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TABLE OF CONTENTS

Radio-activity 4
The radiopharmaceuticals vision — and the next-gen companies seeing it through

mRNA boom: A double-edged sword 17
Did short-term solutions for COVID-19 stifle long-term mRNA success?

What's next in adoptive cell therapy 22
Overcoming new manufacturing challenges as the cellular immunotherapy landscape expands

The importance of keeping up-to-date on emergency safety technology 28
Key considerations for selecting emergency eyewashes and safety showers

Breaking through conventional solutions in aseptic filling 34
How a comprehensive cleanroom concept can push beyond isolators and RABS

AD INDEX

Vetter • www.vetter-pharma.com 3
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Radio-activity

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

By Karen Langhauser, Chief Content Director

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.



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

— Citeline Trialtrove database

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 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 — an 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 pharma industry's

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

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.

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 an alpha radionuclide therapy based on actinium-225 and a small molecule targeting PSMA.

SEPT. 2021 A ustralia-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.

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.

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.



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

— MEDraysintell

"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, 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.

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."

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mRNA boom: A double-edged sword

Did short-term solutions for COVID-19 stifle long-term mRNA success?

Carl Schoellhammer, Senior Project Leader
William Orent, Life Science Expert
Luka Jelcic, Senior Associate

For decades, scientists have viewed mRNA as a promising vaccine and drug candidate. It is easy to synthesize and customize, making it an adaptable platform with a wide range of potential uses. The SARS-CoV-2 pandemic then demonstrated its utility on a global scale, as pharma companies lined up to produce this lifesaving 'quick fix' en masse.

However, this meteoric rise has proven to be a double-edged sword. While the pandemic helped alleviate certain unknowns in the use of mRNA as a drug — like proving the safety of lipid nanoparticles (LNPs) — it created new questions which may have long-lasting effects on the field and what indications are tackled in a post-pandemic world.

THE ROLE OF LIPID NANOPARTICLES

Despite the benefits of mRNA, its candidacy as a potential solution to COVID-19 hinged on the pharma industry's ability to successfully integrate it into manufacturing processes to enable mass vaccination. Thus, the need for durability took center stage as pharma quickly adopted LNPs to ensure mRNA's stability both in shipping and storage, and when it is in the body.

For mRNA to function as a safe and effective therapy, key biological and manufacturing issues had to be overcome. These included drug targeting, stability, unwanted immunogenicity, and relative translation efficiencies. But potentially more impactful was the choice of LNPs and the associated

manufacturing apparatus that was scaled up to produce unprecedented quantities.

The use of LNPs as a delivery mechanism for mRNA vaccines underscores the inability of mRNA to stand alone as a therapeutic modality. For mRNA to have any therapeutic effect, the body needs to translate the encoded message into a protein with the desired biological activity. Inherent in this challenge is that mRNA itself is notoriously unstable, with a very short half-life. As the mRNA degrades, so does the template that codes for the protein conferring therapeutic value. Because mRNA does not incorporate into the genome the way a lentivirus-based gene therapy would, mRNA is a tough sell as a medicine simply from a bioavailability and durability standpoint.

These challenges have driven different groups around the world to research and explore how to make mRNA more stable and viable for longer periods of time. One option is to design and synthesize circular mRNA strands, removing an available 'end' for an enzyme to digest and extending the window for protein expression. This is one of several avenues that could be explored.

However, in the urgent rush of the pandemic, LNPs became the go-to method, to the exclusion of all others.

GOING BEYOND LNPS

In practice, an LNP effectively consists of a few types of lipids for structural properties (like cholesterol) and a special, ionizable lipid, which allows the LNP to achieve intracellular delivery. The LNP formulation also acts as an adjuvant to activate the immune system, which is essential for vaccine development but problematic in other applications (although recent research suggests this can be customized to be tolerogenic). This general mixture dates back at least a decade, and the specific formulation used for the SARS-CoV-2 vaccines was not novel, having previously been tested in humans for other indications.

While LNPs were well suited for rapid use in SARS-CoV-2 vaccines, they are a suboptimal tool for unleashing the full promise of therapeutic mRNA. Their overall delivery efficiency is poor, and they lack real organ or tissue targetability.

For the field to truly commandeer our own bodies as 'drug factories,' as Moderna's CEO Stephane Bancel has touted, the world will need something better than an LNP. Yet, the industry now has an almost unlimited capacity to produce them, and as a result, biopharma has rallied around their use, indirectly shaping their pipelines in profound ways.

