated exception-based reports were used to prioritize anomalies, and to identify top contributing signals outside of the CPP range that would have been previously ignored without this automated monitoring. The report workflow was used to identify deviations from advisory and quality limits, reducing multiple days of SME time for review to just a few hours of work.

Non-conformance investigations

Non-conformances associated with batches are another common contributor to delayed releases, with RCA and the ensuing corrective and preventive actions sometimes delaying product release by weeks or months. Investigation times can be significantly reduced by using integrated batch reports, along with advanced analytics applications and historical batch data. By automatically generating insights and removing the lengthy manual data harvesting process, this software empowers SMEs to rapidly identify root causes and corrective actions (Exhibit 2).

Additional sub-reports can be configured using historical data, along with multivariate and ML models to pinpoint factors contributing to deviations, which can then be further analyzed. This 'one-stop-shop' for addressing atypical events associated with integrated batch reports can greatly increase throughput by reducing overall investigation times, leading to quicker batch release times and faster product delivery.

A large biopharma manufacturer needed to integrate reporting into its RCA process to investigate an in-process drug substance lot that exceeded a CPP in the production bioreactor stage. The lot showed deteriorating conditions, with subsequent lots exhibiting similar trends.

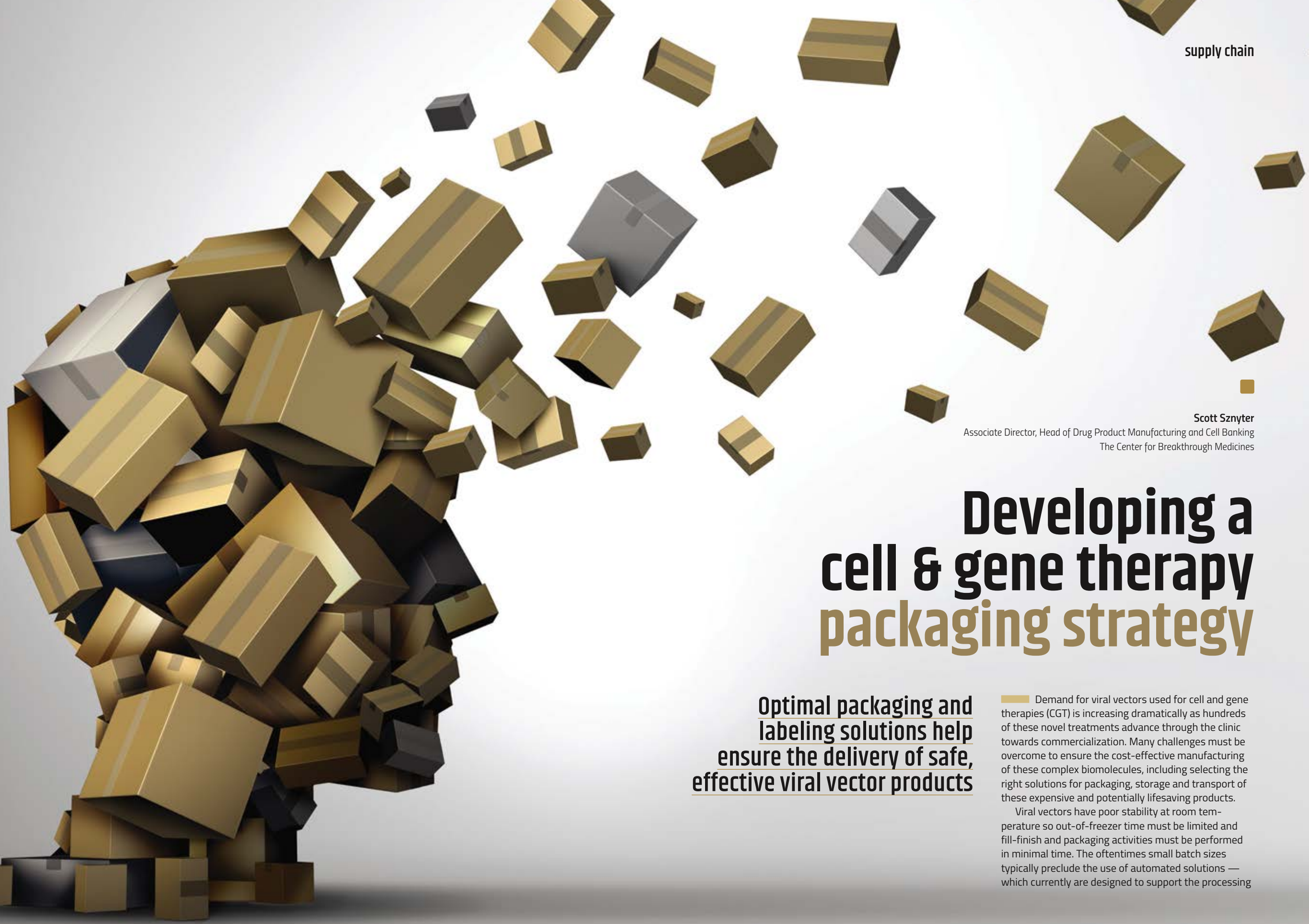
Using pre-built reports and dashboards, the manufacturer was able to rapidly investigate the problem. SMEs identified the root cause and implemented a corrective action in a matter of hours by leveraging the integrated process historian, lab and equipment data. This allowed them to correct the deteriorating behavior, preventing future losses and saving the organization over $2 million.

