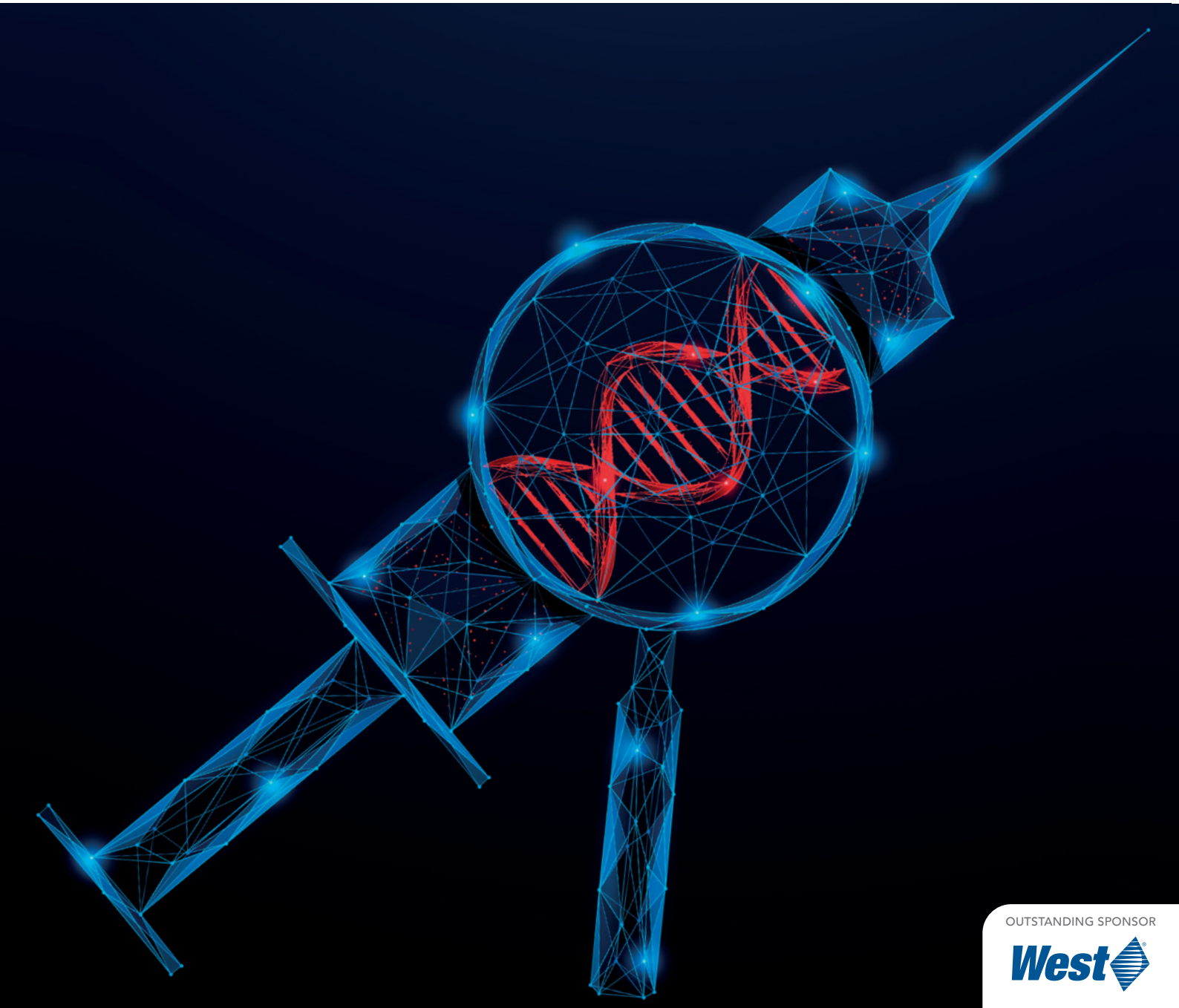
20 YEARS ON

181

Drug Delivery

DECEMBER 17TH 2025

DELIVERING CELL & GENE THERAPEUTICS



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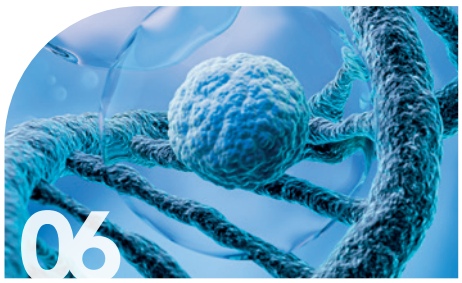

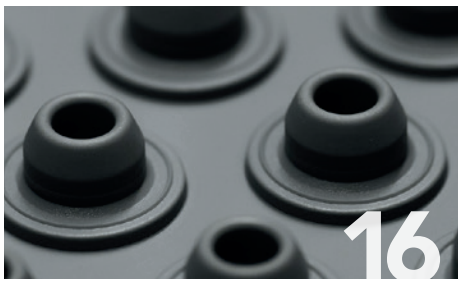

DELIVERING CELL & GENE THERAPEUTICS

ONdrugDelivery Issue N° 181, December 17th, 2025

This edition is one in the ONdrugDelivery series of publications. Each issue focuses on a specific topic within the field of drug delivery, and is supported by industry leaders in that field.

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Cell & Gene Therapies:
A Challenging New Frontier For Drug Delivery

We conclude 2025, and our 20th anniversary celebrations, with the introduction of a second brand new topic – Delivering Cell and Gene Therapeutics. This exciting frontier in the pharmaceutical industry has the potential to open the door to tackling chronic conditions with a single treatment and taking on conditions previously thought untreatable. However, cell and gene therapies present significant challenges, frequently requiring cryogenic storage conditions and being both incredibly delicate and specific to individual patients. Here, our contributors discuss a range of topics within gene and cell therapies, from overviews on the sector to deep dives into tightly focused niches.

Opening the issue, **West Pharmaceutical Services** takes on the key subject of primary packaging and administration (Page 6), giving an overview the approaches and challenges the industry faces. Following that, **Cambridge Consultants** looks at the evolution of cell and gene therapies, from their history their future (Page 12).

On the devices side, **Aptar Pharma** discusses the importance of extractables and leachables for rubber components in cell and gene therapy applications (Page 16) and **PARI** shares insights on using nebulisers for mRNA delivery (Page 24). Later in the issue, **Neurochase and Fearsome** present a joint Early Insight on their novel system for facilitating more effective intraparenchymal delivery (Page 52) and **Mitsubishi Gas Chemical** highlights the benefits of cyclo-olefin polymer vials for cold-chain storage (Page 64).

Broadening the discussion, **Cambridge Design Partnership** goes into detail on the critical importance of precision when delivering cell and gene therapies (Page 28). Taking a wider view, **KnowMade** investigates what patent trends can tell us about activity in the cell and gene therapeutics space (Page 34) and **Bharat Arora** provides an Expert View on how the delivery device and method are inextricable aspects of these therapies, meaning that they must be considered as part of the whole (Page 48).

Diving into more specific niches, **Sanner** discusses the particular vulnerability of cell and gene therapies to shear forces and how to mitigate them (Page 40), and **TrakCel** considers the challenges posed by the fragmented digital ecosystem surrounding these therapies and how a cross-compatible approach is needed to improve usability at point of care (Page 44). Following that, **N4 Pharma** digs into the potential of cell and gene therapies in oncology (Page 56) and **Team Consulting** takes on the particularities of delivery in the ophthalmology space (Pages 60).

Finally, at the conclusion of our 20th year, from all the team at ONdrugDelivery, we would like to extend a big thank you to everyone who has read and contributed to ONdrugDelivery. With the launch of two new topics, and having published our biggest ever issue in October, this has been a superb year for us and we look forward to continuing to bring you the best, most topic-specific drug delivery information and intelligence into the new year and beyond.

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ONdrugDelivery is published by
FURNESS PUBLISHING
The Candlemakers, West Street, Lewes,
East Sussex, BN7 2NZ, United Kingdom
Board Directors: **Guy Furness**, **Audrey Furness**
Registered in England: Company No 8348388
ISSN 2049-145X print / ISSN 2049-1468 pdf

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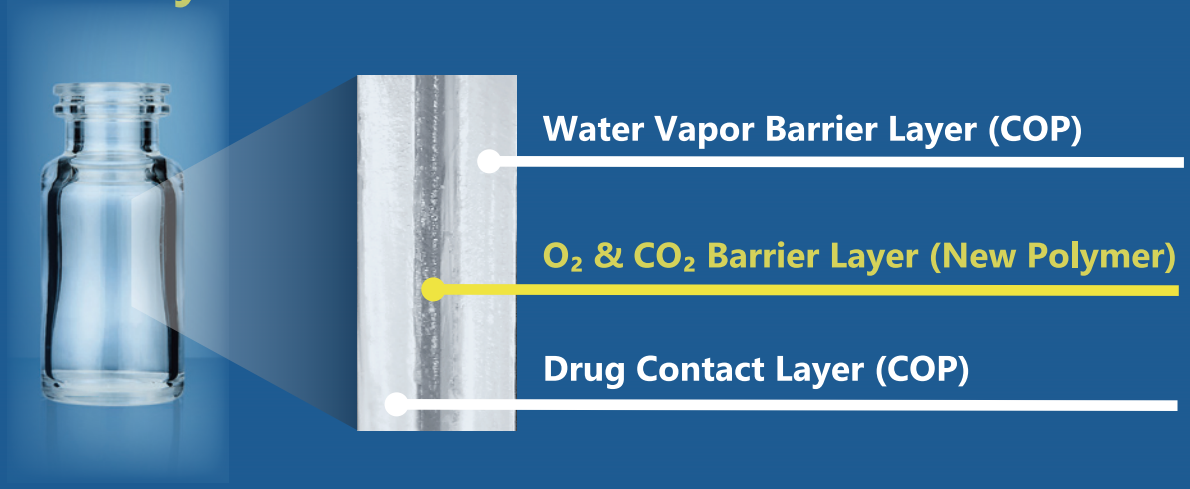