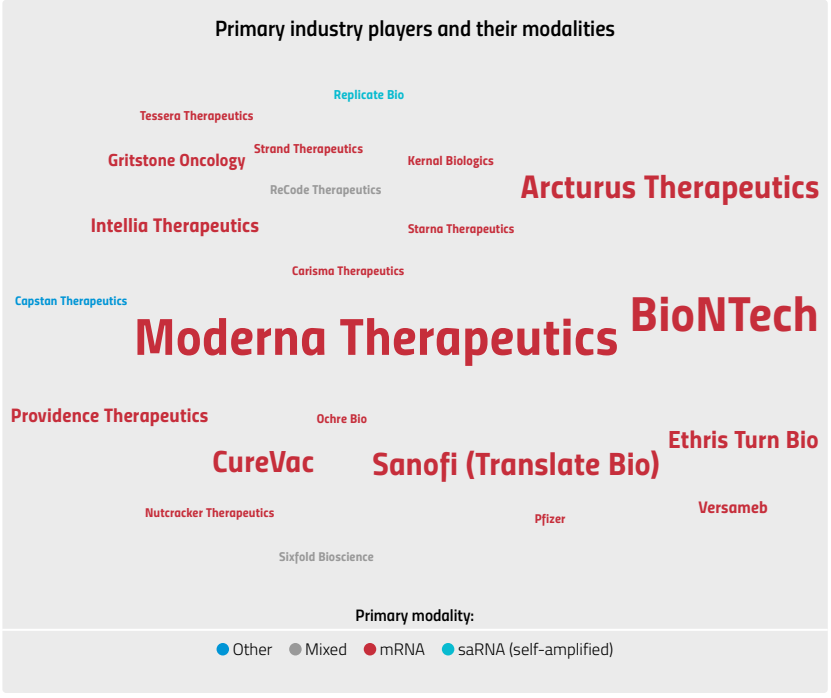
SHORT-TERM FIXES FOR LONG-TERM ISSUES

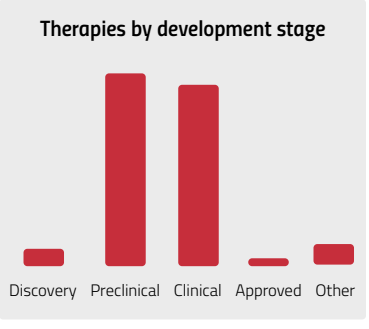
At the start of SARS-CoV-2 vaccine development, there were considerable supply chain challenges limiting the manufacturing of LNP-mRNA formulations. Variable costs and unpredictable supplies of raw materials complicated manufacturing plans. Upstream processing costs were influenced by materials such as enzymes for in vitro transcription and mRNA capping, while downstream processing costs were swayed by the method of purification and overall process yields.

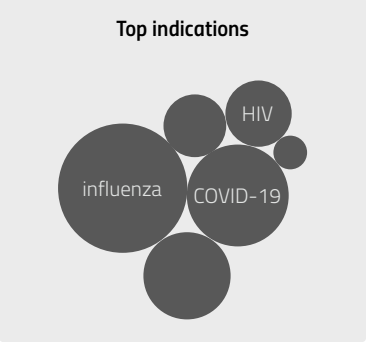
The pharma industry was (and still is) experiencing a labor shortage, driven by a lack of the experienced operators needed for specialized manufacturing processes. With limited human resources, pharma companies faced challenges in bringing production up to required levels and in expanding their manufacturing capacity to meet unprecedented global demand.

To alleviate these pressures, LNP-mRNA innovators entered into various strategic agreements to ensure both critical material supply and manufacturing capacity. Examples include Moderna partnering with CordenPharma for its lipid excipient supply, and with Lonza for additional drug product manufacturing capacity. For its part, Pfizer partnered with Acuitas for LNP delivery technology. Raw material suppliers also rose to the occasion. Avanti Polar Lipid was

Preclinical and clinical mRNA drug programs







acquired by Croda mid-pandemic, while MilliporeSigma increased its lipid production capacity by an astounding 50 times.

Longer term, as the mRNA industry continues to evolve, there is a concern that the collective focus on applications requiring relatively small quantities of mRNA may generate manufacturing challenges. What will happen to all of the production and formulation capacity that came online at the height of the pandemic? If these facilities sit idle, there could be a spike in production costs compared to pandemic levels. This would inevitably impact earlier-stage companies in this space as they vie for funding and growth.

BOLSTERED PIPELINES OR MORE OF THE SAME?

Unfortunately, the newfound availability of lipid inputs may have created a barrier to further innovation in delivery sciences.

The industry was quick to coalesce around the use of LNPs at a time when interest and investment dollars were pouring into the field of mRNA-based therapeutics. This laser focus limited the pursuit of alternative solutions. The mRNA drug pipeline is now dominated by candidates targeting applications amenable to delivery using LNPs. This includes vaccines and other low-dose indications, or drugs for liver-associated diseases. According to DeciBio's therapy tracking platform, TheraTrack, over one-third of public preclinical and clinical mRNA drug programs are vaccines. Of the remaining programs, another third target hepatic diseases or rare indications.

Even in good economic times, targeting indications with a lot of competition and a limited market opportunity is ill-advised. But as we look ahead to the second half of 2022, the general market forecast looks far gloomier. This makes pipeline prioritization an even more important part of any biopharma strategy. Companies need to review the landscape and carefully determine what their first and potentially second program will be and how it will be differentiated. Thus, when the market slows down, they're only focusing on programs that are viable to begin with — there's no need for massive and immediate cuts to a number of other programs.

On a more positive note, this type of lean and efficient pipeline can make for a compelling acquisition target for larger pharma.

FUTURE IMPLICATIONS

The pandemic established the safety of LNPs and mRNA-based therapeutics — several billion times over. While valuable, this rapid progress may have also unintentionally stifled innovation and exploration of better delivery solutions and technologies. These advances are needed for mRNA to live up to its promise. In the short term, biopharma companies should carefully

consider their pipeline and targets to limit later-to-market drugs in indications that will not support them. Moderna may have the resources required to take many shots on goal, targeting many different diseases, but most therapeutic mRNA companies do not. For the health of the field, biopharma companies need to divide and conquer.

While LNPs are ideally suited for various vaccination strategies, therapeutic developers focusing on other mRNA therapeutics (e.g., protein replacement) must carefully consider their targeting strategies. For instance, novel LNP formulations may present additional targeting and delivery options (e.g., switching to pH-dependent ionizable lipids over cationic lipids). Manufacturers of raw inputs need to consider how to scale back their production to suit both extremes of demand, and formulators should be conscious not to take capacity offline at a rate that would cause a shock in production costs and stifle this emerging therapeutic modality.