Ensuring efficiency and quality

Efficient batch reporting is a critical step for accelerating a batch's time to market, and by leveraging advanced analytics applications to create integrated and automated reports, pharma manufacturers can expedite the batch record generation and review process. Efficient batch reporting also empowers manufacturers to unlock the full potential of batch reports by using their data to improve process efficiency, validate quality, increase throughput, maximize profits and guarantee reliable delivery to patients.

EXHIBIT 2

Advanced analytics applications can automatically interconnect data and generate insights, empowering SMEs to rapidly identify root causes and corrective actions.



Scott Sznyter
Associate Director, Head of Drug Product Manufacturing and Cell Banking
The Center for Breakthrough Medicines

Developing a cell & gene therapy packaging strategy

Optimal packaging and labeling solutions help ensure the delivery of safe, effective viral vector products

Demand for viral vectors used for cell and gene therapies (CGT) is increasing dramatically as hundreds of these novel treatments advance through the clinic towards commercialization. Many challenges must be overcome to ensure the cost-effective manufacturing of these complex biomolecules, including selecting the right solutions for packaging, storage and transport of these expensive and potentially lifesaving products.

Viral vectors have poor stability at room temperature so out-of-freezer time must be limited and fill-finish and packaging activities must be performed in minimal time. The oftentimes small batch sizes typically preclude the use of automated solutions — which currently are designed to support the processing

of larger volumes — leading to manual packaging and labeling operations. Solutions must also meet good manufacturing practice (GMP) and country-specific requirements and withstand extremely low temperatures. Additionally, multiple packaging and shipping configurations are needed to cover a broad range of vial sizes and storage temperatures.

The key to overcoming these challenges is to take steps at the start of product development to identify optimal packaging and labeling solutions with commercial considerations in mind. Time-out-of-refrigeration/freezer and various stability studies should be performed as soon as representative material is available. Sacrificing a few extra vials of vector product upfront to establish critical data can help prevent large product losses later on. This approach can also ensure the selection of packaging and labeling solutions that can withstand the stressors from freeze to ship to clinic, and maintain integrity and compatibility with automated tracking, reconciliation and segregation.

Time and batch size

Processing volumes for viral vectors are quite small, with the number of vials filled per batch at typically 500 to 1500. A few outlier batches may comprise less than 100 or greater than 1500 vials. In all cases, vectors are stable for a much shorter timeframe (e.g., between 8-15 hours for lentivirus) than traditional vaccines or monoclonal antibodies, so they require faster processing times.