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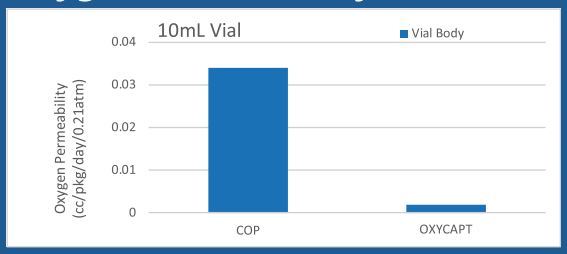

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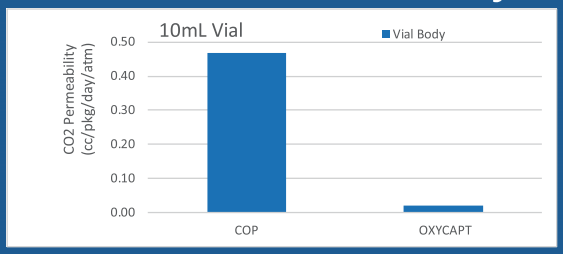

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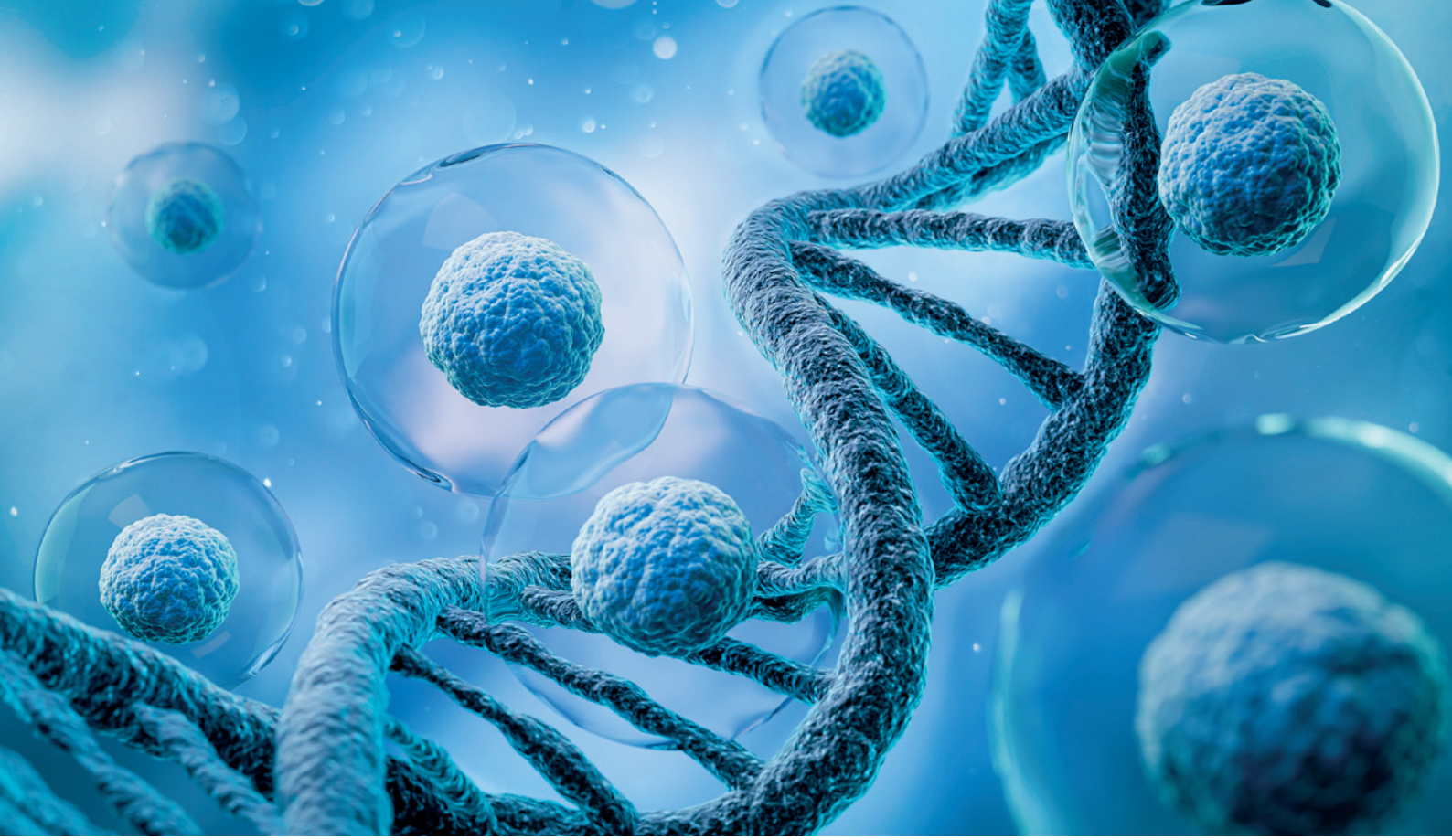

PRIMARY PACKAGING AND ADMINISTRATION OF CELL THERAPIES: CURRENT TRENDS AND CHALLENGES

Dr Krishnendu Khan and **Henry Nguyen** of **West Pharmaceutical Services**

examine factors to consider when designing and selecting primary packaging for cell therapies, exploring the effects of cryogenic storage on packaging and cells, while highlighting the diverse delivery methods and applications for these therapies.

Cell therapies have emerged as a revolutionary approach in modern medicine, offering potential cures for a wide range of diseases, including cancer, autoimmune disorders and genetic conditions. Despite their promise, the containment and administration of cell-based products present significant technical, regulatory and logistical challenges.

The packaging of cell-based products plays a critical role in ensuring the safety, viability and functionality of therapeutic cells from production to bedside administration. As cell therapies continue to advance, innovations in primary packaging have emerged, addressing key challenges while setting the stage for future developments.

At present, all approved cell therapies are autologous, intended for individual patients, and frequently use cryobags as their primary packaging. As attention shifts increasingly towards developing allogenic therapies – which entail significantly larger batch sizes – cryobags may not be suitable for fill-finish operations. Consequently, vials are expected to become the predominant form of primary packaging. This transition will necessitate a significant focus on selecting the appropriate form factor and materials for vial manufacturing to ensure compatibility with these advanced drug products, while also maintaining container closure integrity (CCI) at cryogenic temperatures. Once packaged, clinical application of these drugs involves several intricate processes, particularly administration, which has not yet been standardised for allogenic therapies that are currently in development for various indications.

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"POLYMERIC VIALS HAVE SUPERIOR BREAK RESISTANCE UNLIKE GLASS AND USUALLY HAVE A LOW EXTRACTABLES AND LEACHABLES PROFILE, WHICH REDUCES CONTAMINATION RISKS."

CURRENT TRENDS IN PRIMARY PACKAGING

Cryobags and Polymeric Vials

Cryobags and polymeric vials remain the most widely used primary packaging options for autologous and allogenic cell therapy products. Cryobags are usually made up of ethylene vinyl acetate, fluorinated ethylene propylene or polyolefin-based films. These provide several key advantages, including flexibility, biocompatibility, excellent chemical resistance and reduced gas permeability, depending on the material chosen. The size and port configurations can also be customised, making them adaptable to different cell therapy workflows. One of the major advantages of cryobags is their compatibility with closed system processing that minimises contamination risks.

Vials used in cell therapy however are made up of either cyclo-olefin polymer, cyclo-olefin copolymer, or polypropylene. Polymeric vials have superior break resistance unlike glass and usually have a low extractables and leachables profile, which reduces contamination risks. These containers are also designed to withstand the ultra-low temperatures required for cryopreservation, maintaining cell viability during storage and transport. They are not only sterile and single use but also suitable for both small-scale clinical trials and large-scale commercial production.

Single-Use Systems

Single-use systems include pre-sterilised, disposable components that can be easily replaced between each batch run, not only saving time but also reducing contamination risks. These include a single-use mixing system for buffer and media preparation, single-use bioreactors that are used for cell expansion, single-use tubing and connectors that enable closed-system fluid transfer during cell culture, expansion, washing and final formulation, and single-use fill-finish accessories for final packaging. Single-use technologies, such as pre-sterilised vials and bags, offer streamlined workflows and eliminate the need for cleaning and sterilisation processes. These systems are particularly beneficial for faster turnaround and for regulatory compliance as they support good manufacturing practice (GMP) and US FDA guidelines.

Integrated Monitoring Features

Innovative packaging solutions now often incorporate sensors and monitoring devices that can track temperature and other critical parameters during storage and transportation. Real-time temperature sensors coupled with wireless, cloud-based temperature loggers can ensure that cryopreserved or refrigerated products remain within required temperature ranges. Integrating radio-frequency identification with vials and cryobags can further enable chain-of-custody tracking of cell therapy drug products. Labels that gradually change colour as the packaging material experiences elevated temperatures are a simple but effective monitoring tool. These features enhance quality control and provide real-time data to ensure the integrity of cell-based products.