For these reasons, successful go-to-market strategies will need to balance a therapeutic landscape driven by LNP formulation R&D, nurturing a strong material supply chain and navigating shifting manufacturing capacity.

What's next in adoptive cell therapy

Overcoming new manufacturing challenges as the cellular immunotherapy landscape expands

By Mark White, Associate Director, Biopharma Product Marketing, Digital Biology Group, Bio-Rad Laboratories

Biopharma manufacturers know that adoptive cell therapies (ACTs) such as chimeric antigen receptor (CAR) T-cell therapies are unlike anything that has come before.

ACTs are living drugs. Specifically, they're human cells that, when modified or expanded, gain efficacy in the treatment of cancer. CAR T-cells in particular have shown unprecedented success in the clinic and they are bound to bring much-needed relief to thousands of people with cancer in the years to come. However, increasing demand for ACTs will come with a critical need for a new approach to biopharmaceutical manufacturing. Unlike small molecule and protein-based drugs, whose discovery process is relatively standardized and whose manufacture is stoichiometrically predictable, ACT development and manufacturing involves multiple layers of variability and complexity.

CAR T-cells have progressed far into the clinic despite these manufacturing limitations: Patients in the U.S. with different types of blood cancer can receive CAR T-cell therapy in over 150 treatment centers in 38 states and the District of Columbia. The fact that CAR T-cells reached the clinic at all is a feat of biomedical engineering.1 Still, CAR T-cells are not the end of the story for ACT development. Several other types of ACT are under investigation and in the next decade or so, CAR T-cells might find company in their space.

Other ACTs on their way to the clinic include T-cell receptor (TCR) T-cell



The growing popularity of ACTs cements the reality that the manufacturing process for cancer treatments will never be the same.

therapies, tumor-infiltrating lymphocytes (TILs) and natural killer (NK) cells. This burgeoning pipeline offers hope to people with cancer who do not have access to safe and effective treatments.

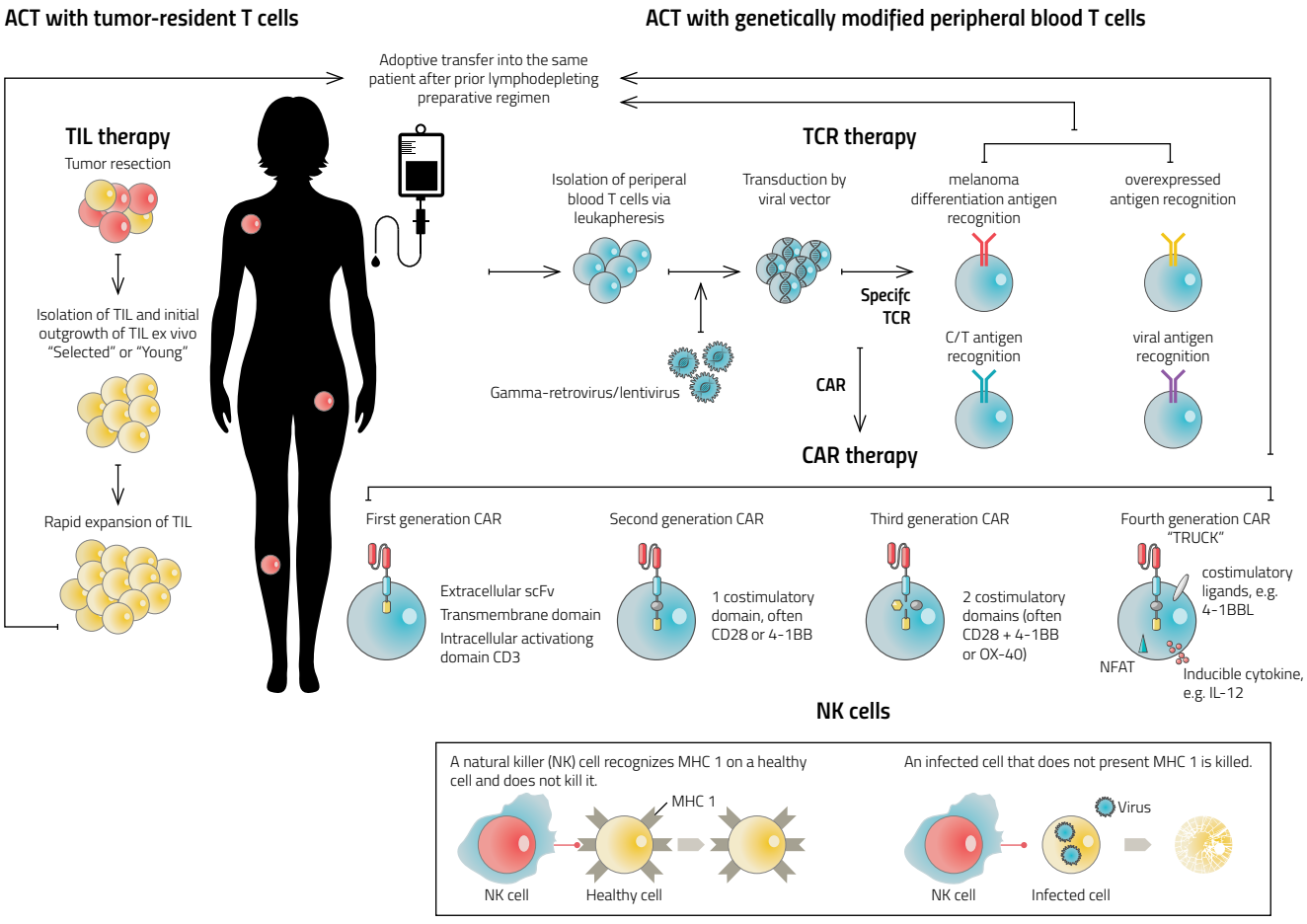
The growing popularity of ACTs also cements the reality that the manufacturing process for cancer treatments will never be the same. This article will explore the manufacturing challenges that still impact CAR T-cell developers and the hurdles that developers must still overcome as other types of ACTs speed towards clinical use.