Fill-finish and packaging operations must be completed quickly while still assuring product quality. The timer starts as soon as the bag of bulk drug substance (BDS) is thawed prior to filling. The product must be inspected, labeled and packaged right after filling. In most cases it cannot be frozen and thawed again. Consequently, the overall time for all operations from filling to packaging must be considered when planning the process.

Primary packaging (filling) is commonly performed in a different location than secondary or tertiary packaging. Most secondary/tertiary packaging consists of cardboard and other materials that are non-sterile and may create particulates in the grade A spaces where product is usually filled.

Once vials are filled, they are visually inspected. Samples for batch-release testing are pulled and segregated from the final product vials. The sample vials and vials going to clinics are labeled as appropriate, with the former then sent to quality control.

Labeled vials for clinical trials are placed in boxes with dividers that hold multiple vials per box. In some cases, it may be necessary to place each vial in an individual carton to meet the requirements of the country receiving the vials. After the boxes are filled with vials, additional labels must be placed on the outside of the boxes, with one label on each part of the box in case the pieces get separated at any point. Tamper-evident tape should also be placed over any edges between sections within the boxes. Depending on site procedures, quarantine labels may be appropriate to ensure the product is not shipped prior to testing or release.

The boxes of packed vials are placed in freezers for storage prior to release, with the most common storage temperature being -80 degrees Celsius. Once the batch is released, the boxes are placed in temperature-controlled shippers with dry ice in a validated configuration. Temperature monitors are placed in the shippers to ensure the temperature is maintained throughout the shipping process.

Mostly manual operations

Currently, most viral vector packaging and labeling operations are manual due to small batch sizes. Most automated solutions, particularly commercial-grade equipment, are designed to process large volumes and are not suitable even for commercial CGT manufacturing, which typically involves small volumes.

For manual operations, it is important to prove processes can be performed aseptically through operator qualifications and aseptic process simulations

Sacrificing a few extra vials of vector product upfront to establish critical data can help prevent large product losses later on.

(media fills). Thorough risk assessments should evaluate possible issues and identify control measures to avoid them.

Whenever appropriate, the use of automated solutions should be considered to minimize risk, increase speed and assure greater sterility. There are a few solutions on the market for primary packaging, and some companies are willing to create custom solutions for small CGT manufacturers. The development of automated inspection, secondary packaging and labeling solutions appears further behind. Most currently available equipment is either slower than manual labeling and packaging or has a large footprint and prohibitive cost, especially for smaller companies getting into the viral vector space.

Coordination and communication are essential

One factor often overlooked by smaller CGT manufacturers when considering packaging and labeling operations is the amount of coordination required between all groups on-site, in both the planning and execution stages. It is imperative that groups communicate during packaging and labeling operations to ensure completion within a set time.

The quality assurance group must be on constant alert to respond to questions, deviations and any needs for split-second decisions during processing. Quality control personnel, meanwhile, must be ready to receive and test samples as soon as they are pulled. Engineering and automation must be ready to respond quickly if any equipment issues arise. In addition, because product, labels and packaging must all be reconciled, periodic communication between groups is key to ensuring no documentation errors occur during concurrent operations.

Considerations when selecting CGT packaging

Packaging systems for viral vectors include primary (vials), secondary (typically cardboard boxes) and tertiary (temperature-controlled shippers) components. They must meet GMP requirements and ensure the quality and integrity of the viral vector is maintained during storage and shipment, while also providing easy access to the product.

Vials as primary packaging for viral vectors must be durable under freezing conditions (-80° C). Unfortunately, at this point there is limited data regarding which vials are best for use with different types of viral vectors, but the stability of the product in different types of vials should be considered. Top-of-the-line vials with low particulates and excellent quality control should always be selected. Given the high value of viral vector products, it is not worth saving a small amount of money using an inferior vial.