Automation-Ready Packaging

With the growing need for scalability, automation-compatible packaging solutions are gaining traction. Automated filling and sealing systems not only reduce human error but also enhance the efficiency of packaging processes. ISO-compliant vials in ISO-compliant packaging (in tubs or nests) allow for seamless integration of the components in diverse fill-finish equipment. Combined with the aforementioned features of cryogenic compatibility and cold chain stability of primary packaging components, as well as integration of monitoring technology, automation will allow for scalability, enhanced product integrity, cost efficiency, regulatory compliance and, ultimately, improved patient safety. These elements are crucial not only for currently approved autologous therapies but also for the extensive scale-up and scale-out of the manufacturing processes that will be necessary for future allogenic therapies.

CURRENT CHALLENGES IN PRIMARY PACKAGING

Form Factor and Material Compatibility

The presence of different vial and bag form factors can add challenges when standardising the packaging process. Non-standard bags or vial shapes may not be compatible with all automated filling, freezing and thawing systems. For early-stage clinical settings, variation in form factor might lead to failures in sealing and crimping of bags and vials, respectively, if suitable training is not provided.

The use of different materials for bag and vial manufacturing is also a deterrent in the standardisation process. Selecting materials that are biocompatible and cryogenically stable is a major challenge. Packaging materials must ensure the stability of cells while preventing any leaching of harmful substances that could compromise product quality. As allogenic cell therapies are stored at cryogenic temperatures for extended periods, there is a risk of gas permeation through the packaging material. To ensure drug stability, it is important to develop a vial material with enhanced barrier properties, which can be achieved through the application of special coatings or the use of a multi-layer system. Establishing standardised materials and formats for primary packaging systems will ensure that the integrity of these advanced drug products is maintained.

"ESTABLISHING STANDARDISED MATERIALS AND FORMATS FOR PRIMARY PACKAGING SYSTEMS WILL ENSURE THAT THE INTEGRITY OF THESE ADVANCED DRUG PRODUCTS IS MAINTAINED."

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Scalability

Scaling up cell therapy production presents unique challenges in primary packaging, as it must balance product integrity, sterility, regulatory compliance and automation readiness. Effective primary packaging solutions must support early-stage clinical trials through to commercial manufacture, all while enabling seamless transitions to higher throughput operations.

Early-stage manufacturing for clinical studies often employs manual filling, sealing and labelling, which evolves as the manufacturing process is scaled up/out due to increases in demand. This then requires automated filling, controlled cryopreservation process and tracking to reduce variability between batches. Adoption of robotics-compatible formats early in the drug development process alongside the use of pre-validated, automation-ready consumables ensures a seamless transition from small- to large-scale operations. Furthermore, enhanced implementation of digital tracking and use of GMP-compliant, pre-validated packaging – which is currently lacking across different manufacturing processes – can help to address the challenges associated with scalability further.

Regulatory Compliance

The regulatory requirements for cell therapies are still evolving with each approved product. At present, US Pharmacopeia (USP) Chapter <1207> serves as a guideline on maintaining the integrity of sterile packaged products, with a particular focus on CCI and leakage. Additionally, in 2024 the FDA released several guidance documents for cell therapy products, offering recommendations on topics such as drug chemistry, manufacturing and controls.

As the field matures, more stringent guidelines surrounding sterility, extractables and leachables testing, cryopreservation stability validation and chain of custody for strict traceability will come into place. Standardisation of packaging designs and validation processes is necessary to ensure compliance and facilitate international distribution. It is therefore essential to choose packaging materials with proven biocompatibility for direct cell contact. Furthermore, implementing standardised chain of custody tracking that is cryo-compatible further streamlines the compliance process.

Cryopreservation Challenges

Cryopreservation techniques place unique demands on primary packaging as they involve maintaining CCI at extremely low temperatures (approximately -196°C). The primary container material should not only maintain its integrity but also preserve cell viability at such temperatures.

Due to their heat transfer properties, the materials used in vial manufacturing can significantly impact the cooling rate

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during the freezing process. This, in turn, may influence how rapidly or slowly the cells are frozen in the cryo buffer, thereby affecting their viability. Many polymers become brittle and crack at cryogenic temperatures, increasing the risk of leaks and microbial contamination.

Most cryobuffers used in cell therapies contain dimethyl sulphoxide, which can have unfavourable interactions with the packaging material, resulting in the release of extractables and leachables into the drug product. In addition, the diverse form factor of different packaging materials can affect controlled freezing and thawing rates that are critical for cell survival. The material should be able to maintain integrity during transient warming that could occur at any time during transportation before administration to ensure drug stability.

Another crucial aspect to consider is selecting label materials with low leachable properties. As the primary packaging undergoes freezing and thawing across a wide temperature range, the risk of adhesive migration from the label to the drug product increases. Condensation that forms during thawing can also compromise labels, negatively affecting the chain of custody. Therefore, performing extractables and leachables testing and choosing the appropriate label for these therapies is critical.

Finally, the form factor should be compatible with current cryopreservation techniques. These therapies should take up minimal space in storage tanks; space being a limiting factor as scale up expands. Identifying materials and form factor of the primary packaging that can address the issues above will ensure safe storage and transport of fully effective cell therapies.

Environmental Impact

Employing single-use plastics in primary packaging raises concerns about environmental sustainability and leads to the generation of biomedical waste that is difficult to recycle. Moreover, maintaining ultra-low temperatures demands significant energy, increasing the carbon footprint of cell therapies. Containers holding live human cells require specialised disposal procedures, further contributing to environmental concerns. Therefore, developing new materials that are not only biocompatible but also biodegradable or reusable can be an alternative. Making cold chain systems more efficient through optimised transport and storage solutions can also be a way to reduce environmental impact. Finally, using sustainable adhesive and non-toxic inks for labelling purposes can go a long way. Balancing the safety and efficacy of cell therapy packaging with environmental sustainability remains a challenge. However, current innovations are helping to minimise ecological footprint while maintaining strict regulatory compliance and product integrity.

"CONTAINERS HOLDING LIVE HUMAN CELLS REQUIRE SPECIALISED DISPOSAL PROCEDURES, FURTHER CONTRIBUTING TO ENVIRONMENTAL CONCERNS. THEREFORE, DEVELOPING NEW MATERIALS THAT ARE NOT ONLY BIOCOMPATIBLE BUT ALSO BIODEGRADABLE OR REUSABLE CAN BE AN ALTERNATIVE."

CURRENT TRENDS AND CHALLENGES IN CELL THERAPY ADMINISTRATION

Intravenous Infusion

Intravenous (IV) infusion is the most common method for delivering cell-based therapies. It involves the injection of therapeutic cells directly into the patient's bloodstream through a vein, allowing for systemic distribution. This method is widely used in haematopoietic stem cell transplantation and chimeric antigen receptor T-cell therapy, such as the FDA-approved drug products Kymriah® (Novartis) and Yescarta® (Kite Pharma, Santa Monica, CA, US). Key advantages of IV infusion include its simplicity, high repeatability and minimal invasiveness; however, systemic delivery may lead to off-target effects or low cell retention in the desired tissues.

Intramuscular Injection

Intramuscular (IM) injection is often used for localised delivery of cell therapies, such as mesenchymal stem cells (MSCs) for muscle repair or regenerative applications for conditions such as amyotrophic lateral sclerosis (ALS), where muscle wasting is common (e.g. Study ID: NCT02017912). The IM route offers controlled delivery to the target tissue and improved cell engraftment in specific cases. However, IM injections are limited by the low volume of cells that can be injected, thus restricting their use.

Intra-Articular Injection

Intra-articular (IA) injections are employed for conditions affecting the joints. Cells are directly injected into the joint space to promote cartilage repair and to reduce inflammation. There are a number of clinical trials examining the safety and efficacy of MSC administration via IA injections for treatment of osteoarthritis (e.g. Study ID: NCT03477942). This localised approach minimises systemic exposure and maximises therapeutic effects at the site of injury.

Intrathecal and Intraventricular Administration

For neurological disorders, cell therapies are often delivered via intrathecal (into the spinal canal) or intraventricular (into the ventricles of the brain) routes. These methods bypass the blood-brain barrier, enabling direct access to the central nervous system. Examples include the administration of neural stem cells for spinal cord injuries and neurodegenerative diseases such as Parkinson's disease or ALS. In a clinical trial completed in 2024, a single, combined intramuscular and intrathecal administration of MSCs for the treatment of ALS was proven to be safe with promising signs of efficacy (Study ID: NCT02017912).

Endoscopic or Catheter-Based Delivery

For targeted delivery to internal organs or specific tissues, endoscopic or catheter-based methods are employed. Endoscopic approaches facilitate precise administration for gastrointestinal or pulmonary

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conditions, while catheter-based delivery is commonly used for cardiac cell therapy, where cells are injected directly into the myocardium. In a completed Phase I trial (Study ID: NCT00314366), aldehyde dehydrogenase bright stem cells were harvested from the bone marrow of patients with ischaemic cardiomyopathy and reinjected via a catheter into the heart.