CAR-T MANUFACTURING CHALLENGES

CAR T-cells are custom-designed and specially constructed immune cells that selectively target tumor cells for destruction. T-cells normally kill foreign invaders in the body, but tumor cells typically evade the body's defenses and grow unrestrained. By transfecting T-cells with the gene for the CAR protein, T-cells can be trained to identify cancer and destroy it as if it were any other foreign invader.

Today's CAR T-cells are autologous, meaning that each therapy is derived from an individual patient's blood. After a patient has their blood drawn, the samples are sent to a CAR T-cell manufacturer, where the manufacturer isolates the T-cells and engineers them to express the CAR gene using a virus or transposon system. The cells are then expanded and returned to the clinic, where a physician reinfuses the cells into the patient's bloodstream.

These cells' autologous nature creates benefits and drawbacks for both patients and manufacturers. Since the cells come from a patient's own body, the chances of eliciting an adverse immune reaction based on incompatibility are slim. On the downside, autologous CAR T-cell production is slow; it can take several weeks for the treatment to arrive at the clinic. Several steps must take place before manufacturing can begin: The patient must be diagnosed, a physician must decide to pursue CAR T-cell therapy, and the patient's blood must be drawn and sent to the lab. Only then can the manufacturer engineer the cells to treat cancer. Every day that a patient must wait for the treatment to arrive is one less day of receiving a treatment that may save their life.



Biopharmaceutical companies are actively seeking ways to develop allogeneic CAR T-cells. These cells could drastically reduce wait times by offering a standardized, off-the-shelf treatment option. However, since these cells are foreign to the body, they pose additional risks. For example, the patient's immune system may kill the cells before they have any therapeutic benefit, or worse, the infusion can cause graft-vs-host disease, where the CAR T-cells attack healthy tissue.

Regardless of their source, CAR T-cells pose several manufacturing challenges. Since their development cannot be completely controlled, the safety and efficacy of any single batch cannot be guaranteed. For example, when introducing the CAR gene to T-cells, the transfection step is not perfectly efficient. Some cells may not accept the transgene and never become CAR T-cells. On the other hand, too many copies of the transgene may integrate into each genome, posing a potential safety issue.

If a cell contains more than four copies of the transgene, the cell can become toxic and cause an inflammatory response that leads to organ dysfunction and death.[2] Consequently, if a batch contains this many copies per cell, the Food and Drug Administration recommends that manufacturers screen it out.[3] Finally, some viral vectors used for transfection may make it through the filter steps and

As TCR T-cells, TILs and NK cells reach the approval stage, they may all one day offer hope to patients with a wider variety of cancers.

end up in the final batch. If these viruses are replication-competent, they could theoretically cause the growth of T-cell neoplasms, another form of cancer. For these reasons and more, manufacturers need to use quality control methods to screen out suboptimal batches before they reach patients.

Fortunately, the tools and techniques needed to monitor the quality of CAR T-cell therapies already exist. Techniques such as flow cytometry and Droplet Digital PCR (ddPCR) can be used to monitor transfection efficiency, CAR-T copy number and the presence of replication-competent viruses and other contaminants.

Currently, researchers are developing novel CAR T-cell therapies, as well as other ACTs, that overcome several of these limitations.

TREATING SOLID TUMORS WITH TCR T-CELLS

One drawback of CAR T-cells is their low efficacy in treating cancers beyond those circulating through the blood. These cells are limited by their relative inability to infiltrate solid tumors (such as those found in breast or prostate tissue). But T-cell receptor T-cells may help solve this challenge.

Like CAR T-cell therapy, TCR therapy involves genetically modifying T-cells to express a protein that targets tumor cells. But unlike CAR T-cells, which only target cells that express certain cell surface proteins, TCRs can direct T-cells towards any antigen, whether it is expressed on the surface of a tumor cell or internally.[4] A fragment of that antigen simply needs to be presented by a tumor cell's major histocompatibility complex (MHC).

MHCs are protein structures that help T-cells differentiate between types of cells. TCRs recognize the MHCs on tumor cells as foreign and then signal T-cells to destroy the cells. In other words, TCR T-cells amplify the adaptive immune response to tumor cells. Since TCR T-cells can identify foreign cells by their intracellular antigens, they could potentially be effective in treating solid tumors.

TCR T-cell manufacturing poses similar challenges to CAR T-cell manufacturing. Manufacturers must still be careful to monitor cells for transfection efficiency and copy number, as well as the presence of harmful contaminants. Also, like today's CAR T-cells, the TCR T-cells currently under development

are autologous and therefore take weeks to manufacture, creating similar delays and risks for patients. An allogeneic TCR T-cell could theoretically reduce wait times and increase the efficacy of this promising therapy.

BOOSTING INNATE IMMUNE ACTIVITY WITH TILS

A tumor-infiltrating lymphocyte (TIL) is any T-cell or B-cell that has successfully entered a tumor mass. These cells' unique ability to infiltrate solid tumors gives them immense therapeutic potential. It also tells us a lot about how these cells could function in the clinic.