Cardboard boxes used for secondary packaging must withstand thermal and mechanical stresses, including freezing conditions and exposure to dry ice and condensation (if warming occurs). Packaging design should take into consideration regulatory compliance requirements, such as separation of leakproof vials, and the needs of clinics, particularly the optimum quantity of vials that will avoid the necessity for further repackaging.

Tertiary packaging must be durable and provide robust temperature control. Here again, use of the highest-quality packaging solutions is recommended, as it is not worth risking product loss. Time must also be invested in conducting thorough shipping validation studies, if not with actual viral vector product, at least with a representative buffer solution.

The right labeling solutions are crucial

Labeling may seem like a simple task, but for viral vector products that must be immediately placed in low-temperature freezers before typical labels have sufficient time to properly adhere to vials, proper label selection is essential. Similarly, the printing ink used for labels must withstand up to freezing conditions and be legible even if vials are covered in frost.

The factors that can impact the specific text that must be included on labels placed on primary, secondary and tertiary packaging for viral vectors should not be overlooked either. The best approach is to establish a procedure for text generation and approval that clearly outlines approval responsibilities. The text must comply with regulatory requirements for each country to which the viral vector product will be shipped.

Planning for all scenarios

Whether viral vectors are produced by a CGT company or a contract development and manufacturing organization (CDMO), planning for possible disruptions to packaging, labeling and shipping operations should be a key focus when establishing a packaging strategy. Being prepared for any scenario that can compromise a lot can be the difference between a viral vector product getting to the clinic or expiring before it ever reaches patients.

The first step is conducting a robust risk assessment to identify possible undesirable scenarios. Most important are those that lead to product being exposed to non-freezing temperatures. For instance, freezers may fail, or a CGT company could be acquired while viral vector product is in the freezer, making it necessary to re-label vials. Delays during shipment or the failure of temperature-controlled packaging are other possible concerns.

Executing comprehensive stability studies allows determination of time-out-of-temperature limits, which will then dictate the speed at which packaging and labeling operations must be performed and the time available for resolving temperature-control failures if they do occur. Shipping validation studies using a representative surrogate provide confirmation that the chosen packaging and shipment solutions provide adequate temperature control and that appropriate procedures are in place to manage unexpected situations.

Selection of multiple packaging and shipping configurations is also recommended. CDMOs will need to meet the varying requirements of clients shipping viral vector products to many different countries.

CGT companies pursuing in-house viral vector production can also benefit from having multiple options available during early development phases. With this approach, different vials and dosages can be sent to clinics as needed, and no additional work will be required once the final configuration is selected.

Indeed, some packaging can have lead times of a year or more depending on the specific configuration. Switching to new configurations and/or adding new suppliers involves significant time and cost later in development. Time spent upfront to plan for multiple scenarios avoids such costly delays.

Testing is fundamental

It is also important for CGT manufacturers to confirm that the properties of the cardboard and the adhesion of glues is sufficient in secondary packaging after exposure to freezing temperatures and during transport.

Labels on primary and secondary containers should be tested as well to ensure they remain adhered at frozen temperatures and that printed text and graphics remain legible even if the package is bent or dented and the labels become scratched, abraded or otherwise affected during shipment.

In general, specific protocols for comprehensive testing of packaging and labeling solutions should be established that accommodate all possible temperature requirements, packaging configurations and transportation arrangements.

Start early

Many CGT candidates receive accelerated development designations from regulatory authorities, leading to dramatically reduced development timelines. For this reason, it is imperative that the evaluation of packaging and labeling solutions be initiated at early development stages — and with commercialization in mind, rather than when viral vector products reach phase 3 trials. The sooner future scale-up of the batch size is considered when selecting filling, inspection, labeling and packaging equipment, the greater the likelihood a program will meet the aggressive timelines.

Selecting primary, secondary and tertiary packaging designs; choosing appropriate labels, adhesives, and inks; putting in place quality agreements with packaging and transport suppliers; and establishing qualification protocols should be initiated in phase 1.