Hydrogel and Scaffold-Based Delivery

Hydrogels and scaffolds act as carriers for therapeutic cells, allowing for localised and sustained release at the target site. These biomaterials enhance cell viability and retention, particularly for regenerative medicinal applications in tissues such as bone, cartilage and skin. At the clinic, these delivery systems are prepared and implanted in co-ordination with surgical procedures.

While there has been significant progress made with this method of administration, there are still hurdles that prevent its clinical application. Namely, the biosafety and the biological degradation mechanism of these complex biomaterials pose significant challenges. Clinical trials looking at hydrogel and scaffold-based delivery are predominantly at early stages with a focus on safety. For instance, in a Phase II trial currently at its recruitment stage (Study ID: NCT04396899), the safety and efficacy of induced pluripotent stem cell-derived cardiomyocytes and stromal cell-laden hydrogel are being explored for heart failure.

"EFFORTS ARE UNDERWAY TO DEVELOP DELIVERY DEVICES THAT CAN SAFELY ADMINISTER CELL THERAPIES THROUGH THESE DIFFERENT ROUTES, AND STANDARDISING PRIMARY PACKAGING WILL FACILITATE THE DEVELOPMENT OF SUCH DEVICES."

Inhalation

Inhalation is an emerging method for delivering cell-based treatments to the lungs. Cells are aerosolised and delivered non-invasively via nebulisers or inhalers, targeting pulmonary diseases such as chronic obstructive pulmonary disease or acute respiratory distress syndrome. In a completed Phase I trial (Study ID: NCT04276987), aerosol inhalation of exosomes derived from allogenic MSCs for treatment of severe novel coronavirus pneumonia resulted in no adverse effects or toxicity. As more drug products are currently being tested, it remains to be determined whether aerosolisation impacts their integrity and efficacy.

CONCLUSION

Primary packaging is a critical component in the cell therapy value chain, ensuring the safe and effective delivery of therapeutic cells. Advances in cryopreservation, single-use systems and integrated monitoring have significantly improved the reliability of packaging solutions. However, challenges related to scalability, regulatory compliance and sustainability must be addressed to meet the growing demands of the field. Collaborative efforts amongst researchers, manufacturers and regulators will be essential to drive innovation and optimise packaging for the next generation of cell therapies.

Currently, all approved cell therapy drugs are administered intravenously. However, various alternative administration routes are being investigated, each presenting challenges in terms of standardisation and ensuring the precise delivery of the drug to the intended site. Efforts are underway to develop delivery devices that can safely administer cell therapies via these different routes, and standardising primary packaging will facilitate the development of such devices. As vials are being considered for the storage of allogenic therapies, creating specialised vial adapters for drug extraction and delivery devices that can integrate with vials will be crucial for optimising the entire administration process. Addressing this and associated challenges will be key to advancing the efficacy, safety and accessibility of cell-based therapies in the future.

Dr Krishnendu Khan

Krishnendu Khan, PhD, is Senior Manager, Advanced Therapies Innovation & Strategy at West. He serves as a subject matter expert in cell and gene therapy primary packaging and administration, spearheading West's efforts in this area. Dr Khan earned his PhD in Biochemistry from the Indian Institute of Science (Bengaluru, India), after which he engaged in post-doctoral research in Germany and the US. Before joining West, he was active in the commercialisation of innovative biologics and diagnostics.

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Henry Nguyen, Associate Scientist, West, is a CCI subject matter expert for the Advanced Therapies group, supporting initiatives for primary packaging and delivery of cell and gene therapies. Mr Nguyen received his master's degree in Biomedical Engineering from Drexel University (Philadelphia, PA, US).

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Expert View

DRUG DELIVERY DEVICE INNOVATION IN CELL AND GENE THERAPIES

Dr Alejandra Sanchez and **Charlie Dean**, both of Cambridge Consultants, consider the evolution of drug delivery technologies and how cell and gene therapies are showing promise as a new class of medicine to correct disease at its source.

Drug delivery devices do more than deliver medicine into the body – they enable breakthroughs in treatment. Their evolution has always been closely tied to the therapies they support and the diseases they treat. As medicine has moved from pills to complex biologics, and now to cutting-edge cell and gene therapies (CGTs), the ways that these treatments are delivered have had to keep up. For pharmaceutical companies, device developers and innovators in the drug delivery space, the advent of CGTs presents a turning point full of exciting challenges.

EVOLUTION OF DRUG DELIVERY TECHNOLOGIES

For decades, small molecules dominated medicine – stable compounds primarily administered as pills and easily absorbed through cell membranes. When biologics arrived, they rewrote the rules. These large, delicate molecules cannot survive the gut, which makes oral delivery mostly impossible and injections essential.

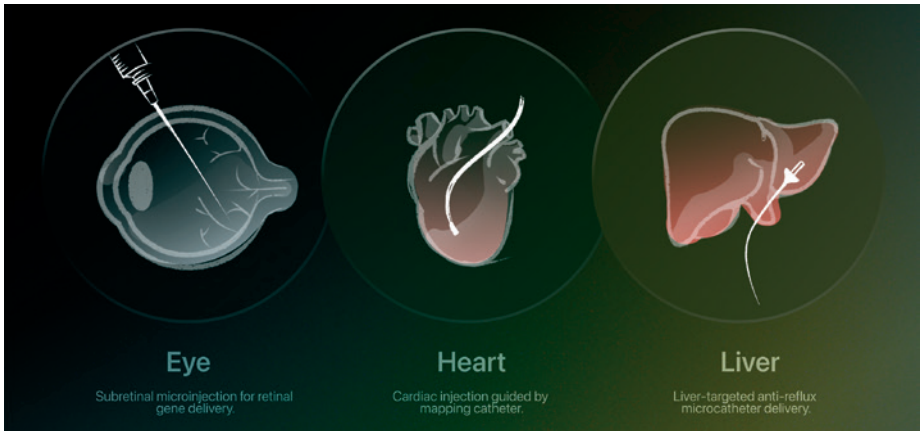

Figure 1: Precision routes for CGTs – tailored delivery systems are designed to accurately target specific organs and tissues.

> "THE ONGOING BIOLOGICS BOOM OVER THE PAST DECADES SHOWS WHAT EFFECTIVE COLLABORATION AND INNOVATION CAN ACHIEVE."

The ongoing biologics boom over the past decades has shown what effective collaboration and innovation can achieve. The need to improve adherence and the patient experience drove the development of autoinjectors, pen devices and connected drug delivery systems. Features such as needle safety, variable dosing and temperature monitoring transformed treatment, making it safer, more reliable and more convenient. These advances did not just improve care; they enabled new commercial models and patient-engagement strategies that reshaped entire markets.

Now, as the industry enters the era of CGTs, the stakes are even higher. The need for user-centric innovation remains, but the complexity, cost and risk demand solutions that go far beyond what has worked before.

THE CHALLENGE OF LIVING MEDICINES

CGTs represent a new class of medicine – living or genetic treatments that repair, replace or reprogram cells to correct disease at its source. Unlike traditional drugs, these therapies are not mass-produced or repeatedly dosed. They are

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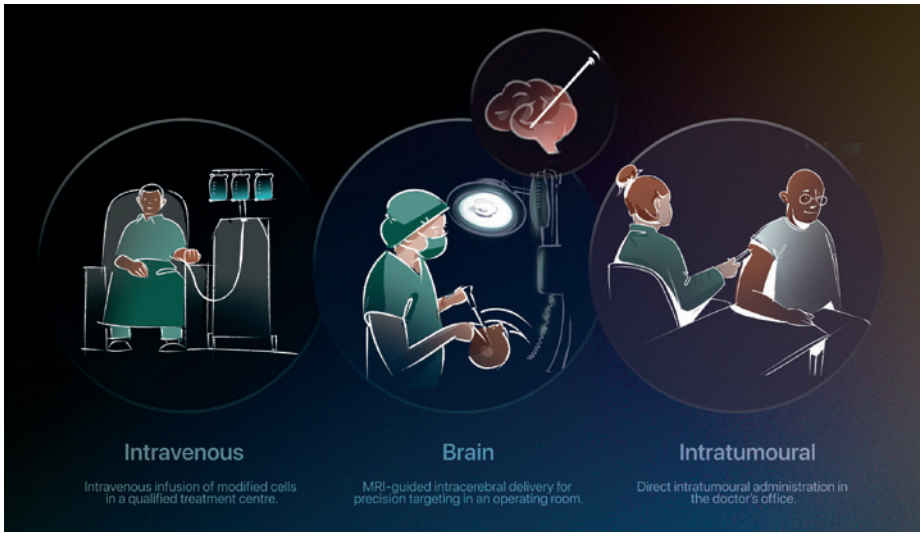

Figure 2: Each therapy requires a specialised clinical setting for safe and effective delivery.

usually tailored to individual patients and delivered as one-time, potentially curative interventions, often described as "one-and-done" solutions.

Delivering such treatments, however, is far from simple. CGTs are fragile, some of them requiring cryogenic storage and careful handling to preserve viability. Even administration poses unique hurdles – most must be infused by specialists in controlled environments, sometimes directly into target tissues such as the retina, liver or heart (Figures 1 & 2).