For instance, TILs naturally recognize tumor antigens and do not need to be genetically modified. Rather, to be used as an autologous therapy, they merely need to be made stronger. This involves taking a blood sample, isolating and expanding the TIL cells and returning them to the patient.

No TILs have achieved FDA approval yet, but it is neither safety nor effectiveness concerns that have held them back. Rather, it is the challenge of manufacturing them at scale. The manufacturing process for TILs is complex, requiring technical skill and six to eight weeks to accomplish. First, the TILs can only be harvested from tumor tissue, which means a patient must undergo an invasive tissue biopsy. Then, the tissue gets dissected in the lab, and scientists plate the cells and employ a multifaceted digestion process to isolate the lymphocytes. Finally, the cells get expanded and returned to the patient for treatment. The complexity of this protocol makes it challenging to implement the therapy in the clinic.

NK CELLS: A DIFFERENT KIND OF LYMPHOCYTE

Not all ACTs rely upon T-cell activity. For example, natural killer cells are another type of lymphocyte that evolved specifically to attack tumor cells. These cells' unique mechanism of action gives them potential in the clinic and might make the manufacturing process simpler and cheaper.

When NK cells identify a tumor cell, they attack the tumor and release chemical signals that activate the adaptive immune system against it. Since these cells seek out tumor cells on their own, they do not need to be genetically modified to be used as cancer therapy, making the discovery and manufacturing process much simpler.

NK cells are considered safe, even when they are allogeneic.[5] This characteristic makes them a suitable source of off-the-shelf ACTs. With this flexibility, manufacturers can save time and money by manufacturing larger batches. This pays off for patients, as well, who will not have to wait weeks to receive ACT.

Despite their natural tendency to attack tumors, NK cells cannot overcome tumors

without help because the tumor microenvironment suppresses their activity.6 Here, the CAR protein may be able to help. Engineering NK cells to express the CAR protein may boost their activity and help them overcome the immunosuppressive behavior of tumor cells.

NK cell manufacturing is not without its challenges. NK cells are difficult to expand in vitro. Also, in most cases, NK cells do not infiltrate solid tumors, limiting their potential in treating cancers beyond blood cancer. However, as a treatment for leukemia and lymphoma, NK cells promise a more effective, easier-to-produce ACT option.

ADOPTIVE CELL THERAPY'S NEXT ACT

The FDA approval of CAR T-cell therapy was only the beginning for ACTs. As TCR T-cells, TILs and NK cells reach the approval stage, they may all one day offer hope to patients with a wider variety of cancers.

As manufacturers aim to produce safe and effective therapies quickly and inexpensively, all of these therapies will create new challenges. But biomanufacturers do not have to face these challenges alone: regulators believe in these therapies so much that the FDA has published several guidances aimed at helping biomanufacturers improve their ACT manufacturing practices.

With support from regulators and unrelenting demand from patients and physicians, biomanufacturers will hopefully discover new ways to make ACT manufacturing more efficient so more treatments can reach more patients while they can still make a difference.

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The importance of keeping up-to-date on emergency safety technology

Key considerations for selecting emergency eyewashes and safety showers

By Ryan Pfund, Senior Product Manager, Bradley Corp.

As we gradually enter the post-pandemic era, providing dependable health and safety protocol for employees and building occupants is more crucial than ever. As part of any workplace safety plan, preparing facilities that deal with any type of chemicals with proper plumbed emergency eyewash and safety shower equipment are essential safeguards that should not be overlooked.

Plumbed emergency shower equipment is essential in all types of commercial settings that involve any types of chemical, flammable and particulate hazards, including pharmaceutical manufacturing plant floors, laboratories, and R&D settings.

The Centers for Disease Control and Prevention (CDC) estimate more than 13 million workers in the U.S. are potentially exposed to chemicals that can be absorbed through the skin. Some exposure to chemicals may result in immediate injuries such as chemical burns. In fact, direct or indirect contact can damage the skin or pass through the skin, eyes and/or into the bloodstream.

According to the U.S. Environmental Protection Agency (EPA), there is no comprehensive list of hazardous chemicals. The EPCRA regulations in 40 CFR Part 370 cite OSHA's broad definition of hazardous chemicals (with certain exceptions listed in EPCRA Section 311(e)), which includes any element, compound, or mixture of

elements that is a physical hazard or a health hazard (29 CFR Section 1910.1200(c) and 40 CFR Section 370.2). OSHA's Hazard Communication Standard (29 CFR Section 1910.1200) requires chemical manufacturers and importers to obtain or develop Material Safety Data Sheets (MSDS) for each hazardous chemical that they produce or import. It also requires employers to have an MSDS available for each hazardous chemical that they use (29 CFR Section 1910.1200(g)).

While personal protective equipment is an excellent first line of defense against chemical splashes, having immediate, clear and unobstructed access to emergency showers and eyewashes is also of paramount importance. Therefore, it's important to keep up-to-date on placement, maintenance, and the newest equipment trends and technologies, and determine whether your equipment is effectively optimizing the best protection for its employees and occupants.