Thought should also be directed toward the possible storage solutions that may be applicable at different development phases. Storage at -80 degrees Celcius is commonplace for preclinical and phase 1/2 clinical materials because at this stage using a conservative approach is best, and most vectors are expected to be stable at this low temperature. As products advance to later clinical stages, however, having data that demonstrates stability at -30 degrees or even warmer can have a significant impact on storage, transportation, and general logistics costs and be a game-changer for the transition to commercialization.

Rapid advances anticipated

Packaging and labeling of viral vector products for cell and gene therapy applications currently present some significant challenges. The packaging industry is moving forward at lightning speed, recognizing the issues faced by CGT companies and responding appropriately. Effective solutions for faster, more automated viral vector packaging and labeling processes, even for small batches, are already anticipated. Each year, growing numbers of vendors are bringing measurable improvements to the packaging and labeling space.

As CGTs continue to increase in importance from a market perspective, further developments are expected at an even more accelerated pace. Viral vector batch sizes will also likely increase as advances in gene and gene-modified cell therapy manufacturing are achieved and more candidates targeting diseases that affect larger patient populations move closer to commercialization. Regulations will simultaneously evolve and drive further solutions for inspection, packaging, labeling, serialization and more.

Throughout all of these changes, the focus will always remain on making sure the quality and integrity of viral vector products is maintained during packaging, labeling, storage and transport — ensuring the delivery of safe and highly efficacious medicines to patients.

product focus

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

Predictive maintenance in a GxP-compliant environment

Keeping manufacturing assets in effective working order can be costly and wasteful. A schedule-based approach to maintenance often results in the unnecessary repair or replacement of equipment in acceptable working condition or conversely, in catastrophic failure of equipment due to undiagnosed issues.

To combat this, Aizon launched its Asset Health application earlier this year, allowing pharma companies to leverage predictive power to monitor the health of assets, and — based on the prescriptive and conditional data-driven insights that the solution provides — receive advanced warnings on their conditions.

Built on the company's GxP-compliant AI SaaS Platform, the new application is designed to provide intelligent historical maintenance analysis, proactively monitor the condition of critical assets in real time, identify potential problems, and provide actionable maintenance recommendations that keep equipment up and running optimally.

Packaging quality control

Pharma manufacturers need to be able to track individual products throughout the production and supply chain, facilitating simpler and more targeted product recalls where necessary, and improving levels of product safety.

Mettler-Toledo's new Integrated Mark & Verify systems and software are designed to help pharma manufacturers fulfill their increasing product safety and compliance requirements by making it easier to integrate code marking and verification capabilities into their existing production lines with minimum disruption. The systems enable the printing and verification of 1D and 2D codes and alphanumeric text such as those used for accurate identification of individual products (serialization) and those aggregated into cases or pallets.

Integrated smart cameras allow for both presence and quality checks — verifying the presence of required labels and information, and that printing and labeling quality is high, with no damaged labels or smeared ink.

Democratization of machine learning

Earlier this year, Software AG's TrendMiner took home the "IoT Analytics Solution of the Year" award from market intelligence organization, IoT Breakthrough.

TrendMiner's self-service analytics platform features advanced search technology with pattern recognition and machine learning and connects easily with existing time-series databases (historians) and other operational business

Mettler-Toledo
Mark & Verify systems

applications — empowering engineers with analytics for improving operational excellence, without the need to rely on data scientists.

The TrendMiner 2021.R2 software extends the reach of previously released notebook integration, allowing analytics expert-users to make their data model outputs available to the rest of the organization, giving operational experts better insights. The new multi-variate Anomaly Detection Model allows optimal process conditions to be trained on historical data and has the ability to detect anomalies on new incoming data.

Syntegon
Versynta Flexible Filling Platform

Flexible small batch filling

The pharma industry has shifted towards more high-priced biopharma drugs for small patient populations and these drugs require highly flexible small batch filling solutions that achieve precise product yields at low output.