Precision and protection are everything. While many existing CGTs are delivered via intravenous infusion, others require highly specialised devices to ensure accuracy and cell viability. For instance, chimeric antigen receptor t-cell (CAR-T) therapies, such as KYMRIAH (tisagenlecleucel, Novartis) and Yescarta (axicabtagene ciloleucel, Kite Pharma, Santa Monica, CA, US), are administered as one-time intravenous infusions within certified treatment centres under strict handling protocols. In contrast, LUXTURNA (voretigene neparvovec-rzyl, Spark Therapeutics, Philadelphia, PA, US) is delivered under anaesthesia in a controlled surgical environment using a customised subretinal injection tool and advanced vitreoretinal techniques. Similarly, KEBILIDI (eladocagene exuparvovec-tneq, PTC Therapeutics, Warren, NJ, US) requires precise intraputaminal administration, involving the creation of a small entry point through the skull and dura to safely reach the target brain region.

Technology is pushing the boundaries even further. Mapping catheters are now being explored to guide cardiac injections with millimetre accuracy, while hepatic-artery and intracoronary microcatheters enable precise gene delivery to the liver and heart. Anti-reflux microcatheters, which temporarily block blood flow to prevent vector leakage, are also improving targeting efficiency.

Most currently approved CGTs focus on rare diseases, but the next wave aims to tackle more common conditions such as Parkinson's disease and dementia. In the UK alone, the number of patients eligible for these treatments could rise from 2,500 in 2021 to around 10,000 per year by 2028.[1] As these therapies scale, delivery will need to become safer, more efficient and more accessible.

FUTURE OUTLOOK: BEYOND SPECIALISED CLINICS

Inspired by delivery systems for small molecules and biologics, advanced therapies are now edging closer to patients with greater safety and precision (Figure 3). Emerging platforms – from microneedle

"PRECISION AND PROTECTION ARE EVERYTHING. WHILE MANY EXISTING CGTS ARE DELIVERED THROUGH INTRAVENOUS INFUSION, OTHERS REQUIRE HIGHLY SPECIALISED DEVICES TO ENSURE ACCURACY AND CELL VIABILITY."

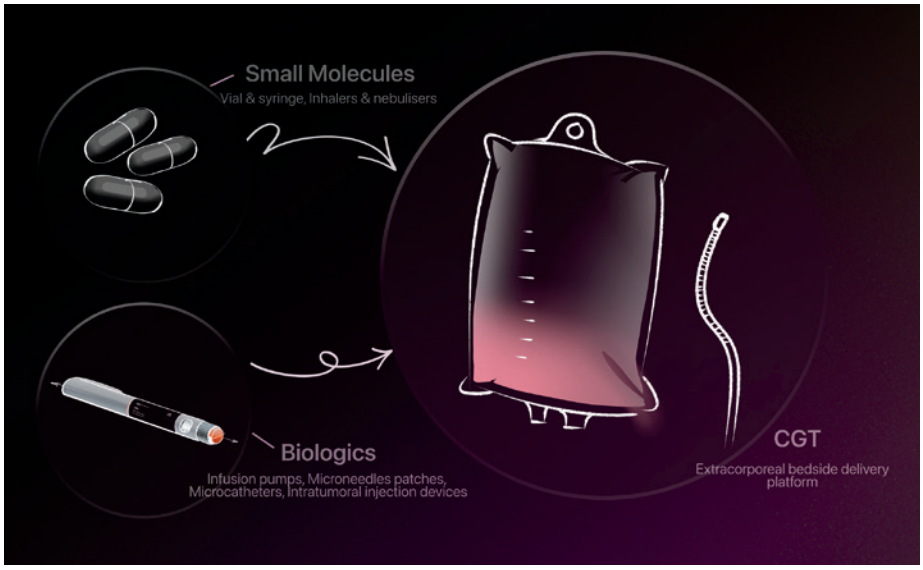

Figure 3: Examples of systems once built for more conventional therapies that are now being reimagined for cell and gene treatments, with new innovations still unfolding as these therapies advance.

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patches delivering complex biologics, such as RNA payloads, to wearable injectors for large-volume infusions and inhaled gene therapy systems – are beginning to redefine what is possible. Bedside delivery systems are also being developed to enable both *in vivo* and *ex vivo* treatments directly at the point of care. While many of these technologies remain in early stages, they signal a clear shift towards decentralised care, where device engineering, formulation science and digital health converge to make CGTs more scalable, accessible and patient centric.

THE NEXT CHAPTER IN CGT

While the experience gained from biologic drug delivery offers valuable insights for CGTs, these advanced treatments require a fundamentally different approach. With biologics, treatments are typically used for chronic conditions, where patient convenience, usability and long-term adherence are key to therapeutic success. In contrast, CGTs are often one-time, highly personalised interventions, where the priority shifts to safeguarding the viability, sterility and potency of living cells or viral vectors.

Unlike conventional medicines, most CGTs are "one-and-done" therapies, where a single dose can correct a genetic fault for life. This changes everything. Success is no longer about adherence or cost efficiency but about protecting the therapy's integrity from the moment it leaves the manufacturing line (or the patient or donor's body) until it reaches its destination. Every step – storage, transport, thawing and infusion – must safeguard the therapy's potency and stability.

To meet this challenge, next-generation devices are being engineered to protect delicate materials from mechanical and thermal stress by using low-shear pumping, temperature-controlled flow paths, and integration with cryogenic storage and thawing systems. Closed, single-use designs now minimise contamination risk, while embedded sensors and connected data platforms enable real-time tracking and control throughout the therapy's journey.

Looking ahead, innovation will hinge on simplifying complexity while maintaining viability. Redesigning delivery routes, whether for the brain, retina or heart, requires sub-millimetre precision and image-guided accuracy, yet future progress may come from rethinking administration itself – exploring minimally invasive or alternative routes, closed-loop systems and intelligent feedback mechanisms that could one day make bedside, or even at-home, CGT delivery possible.

Ultimately, the further evolution of delivery technology will determine how far these therapies can go. For CGT, the device is no longer just a vessel, it is the guardian of the cure and a critical enabler of therapeutic success.

ABOUT THE COMPANY

Cambridge Consultants, part of Capgemini Invent, helps clients to transform opportunities for innovation into market-ready solutions. The company's deep technical expertise spans inhalers, injectors, connected platforms and more. By integrating engineering, design, human factors, sustainability and digital health, Cambridge Consultants strives to improve patient outcomes and adherence with scalable and defensible technologies. Backed by over 750 engineers, scientists and designers across offices in Cambridge (UK), Boston (MA, US), Tokyo (Japan) and Singapore, the company brings cross-sector insights and advanced technologies to create robust, future-ready devices. Partnering with healthcare and life sciences companies, Cambridge Consultants delivers breakthroughs that redefine what is possible in drug delivery.

REFERENCE

1. *"Unlocking access to future ATMPs in the UK: Comparing international approaches". ABPI, Jul 2024.*

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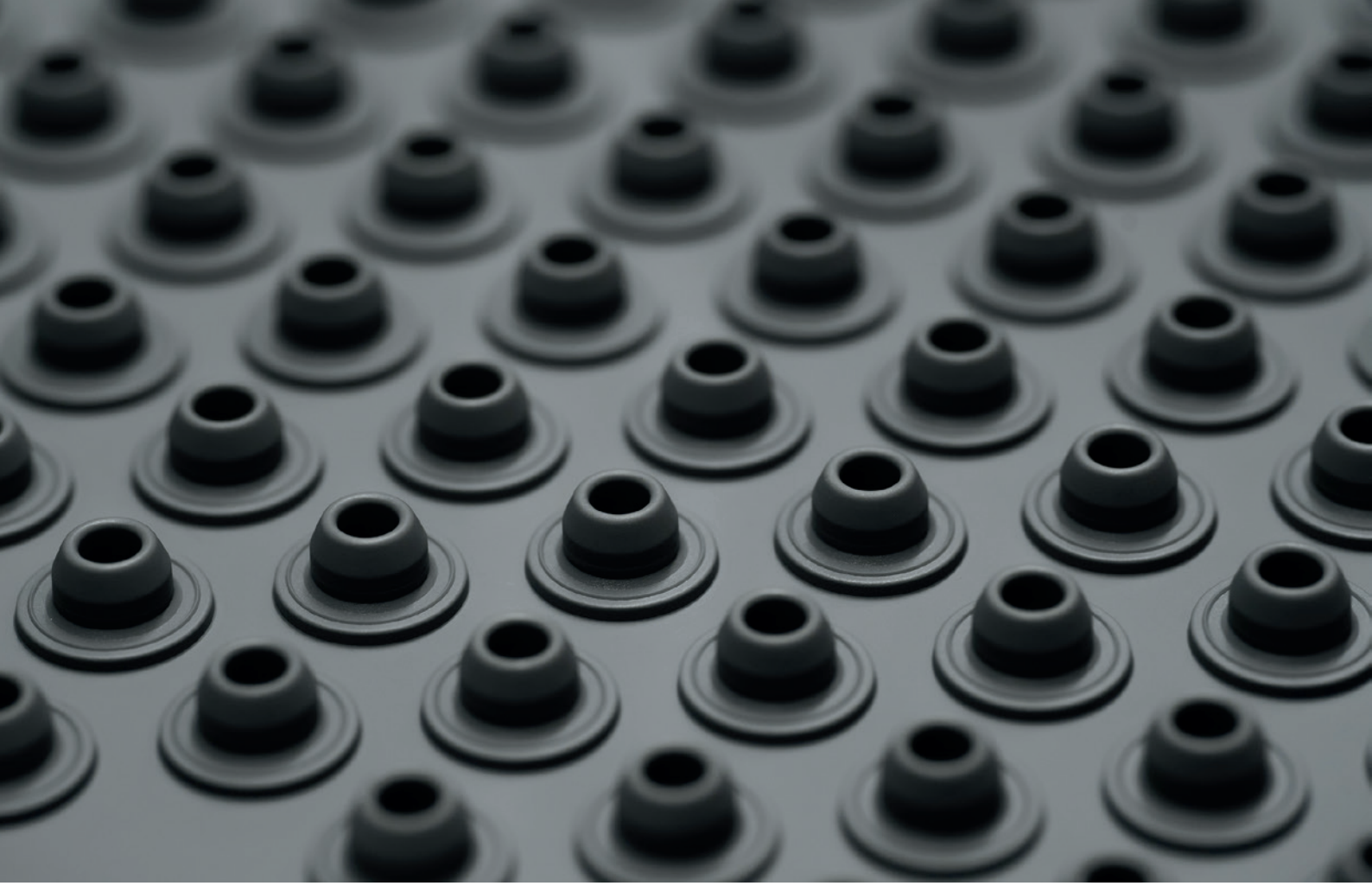