KNOW YOUR HAZARDS

To begin the selection process of emergency shower and eyewash equipment, start by identifying potential hazards in a particular work setting. Safety data sheets (SDS) for hazardous substances should be carefully reviewed to ensure the proper protection and safety plan is in place to protect the workers. Eyewashes and eye/face washes, as well as drench showers, should be selected based on the type and level of potential exposure to workers and how many individuals could be affected. Potential hazards may include hazardous chemicals or flammable materials. For example:

- **Emergency eyewash stations**
  - o effective for spills, splashes, dust or debris likely to affect only the eyes
  - o provides a controlled flow of water to both eyes simultaneously
  - o delivers an uninterrupted, 15-minute supply of tepid water. Plumbed units can supply a greater volume of water available – between 2.0 and 5.0 gallons (7.5 and 19.0 liters) per minute
- **Emergency eye/face wash stations**
  - o used when the entire face is at risk from spills, splashes, dust and debris
  - o irrigates the eyes and face simultaneously
  - o provides a large distribution pattern of water (minimum 3.0 gpm/11.4 lpm) to effectively rinse the entire face
- **Drench showers**
  - o used when larger areas of the body are at risk
  - o flushes a larger portion of the body but is not appropriate for the eyes (a combination eyewash and drench shower may be used to simultaneously flush the eyes and rinse larger areas of the body)

Further, ANSI/ISEA Z358.1–2014 American National Standard for Emergency Eyewash and Shower Equipment requires that tepid water be delivered to emergency fixtures, which encourages an injured party to complete the full 15-minute flush during an emergency. ANSI/ISEA suggests an incoming water temperature between 60˚ F and 100˚ F (15.6-37.8° C).

EVALUATING AND RE-EVALUATING EQUIPMENT PLACEMENT

Since work environments are dynamic and change over time, assessments should be conducted annually to ensure the proper type, quantity and location of emergency fixtures. Some emergency equipment manufacturers offer free job site evaluations and can be instrumental in assessing potential problems.

During a walk-through, it is essential to reference the ANSI/ISEA Z358.1–2014 emergency equipment standard, which outlines the specific requirements for emergency eyewash and drench shower equipment installation, testing, performance, maintenance, training and use. Safety data sheets are another excellent source for determining protection needs, as they contain the first aid information indicating if drenching facilities are required.

Too often, facility managers underestimate the maximum distance allowed between a critical work area and eyewash/safety shower product. This is an issue since the first seconds following eye and skin exposure are critical to minimizing injury.

ANSI provides the following guidelines for product placement:

- A drench shower, eyewash or combination unit should be located within 10 seconds of a potential hazard or approximately 55 ft. with unobstructed access.
- The equipment must be on the same level the user is working on. If there are doors between the hazard and the fixture, they must swing in the direction of travel.
- The height of the eyewash flow pattern should be between 33 and 53 inches, and measured from the floor to the water flow.
- If the worker's ability to walk or move might be impacted by the chemical exposure, the fixture should be placed closer to the worker.
- If highly corrosive chemicals are used, the drench shower or eyewash should be placed immediately adjacent to the hazard.
- If a potential chemical spill in an area is likely to affect multiple workers, a sufficient number of fixtures should be in place to prevent one worker from having to wait 15 minutes while another is drenched.

It's also important for safety fixtures to be clearly identifiable and easy to reach:

- The area around the fixture should be well-lighted.
- Each fixture should be identified with a highly visible sign.
- A drench shower or eyewash in a bright color like yellow is easiest to spot in a busy industrial environment.
- Eyewash spray heads should be a minimum of 6 inches from walls or obstructions to allow the user clear access for eye flushing.
- The area for flushing under the drench shower should be unobstructed. The only exception is the eyewash on a combination drench shower and eyewash fixture. In this case, the eyewash is placed in line with the drench shower to allow for simultaneous use.

ENSURING THE BEST WASHDOWN COVERAGE

When harmful contaminants reach the delicate eye area, and extend to the outer portions of the face, or contact the body, every second counts. Therefore, evaluating the amount of total face and body coverage provided by the eye/face wash and/or shower is key. The newest generation of emergency fixtures is designed to deliver a more uniform and complete spray pattern distribution. Older shower designs push the flow of water to the outer rim of the showerhead, creating a hollow space in the center of the pattern that can miss affected areas.

Using the latest technology in fluid dynamics, new eyewash designs work in tandem with a pressure regulated flow control and the spinning motion of water, which creates an optimal spray pattern to rinse off contaminants as quickly and thoroughly as possible. The contoured shape combined with the spinning water funnels the water into a concentrated, yet gentle, deluge to ensure the most effective flush available.

Modern eye and eye/face wash models utilize a much more accurate method to maintain the flow of water over varied pressures. With the right flow control, a gentle, non-injurious flow of water can be delivered based on the pressure supplied to the fixture, allowing for minimal variance across a wide range of pressure.

Due to advances in fluid dynamics technology, these types of eye/face washes provide 20 percent better protection than other designs.

NEW SWING-ACTIVATED EYEWASH MODELS

For facilities such as chemical plants, laboratory environments and tight workspaces, a new generation eyewash model combines a sink faucet with an eyewash built in for emergency eyewash use, offering a

highly efficient and convenient space-saving solution.

During regular faucet use, the eyewash is stored out of the way. In an emergency, the eyewash is immediately activated when it is swung out 90 degrees over the sink. When the eyewash is activated, the swing-activated design ensures that the faucet moves out of the way, positioning the eyewash directly over the sink and allowing clear access to the fixture. With the eyewash in the optimal position over the sink, water is contained in the sink without dripping or spraying on countertops and floors, which can create mess and risk of slipping and falling.

Newer models are mounted lower to the deck rather than on the top of the faucet, providing more convenient and comfortable use of the emergency fixture compared with other models on the market, and reinforcing stability and durability of the fixture during use.