With that in mind, Syntegon's Versynta Flexible Filling Platform (FFP) offers an individually configurable machine for aseptic small batch filling, including high potent and BSL (Bio-Safety Level) pharmaceuticals. According to Syntegon, it's the first filling platform of its kind worldwide, featuring an integrated system for automated HEPA filter scans for RABS and isolators. The goal? Faster, reproducible results in real time, with more reliable filter integrity tests.

And because modularity and automation are major requirements for liquid aseptic filling, the platform is comprised of pre-developed modules that can be flexibly combined to individual machine configurations. The FFP's production cell and handling unit are highly autonomous systems that reduce manual intervention.

TrendMiner
TrendMiner 2021.R2

Biodegradable nitrile gloves

When it comes to industrial hand protection, pharma must balance worker safely with a growing desire for greater environmental awareness.

Unigloves has launched a new nitrile disposable glove — called BioTouch — that combines chemical resistance, comfort and grip with innovative, environmentally friendly, biodegradable technology and medical grade standards.

The glove is ideally suited to the pharma sector, offering resistance to a range of chemicals and improved grip in wet and oily conditions thanks to its textured fingertips. After its working life, BioTouch will achieve 90% biodegradation in landfill after just 490 days compared to traditional nitrile gloves which can take over 100 years.

Biodegradability performance is achieved thanks to an organic additive, which attracts microbes found in landfills. Importantly, on the shelf, the physical properties of the gloves remain unchanged for up to three years.

Jim Love
Market Leader for Oligonucleotides, CRB

Planning your oligonucleotide facility

Two key facility considerations that will impact pharma's business case

Oligonucleotide production and development have continued to expand rapidly. A recent CRB report tells us that there will be a significant push for existing companies to enter the oligonucleotide market — whether startups, large pharma companies or CMOs — in the near future, with the majority planning for capital investment within the next four years. This data paints a picture of an industry where successful development has outstripped available production capacity.

The report also tells us that the sector continues to focus on the development of a diverse group of molecule types. However, public information indicates that 75% of the approved oligonucleotide therapies on the market today are either antisense (ASO) or siRNA technology.

As innovators, licensers and CMOs alike look to transition from adjacent industries or expand existing capacity to fill this need, there are two key facility considerations that will impact the CapEx business case initially and throughout the life of the facility.

Molecule type and facility throughput

ASO and siRNA represent two key molecule types, and they are largely similar in the synthesis operation. However, siRNA is a dual-stranded molecule where independently synthesized strands must be annealed together, often in a separate suite. Additional variations on these molecule types can increase purification suite time and the number of required process steps before the lyophilization (freeze-drying) operation that yields the final bulk drug substance. All of these variations can affect the throughput and flexibility of the facility.

Because of this, initial facility programming should take into account the intended molecule production goals of the facility. A facility designed to maximize throughput only for a simple ASO can require less capital investment but will suffer bottlenecks if it needs to pivot to support siRNA production or molecules requiring more complex purification.

The additional purification requirements of some molecules will also impact flammable buffer storage requirements, which with increasing scale, become more capital-intensive areas of the facility due to building and fire code requirements.

For multi-product facilities that require flexibility, a facility programming approach might consider a simple ASO and a more complicated siRNA molecule type as boundary cases for what the facility will produce. This can help create a phasing plan that balances initial capital investment against future throughput goals.

It is important to understand and articulate this vision for the facility at the programming phase, as it can help lead to more efficient overall use of capital via interior fit-out of shelled space versus a lower first cost exterior future build-out. Either approach should incorporate an expansion strategy that minimizes ongoing production downtime.

Planning for tomorrow

For a multi-product facility, it is important to keep a steady eye on the capabilities of the facility as new contracts fill the capacity. Even before large capital expansion plans are triggered, there are other facility planning considerations that can allow for incremental throughput gains.

For example, manufacturers may look to increase synthesis batch size by allowing for parallel synthesis columns to increase batch output. This strategy can further enhance a large batch campaign strategy that enables final bulk product lot pooling at the lyophilization operation, a common bottleneck due to the length of the freeze-drying process.