EVOLVING ELASTOMER STOPPER TECHNOLOGIES FOR A CHANGING REGULATORY LANDSCAPE

Dr Laure-Hélène Guillemot and **Edouard Pagnoud**, both of **Aptar Pharma**, assess the impact of the per- and polyfluoroalkyl substances ban on elastomer stoppers and the resulting extractables and leachables challenges, highlighting how Aptar Pharma is developing new solutions to meet both regulatory expectations and customer needs.

In parenteral drug delivery, extractables and leachables (E&L) continue to be one of the most critical considerations for scientists and regulatory authorities alike. As drugs become increasingly complex, the integrity of the packaging system directly influences both product efficacy and patient safety.[1]

Within this framework, elastomeric stoppers and plungers play a pivotal role in maintaining container closure integrity and drug stability.[1] However, as they are the primary interface between the drug product and packaging materials, there is potential for unwanted chemical migration.[2]

The evolving regulatory landscape, notably the global movement towards restricting per- and polyfluoroalkyl substances (PFAS), is reshaping material strategies and accelerating innovation across the parenteral packaging industry (ECHA, Annex XV, 2023).[3,4]

IMPACT OF EXTRACTABLES & LEACHABLES

Traditional Migration Dynamics

Chemical migration between the stopper surface and the drug product occurs primarily through direct contact, particularly in liquid and long-term formulations.[2,5] Migration can occur bidirectionally:

- **Drug-to-Stopper Migration:** API or formulation excipients can diffuse into the elastomer matrix, which can lead to chemical degradation of the stopper, changes in physical properties or altered

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surface characteristics. Such interactions can reduce drug potency or modify release profiles, ultimately compromising therapeutic performance.[5,6]

- **Stopper-to-Drug Migration:** Additives, vulcanising agents, lubricants, plasticisers and other constituents of the elastomer can leach into the drug solution. These leachables can interact chemically with the API, leading to degradation, loss of bioactivity or the formation of impurities. In some cases, they may elicit immunogenic or toxic responses, resulting in serious patient safety concerns.[2,6,7]

Consequences for Safety and Efficacy

The implications of E&L dynamics are multifaceted, encompassing both scientific and operational challenges. Leachables or degradation products can lead to reduced drug efficacy or altered pharmacokinetics, directly impacting therapeutic performance.[2] In some cases, these unwanted interactions may cause unexpected adverse reactions in patients, posing potential safety risks.[2]

From a compliance standpoint, regulatory non-conformance can lead to batch rejection or delayed product approval.[5] Moreover, the need for additional testing, reformulation or product recalls can significantly increase costs and extend development timelines, making proactive E&L control a critical element of both quality assurance and risk management in parenteral packaging.

> "LEACHABLES OR DEGRADATION PRODUCTS CAN LEAD TO REDUCED DRUG EFFICACY OR ALTERED PHARMACOKINETICS, DIRECTLY IMPACTING THERAPEUTIC PERFORMANCE."

Given these risks, global regulatory bodies are now increasing scrutiny on E&L profiles in parenteral packaging systems.[8] Advanced analytical techniques such as mass spectrometry, gas chromatography-mass spectrometry (GC/MS), liquid chromatography-mass spectrometry (LC/MS) and inductively coupled plasma mass spectrometry (ICP/MS) have become standard tools for characterising material interactions and ensuring compliance.[7]

BARRIER FILMS AND THEIR ROLE IN REDUCING MIGRATION

How Barrier Coatings Work

To minimise direct contact between the elastomer and the drug product, manufacturers employ barrier films that act as chemically inert shields.[9] One of the most established solutions is ethylene tetrafluoroethylene (ETFE), used for instance in Aptar Pharma's PremiumCoat®. This coating forms a thin, highly stable film that significantly reduces extractables and limits leachables, protecting sensitive molecules from unwanted interactions.[10]

Analytical Validation

Comparative studies consistently demonstrate the benefits of ETFE-coated stoppers in reducing chemical migration. PremiumCoat®, in particular, shows lower overall extractable levels compared with an uncoated equivalent (Figure 1).

A Benchmark for Clean Performance

Formulated and engineered to the highest pharmaceutical standards, PremiumCoat® components share Aptar Pharma's proven bromobutyl formulation (6720GC), a high-purity elastomer containing few ingredients to ensure consistent chemical and mechanical properties. The ETFE coating provides an additional protective barrier between the drug product and the elastomer, further minimising the risk of interaction and contamination.

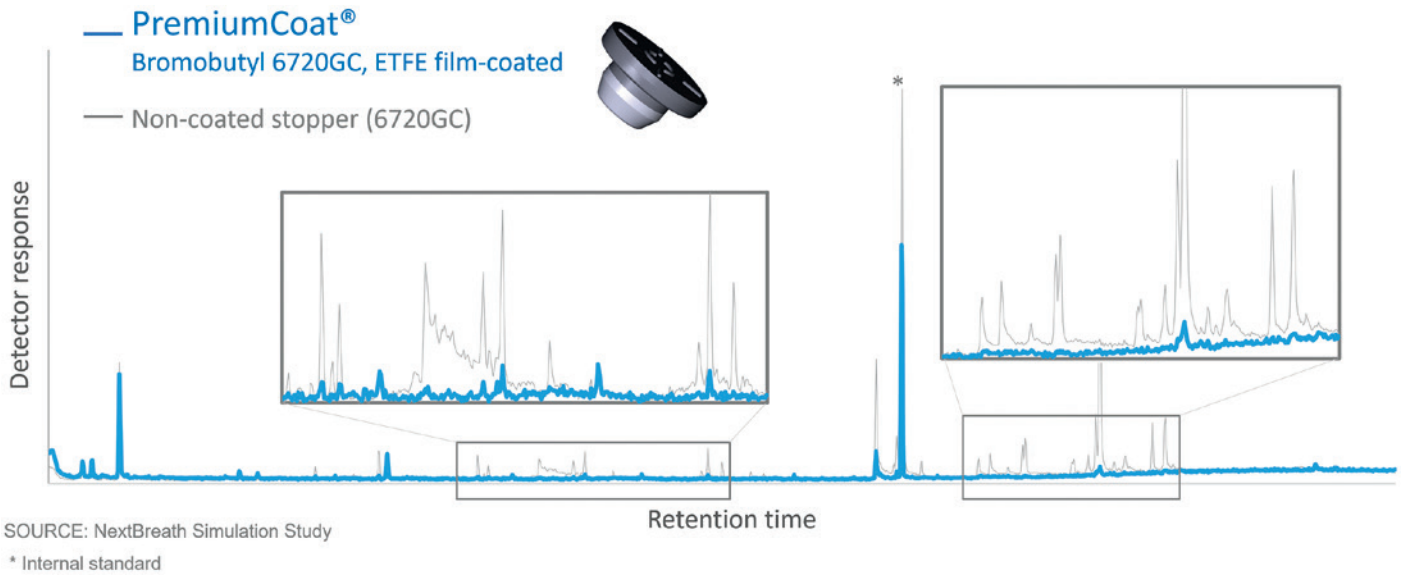

Figure 1: Chromatogram from a simulation study showing probable leachables extracted using a water–ethanol solvent system after 12 months of storage at 25°C, comparing PremiumCoat® with an uncoated stopper. The results highlight the substantially reduced extractables profile of PremiumCoat®, demonstrating the coating's effectiveness in limiting chemical migration and enhancing long-term stability compared with its uncoated version.