TMVS FOR TEMPERATURE CONTROL

Newer models of thermostatic mixing valves (TMVs) deliver safe water temperatures to commercial faucet applications and emergency safety eyewash fixtures. One TMV model features a "dual use" design for supplying heated water. With two valves in one, this design saves installation time and conserves space under sinks.

During regular faucet use, the TMV delivers tempered water for uses such as handwashing; in an emergency, it delivers ANSI/ISEA-required tepid water. Again, this single source design is especially useful for cloistered work applications and laboratory settings.

EYEWASH DESIGNS FOR INCREASED HYGIENE

It is important to keep eye/face wash systems clean and bacteria-free. However, sometimes stagnant water can accumulate due to improper maintenance and testing, false activations, tampering and other misuse by workers, leaving equipment and water vulnerable to contamination. Stagnant or untreated water is more likely to contain organisms (e.g., Acanthamoeba, Pseudomonas, Legionella) that cause infection. When a worker uses an eyewash station that is improperly maintained, organisms in the water may come into contact with the eye, skin, or may be inhaled, risking infection.

Contamination issues can be mitigated by improving equipment testing and maintenance, installing an eyewash alarm system, and selecting equipment with safeguards against water contamination.

A newer eye/face wash model utilizes a self-draining design that eliminates any settled water in the system. This model also incorporates separate supply and waste

pipes to prevent cross-contamination from the clean inlet and wastewater.

Another feature to look for is hinged see-through plastic or stainless steel bowl covers that shield the entire bowl from misuse and contamination. The see-through plastic allows for quick and easy visual inspection and the hinging mechanism provides a more secure hold. The fixture is activated as the cover is opened and may be installed on barrier-free fixtures.

A final note on emergency eyewashes and safety showers: While selection of proper emergency eyewash equipment is crucial, ultimately, workers must be trained and knowledgeable about the location of the fixtures and how to properly use them. Some emergency equipment manufacturers offer free job site evaluations to help with product selection, ANSI/ISEA compliance and training to enhance protection for all.

Breaking through conventional solutions in aseptic filling

How a comprehensive cleanroom concept can push beyond isolators and RABS

By Matthias Piloty, Project Manager, Site & Plant Development
Vetter Pharma-Fertigung GmbH & Co KG

On a global basis, pharmaceutical manufacturers face complex challenges to their aseptic fill-and-finish process. On the one hand, there is still a high demand for blockbuster drugs that require large batch manufacturing. On the other hand, intensifying research in areas such as rare diseases is driving the demand for smaller batch sizes.

Taken together, this balancing act creates numerous challenges and consequences for the aseptic filling of drugs. As a result, greater pressure is being put upon the industry to meet the increasing flexibility — especially for production processes that enable individual line set-up for product changeovers.

Additionally, many global authorities have been increasing their regulatory requirements for process safety. There are new and revised regulatory guidelines such as Annex 1 of the EU GMP Guide "Manufacture of Sterile Medicinal Products", considered the most important European regulatory standard for manufacturing sterile pharmaceutical products. Emphasis is placed on more stringent requirements for microbial and particulate contamination control with the expected result of microbiological findings within isolators and restricted access barrier systems (RABS) to be 0 colony forming units (cfu) recovered, and that "all critical surfaces that come into contact with sterile materials should be sterile."

FIGURE 1

Cleanroom view from insight the barriers



Regulatory obligations such as visual inspection requirements for particles are also becoming increasingly stringent with regulatory trends shifting from today's best practice of "essentially free" toward the more demanding standard of "practically free."

For today's manufacturers of aseptic drugs, being successful demands that new technologies have sufficient built-in versatility. As such, many are adapting accordingly by taking on new approaches to high-quality drug manufacturing that go beyond current manufacturing processes.

A NEW APPROACH TO CLEANROOMS

Today, the conventional approach taken by most drug manufacturers for their aseptic manufacturing needs is a reliance on the technology of both isolators and RABS. The isolator is a completely sealed unit and entirely "isolated" from the outside environment. And while isolators are widely used throughout the drug manufacturing industry, they do have their limitations since they are required to undergo extensive decontamination. This decontamination step limits the level of adaptability and efficiency they can achieve.

Another highly employed technology, restricted access barrier system (RABS), involves barrier and dynamic airflow separation between environment and drug product and offers the advantage of faster set-up, efficient product changeover, and variability. As a result, RABS enables multi-product manufacturing operations with shorter downtimes. However, with global demand increasing and regulatory requirements becoming ever-stricter, drug manufacturers need new and innovative approaches that push beyond isolators and RABS.

To meet the above-mentioned increasing regulations, a holistic concept that combines the advantages of both isolators and RABS was required. New technology is available that acknowledges all working steps related to aseptic filling including decontamination, set-up and filling, monitoring, and analytics. Designed to optimize the versatility and efficiency of pharmaceutical production processes, the technology minimizes the risk of contamination, and offers several advantages over existing concepts such as the alleviation of the risk of microbe carry-over from grade B to grade A, while still enabling rapid product changeover.

RIGOROUS PREPARATION IS CRUCIAL

While automated H2O2 decontamination plays a crucial role, some important preliminary work must first be considered:

1. The cleanroom must be carefully prepared and machine surfaces wiped off before automated H2O2 can begin.
2. Cleaning, sterilizing and installing in the cleanroom any equipment that does not touch the product and which cannot be transported in a sterile container.
3. The installation of storage holders in the barrier equipped with wrapped microbiological monitoring plates to avoid later transport from grade B to grade A.
4. Installation of gloves and glove extenders after the closing of barrier doors. Any remaining equipment parts must be brought into the barrier using sterile containers.