Especially within multi-product facilities, process characterization of purification is still handled carefully, with purification fractions often stored within cold rooms until they can be analyzed for potential inclusion in downstream batches. However, as companies look forward to performing more robust characterization of some products and readily improving online analytical capabilities, their plans may consider providing spaces for hold tanks that bypass the fraction storage and analysis step. This can free up overall facility time and reduce bottlenecks for fraction analysis, and storage for products that still require it.

As the oligonucleotide industry continues to gain momentum and take shape, it will be key that facilities continue to anticipate and plan for tomorrow as they build the capacity to meet today's burgeoning demand.

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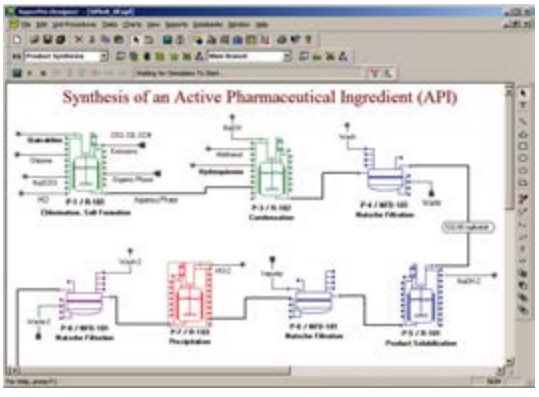

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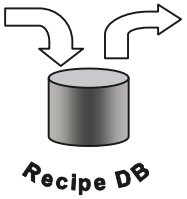

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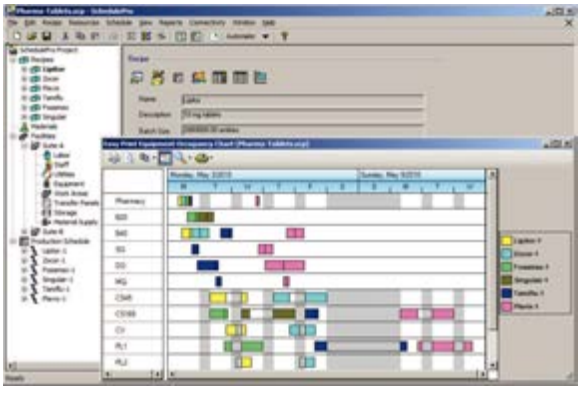

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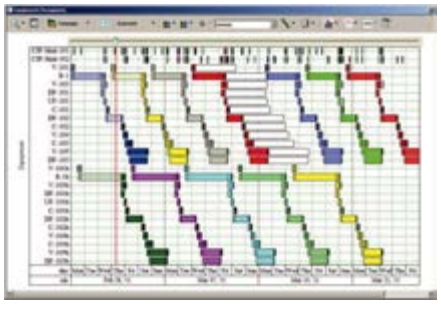

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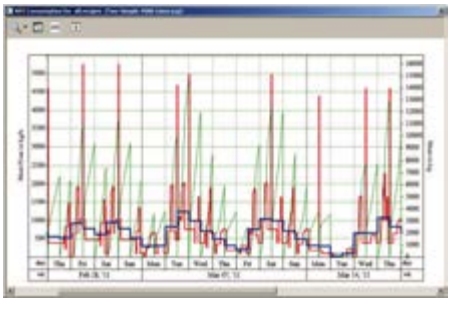
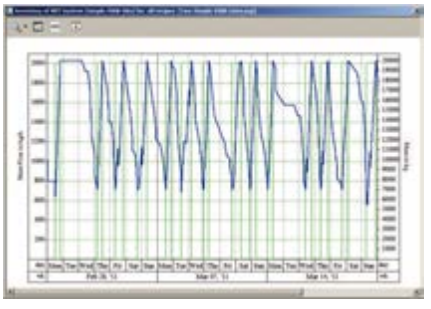


Tracking demand for resources (e.g., labor, materials, utilities, etc.)