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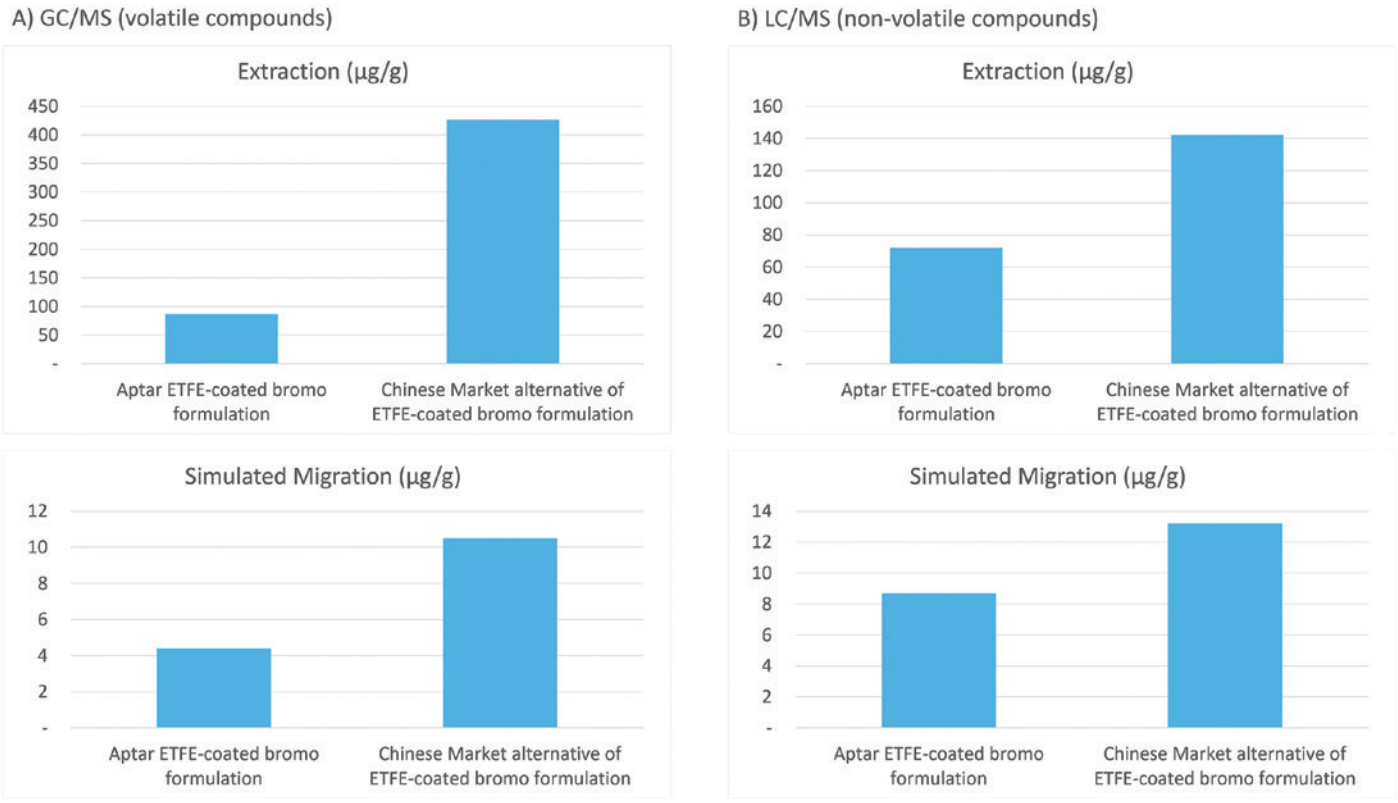

Figure 2: Analytical comparison of volatile and non-volatile E&L using GC/MS and LC/MS, including both extraction and simulated migration studies. PremiumCoat® is compared with another ETFE-coated stopper, illustrating that overall performance depends on both the barrier film and the quality of the elastomer.

This combination provides excellent chemical resistance across a broad pH range and against common solvents, while ensuring consistent E&L profiles that simplify regulatory documentation and qualification. PremiumCoat® is also compatible with standard sterilisation modes, maintaining long-term material stability and barrier performance.

To offer deeper insight into how formulation purity and barrier performance are linked, Figure 2 compares extractables and migration results for PremiumCoat® and another ETFE-coated stopper. Extractables testing primarily reflects the composition and cleanliness of the rubber base, while migration studies demonstrate the added protection provided by the ETFE coating. These results show that PremiumCoat® is superior in limiting compound transfer, largely due to the high-purity underlying elastomer. While the ETFE film reduces migration, the inherent quality of the elastomer remains the key determinant of overall performance.

"PREMIUMCOAT® IS COMPATIBLE WITH STANDARD STERILISATION MODES, MAINTAINING LONG-TERM MATERIAL STABILITY AND BARRIER PERFORMANCE."

Regulatory Context: PFAS Restrictions

PFAS substances have long been valued for their chemical resistance, low surface energy and durability in coating applications. These attributes made fluoropolymer chemistries, such as ETFE, an ideal choice for high-purity pharmaceutical packaging.[9]

In recent years, however, growing environmental and health concerns have prompted regulatory measures to limit PFAS use.[3] The EU's proposed Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) restriction and the US Environmental Protection Agency's PFAS Strategic Roadmap are pushing the industry to lower fluorine content or introduce PFAS-free solutions.[3,11] An update to the EU PFAS restriction proposal introduced a new sector – "other medical applications" – which specifically covers immediate packaging components such as fluoropolymer-coated plungers for prefilled syringes and rubber stoppers for vials. Given the low substitution potential, a 12-year derogation period following a 1.5-year transition period has been proposed for this sector. ECHA's final opinion is expected to be submitted to the European Commission by the end of 2026.[12]

For pharmaceutical packaging suppliers, the question is not only about regulatory compliance but also portfolio continuity. Depending on future exemption definitions, polymeric PFAS materials may remain permissible within strict limits (e.g. individual non-polymeric PFAS <25 ppb) or may require total substitution.[3]

The key challenge is ensuring that any transition occurs without compromising drug compatibility, safety or supply reliability.

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"THE ONGOING PFAS TRANSITION REPRESENTS BOTH A PIVOTAL CHALLENGE AND A SIGNIFICANT OPPORTUNITY FOR THE PHARMACEUTICAL PACKAGING INDUSTRY."

The Search for Alternatives

The ongoing transition away from PFAS represents both a pivotal challenge and a significant opportunity for the pharmaceutical packaging industry. As regulations evolve, finding viable alternatives demands a careful balance between performance, purity, regulatory compliance and cost-effectiveness. Achieving this balance demands a comprehensive approach that simultaneously addresses material composition and coating strategies, ensuring future solutions can match or exceed the functionality of current fluoropolymer-based systems.

Technical Requirements for New Generations of Stoppers

Future-ready elastomer stoppers must effectively manage E&L while ensuring overall stability and performance in pharmaceutical applications.[6] To achieve this, stoppers must meet functional performance expectations defined in international pharmacopoeias and ISO guidance, such as US Pharmacopeia (USP) Chapter <381>, Ph. Eur. 3.2.9 and ISO 8871-5, including fragmentation resistance, self-sealing capacity and penetrability under repeated needle penetration.[13–15] They must also maintain chemical resistance, preserve closure integrity and feature non-stick surface properties to minimise particle generation.[6,8,13]

Compatibility with multiple sterilisation methods, including steam and gamma irradiation, is essential,[13,14] as is biocompatibility in accordance with ISO 10993 and other applicable local requirements.[15] Finally, stoppers must exhibit mechanical robustness under repeated stress to ensure dependable performance throughout their lifecycle.[6,13]

Achieving this balance also depends on high processability and scalability, enabling consistent manufacturing at industrial volumes without compromising quality or sustainability.

Simplifying Base Formulations

One of the most effective pathways to lower E&L risk is to simplify the elastomer composition itself. Reducing the number of additives and optimising the curing system can lead to cleaner base rubbers with fewer potential extractables.[13]

Different elastomer families offer distinct trade-offs that must be considered:

- Chlorobutyl provides low gas permeability and excellent chemical resistance, but has more limited processability[16]
- Bromobutyl offers faster curing and good heat stability, although it can present with slightly higher extractables than chlorobutyl, depending on the specific formulation[17,18]
- BIMS delivers outstanding gas barrier properties but comes with more complex processing requirements.[19,20]

Choosing the right base requires careful evaluation of drug compatibility, coating adhesion, sterilisation methods and alignment with emerging PFAS-free strategies to ensure both performance and compliance.

"CHOOSING THE RIGHT BASE REQUIRES CAREFUL EVALUATION OF DRUG COMPATIBILITY, COATING ADHESION, STERILISATION METHODS AND ALIGNMENT WITH EMERGING PFAS-FREE STRATEGIES TO ENSURE BOTH PERFORMANCE AND COMPLIANCE."

Customer Needs and Portfolio Adaptation

For pharmaceutical companies, change management is as critical as technical performance. Customers seek continuity of supply for validated components, transparent data packages supporting comparability and regulatory filings, and predictable transition plans that minimise the need for reformulation or requalification.

Packaging suppliers such as Aptar Pharma, in turn, are adapting their portfolio to offer dual-track solutions: maintaining existing coating technologies for current markets, where compliant, while developing PFAS-free alternatives to ensure future readiness.

This approach enables pharmaceutical customers to plan transitions strategically, selecting the most appropriate materials based on regulatory timelines, drug sensitivity and risk tolerance.

Ongoing R&D Directions

With more than 50 years of experience in the development of elastomeric formulations to address existing and emerging therapeutic classes and de-risk drug development, Aptar Pharma Injectables is actively exploring fluorine-free barrier coatings that replicate the protective benefits of ETFE without relying on PFAS chemistries.

These strategies can be combined – high-purity rubber formulations with fluorine-free barrier coatings – to achieve pure, reliable elastomer solutions. Such developments aim to establish a new standard for parenteral packaging: PFAS-free, low E&L and regulatory-ready, ensuring that future elastomer systems continue to safeguard drug integrity and patient health.