To enhance the level of purity achieved through this system, the preparation of the manufacturing line takes place behind closed barriers in an aseptic environment. All equipment parts brought in before or after decontamination are steam-sterilized in an autoclave before entering the cleanroom. With this approach manual cleaning is minimized, downtime is reduced and overall equipment effectiveness (OEE) is increased. In addition to these steps, further parameters are monitored and controlled in preparation for the actual decontamination process, such as relative air humidity. The cleanroom is then sealed air-tight using inflatable door gaskets and the actual H2O2 decontamination can begin.

AUTOMATED H_2O_2 DECONTAMINATION

As decontamination begins, a system of stainless-steel pipes built into the cleanroom walls and ceiling aerosolizes the H2O2 solution into a class ISO 5 and 7 cleanrooms. This is achieved by installing dual-substance jets inside and outside the barrier. As a result of these permanently installed nozzles, automatic and autonomous decontamination of the entire cleanroom is accomplished.

Following the required reaction time, the laminar airflow flushes the entire cleanroom. Appropriate catalysts ensure rapid degradation, and a High-Efficiency Particulate Air (HEPA) filter prevents particles from entering the room. After a maximum of 180 minutes of decontamination, the cleanroom is ready for use.

By utilizing an automated approach manual processes are eliminated, and the sources of error associated with manual decontamination methods like formaldehyde fumigation are minimized. Automated H2O2 decontamination also provides greater protection against microbiological contamination when compared with wipe-and-spray disinfection. The H2O2 eliminates critical grade A microorganisms and is practically residue-free since the solution quickly breaks down into water and oxygen.

FIGURE 2

Built-in jet used for automated H_2O_2 decontamination



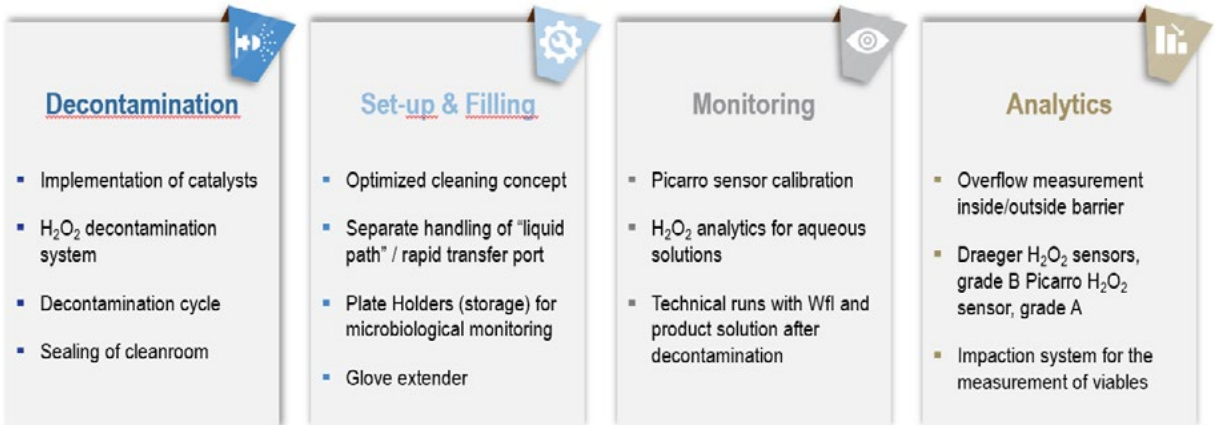
A HOLISTIC APPROACH THAT ENSURES SAFETY AND VERIFICATION

Employing a holistic cleanroom concept, integration, monitoring, and analytic measures not only tracks the aseptic filling process but also ensure that both products and employees are fully protected from H2O2. The differing variables are tracked using sensors inside and outside the barrier and two Polytron sensors measure H2O2 decay within the cleanroom in grade B, while a Picarro sensor follows the same process in grade A. A flowmeter continuously measures the airflow from inside the barrier area into the ambient cleanroom air. Because the analytics concept also includes H2O2 analysis for aqueous solutions, H2O2 concentrations in WfI (water for injection) or other product solutions can be verified in the lab.

There are distinct advantages to this holistic cleanroom concept including the significant advantage of speed as well as high

FIGURE 3

: A holistic cleanroom concept considers all working steps around aseptic filling



reliability and reproducibility. Depending on the size of the cleanroom, the entire decontamination cycle can be completed in just three hours. Suitable catalysts and a highly effective ventilation system enhance H2O2 degradation and lead to short decontamination cycles. Preparations for production and the aseptic set-up of the cleanroom can begin immediately. Also, a shorter downtime streamlines processes and improves overall equipment effectiveness.

Capture: A holistic cleanroom concept considers all working steps around aseptic filling

TOMORROW'S CHALLENGES ARE BEING MET TODAY

Drug manufacturing today requires ever-increased flexibility and dealing with stringent requirements for microbial and particulate contamination control. Pharmaceutical and biotech companies around the world are feeling these pressures on their aseptic filling processes. That is why many of these organizations are adapting their strategy accordingly and taking advantage of innovative production methods that are designed to enhance and advance current manufacturing processes.

The combined concept makes it possible to achieve safety and quality standards that keep up with the performance of isolators while still offering the flexibility advantages of RABS. The holistic cleanroom concept is designed to deliver all benchmarks – safety, versatility, efficiency, and above all, quality. This can help pharmaceutical and biotech companies prepare for success in a challenging industry and meet the ever-evolving demands of the world's dynamic healthcare market.



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