Managing inventories for input, intermediate, and output materials

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

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

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michael connaughton
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Senior Advertising Consultant
gzamin@endeavorb2b.com

hillary freeley
Digital Marketing Solutions
hfreeley@endeavorb2b.com

carmela kappel
Advertising Coordinator
ckappel@endeavorb2b.com

lisa payne
Reprint Marketing Manager
Mossberg & Company
lpayne@mossbergco.com
(574) 303-8511

PRODUCTION

rita fitzgerald
Production Manager
rfitzgerald@endeavorb2b.com

ADMINISTRATION

carmela kappel
Assistant to the Publisher
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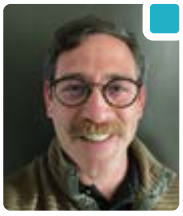

Resiliency starts on the plant floor

In a world mired in supply issues, focusing on machine health can provide relief

The demand for lifesaving therapeutics and vaccines never stops, despite growing supply chain issues, difficulties in sourcing raw materials, and capacity constraints. There are many processes in the pharma industry that make the products people need, but one thing is true: those processes are supported by machines so making sure the machines run optimally is key to meeting demand.

In this heavily regulated industry that is not keen to take perceived new risks, introducing new technology solutions can be slow. But machine health, which uses IoT and AI to predict and prevent machine failure and improve machine performance, has become a proven predictive maintenance solution for other manufacturing industries.

Yet, according to Pharma Manufacturing's report "The true impact of machine failure in pharma," 83% of pharma plants still rely on preventative maintenance approaches. Improving supply chain resiliency is crucial to the livelihood of companies and patients. It is time to reset and innovate — and that starts with machine health.

Data you can trust

Pharma companies are continuously collecting data to meet regulatory requirements. Lots of information is generated through electronic batch records, quality management systems and equipment performance. But in the case of machines, that data is generated after they fail or malfunction, giving teams no time to act on those insights.

Supply chain leaders were stress tested during COVID and found themselves being more reactive to their data instead of being guided by it. In order to see what's going on across operations while maintaining the highest quality standards, now is the time to become more proactive and predictive with that information. There are many technologies that use words like 'AI,' 'machine learning,' and 'insights.' For data you can trust, you should consider the collection methods and strategies of each solution. Ideally you want sensors that continuously monitor machines and a supportive ecosystem that interprets the data.

Once you select a machine health solution, you can quickly validate its impact by acting on the data you receive. Machines that do not run optimally or run to failure can cause inefficient planned maintenance, unplanned downtime and quality issues. Real-time machine health alerts tell you about failures before they happen and how to fix them. Acting on those insights and doing the necessary repairs can be quantified by the downtime hours, costs and material saved — proof that the technology works.

Insights for global teams

Innovation really comes down to making sure that the people involved are enabled to do their job in more meaningful ways. Many maintenance and reliability professionals spend too much time being reactive to machine issues. But mindsets are difficult to change, especially when teams have a set way of doing things. Luckily, machine health provides quick wins that can be shared throughout an organization, which can support the shift and get everyone on board. The supply chain is an ecosystem that starts with people — upskilling these teams with better reliability and maintenance programs creates better jobs, higher level work and less wasteful processes.

With fewer machine failures, teams can use machine data to transition from calendar-based schedules to predictive maintenance, where higher level work can be strategized and spare parts programs optimized. All of this leads to unlocking the capacity that is necessary for companies to get products to market at the highest quality.

Data can also be used to gain insights into specific machine uses across production lines and portfolios and can inform new production goals. Once you establish a machine health layer to your operations, you can leverage it to inform site and global teams to make strategic decisions that drive top- and bottom-line initiatives.

According to the previously mentioned Pharma Manufacturing report, close to 80% of executives said standardizing global maintenance and reliability programs was critical and important. Machine health has proven itself to be a game-changer for those looking to digitally transform and gain a competitive advantage.

If you're looking to respond to today's challenges by increasing your supply chain resiliency and ultimately achieving better patient outcomes, start with your machines.

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