CONCLUSION

The evolving regulatory landscape, particularly PFAS-related restrictions, is driving a fundamental shift in parenteral packaging design. Elastomer stoppers and plungers must now balance multiple, often competing, requirements: minimising E&L, ensuring chemical and mechanical stability, maintaining closure integrity and complying with global biocompatibility standards. Achieving this balance requires innovation in both base elastomer

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formulations and coating strategies, with simplified high-purity materials and advanced barrier films providing promising pathways towards future-ready solutions.

For pharmaceutical companies, these developments highlight the importance of proactive portfolio adaptation. Selecting stoppers that meet evolving regulatory and technical standards while supporting operational continuity is critical for safeguarding drug efficacy, patient safety and supply reliability. As research continues into fluorine-free coatings and optimised elastomer systems, the industry is moving towards a new benchmark for parenteral packaging.

REFERENCES

1. *Lv Y et al, "Pharmaceutical Packaging Materials and Medication Safety: A Mini-Review". Safety, 2025, Vol 11(3), p 69.*
2. *Cartledge B et al, "Predicting Extractables and Leachables from Container Stoppers". BioPharm International, 2020, Vol 33(8), pp 40–44.*
3. *"Annex XV Restriction Report". European Chemicals Agency, Mar 2023.*
4. *Scheringer M, "Innovate beyond PFAS". Science, 2023, Vol 381(6655), p 251.*
5. *"Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics. US FDA, May 1999.*
6. *Mathaes R, Streubel A, "Parenteral Container Closure Systems". In "Challenges in Protein Product Development" (Warne N, Mahler HC, eds). AAPS Advances in the Pharmaceutical Sciences Series, Vol 38, pp 19–202.*
7. *Sica VP et al, "The role of mass spectrometry and related techniques in the analysis of extractable and leachable chemicals". Mass Spectrom Rev, 2020, Vol 39(1–2), pp 212–226.*
8. *Kikovska-Stojanovska E, Agarwal S, "Chapter 30 - General analytical considerations for parenteral products". In "Specification of Drug Substances and Products (Third Edition)", 2025, pp 715–725.*
9. *Kushwaha P, Madan AK, "Extractables and Leachables: An Overview of Emerging Challenges". Pharmaceutical Technology, 2008, Vol 32(8).*
10. *Gardiner J, "Fluoropolymers: Origin, Production, and Industrial and Commercial Applications". Aust J Chem, 2014, Vol 68(1), pp 13–22.*
11. *"PFAS Strategic Roadmap: EPA's Commitments to Action 2021—2024". US Environmental Protection Agency, Oct 2021.*
12. *"Per- and polyfluoroalkyl substances (PFAS)". European Chemicals Agency, Jun 2024.*
13. *Hopkins GH, "Elastomeric closures*

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for pharmaceutical packaging". J Pharm Sci, 1965, Vol 54(1), pp 138–143.

14. *Straka A, "Sterilization Effects on Elastomers in Sterile Parenteral Drug Products". Pharmaceutical Technology, 2015, Vol 2015(2).*
15. *"Guidance for Industry: Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process". US FDA, Sep 2023.*
16. *Sreehari H et al, "Evaluation of solvent transport and cure characteristics of chlorobutyl rubber graphene oxide nanocomposites". Mater Today Proc, 2022, Vol 49(5), pp 1431–1435.*
17. *Gökekin Y et al, "Evaluation and characterization of different extraction methods for obtaining extractable and leachable materials from rubber stopper systems used in pharmaceutical products". Eur J Pharm Biopharm, 2025, Vol 216, art 114844.*
18. *Pöschl M, Sathi SG, Stoček R, "Tuning the Curing Efficiency of Conventional Accelerated Sulfur System for Tailoring the Properties of Natural Rubber/Bromobutyl Rubber Blends". Materials (Basel), 2022, Vol 15(23), art 8466.*
19. *Dakin JM, Whitney RA, Parent JS, "Imidazolium Bromide Derivatives of Brominated Poly(isobutylene-co-para-methylstyrene): Synthesis of Peroxide-Curable Ionomeric Elastomers". Ind Eng Chem Res, 2014, Vol 53(45), pp 17527–17536.*
20. *Jacob S et al, "Brominated isobutylene-co-paramethylstyrene with superior impermeability for tire innerliner applications". Rubber Chem Technol, 2021, Vol 94(3), pp 549–574.*

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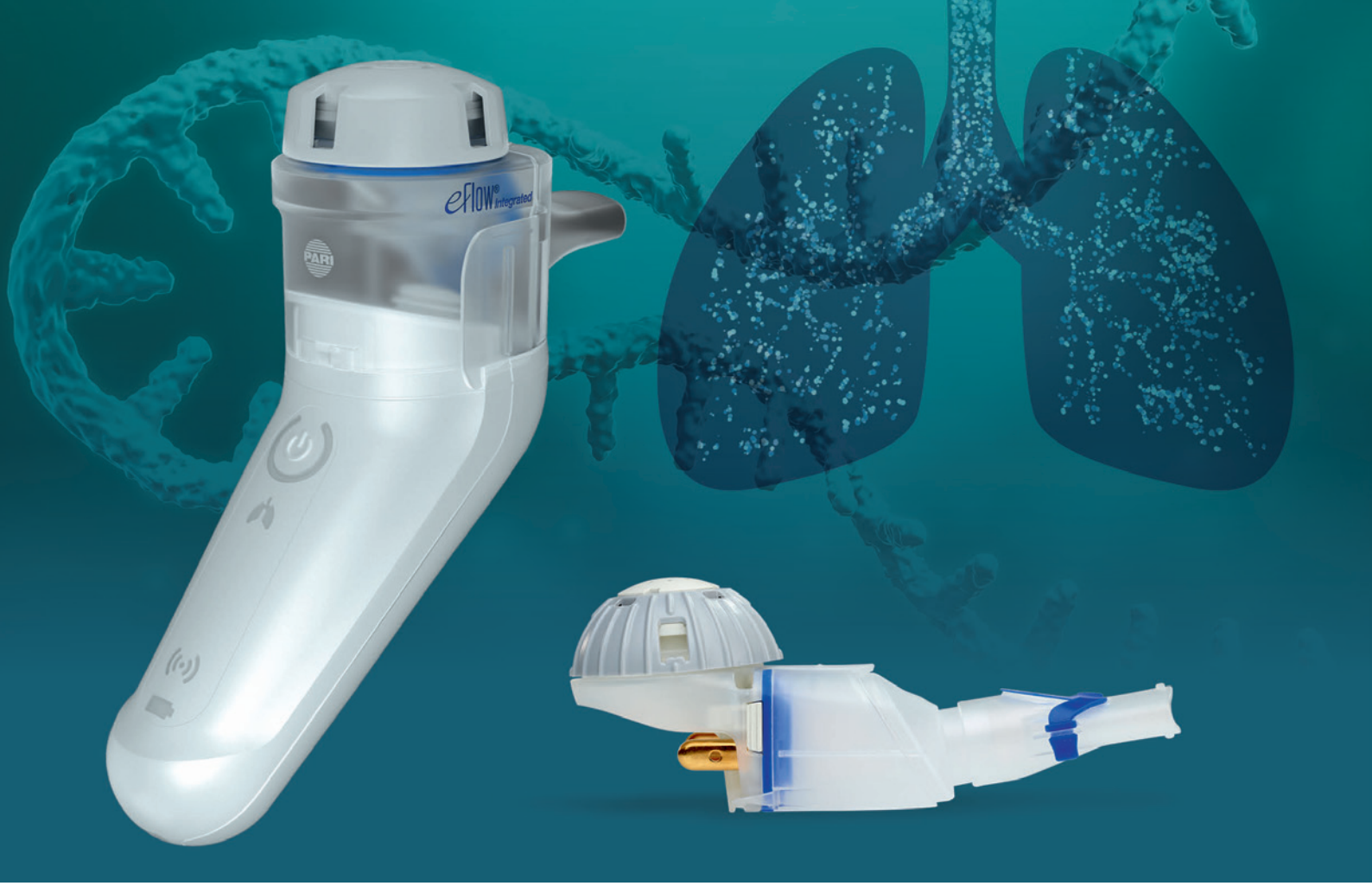

THE IMPORTANCE OF MESH NEBULISER CONFIGURATION IN mRNA-LNP DELIVERY PERFORMANCE

Hanna Beike and **Dr Benjamin Heine** of **PARI Pharma**, highlight the superior performance of customisable drug-specific nebuliser platforms, such as eFlow® Open System and eFlow® Integrated, for the delivery of messenger RNA-based inhalation therapies.

INHALABLE mRNA FOR THE TREATMENT OF RESPIRATORY DISEASE

During the covid-19 pandemic, the use of messenger RNA (mRNA) encapsulated in lipid nanoparticles (LNPs) came to the fore as new mRNA vaccines were rapidly developed, approved and rolled out in large-scale vaccination programmes. During this time, the preclinical development of inhalable mRNA vaccines was initiated, in addition to the more commonly used intramuscular injection delivery method.

In fact, inhalable mRNA was already being investigated prior to the pandemic as a potential therapy for respiratory disease, with the direct route of inhalation providing faster therapeutic effect, while reducing the extent of systemic drug exposure.

Today, numerous research programmes are underway with the aim of using inhalable mRNA therapies to treat various lung diseases including, among others, cystic fibrosis (CF), lung cancer and primary ciliary dyskinesia, with some promising early results.[1–4] For example, although not yet proven to be efficacious, interim results from a randomised placebo-controlled Phase I/II trial have shown that MRT5005 – an investigational codon-optimised cystic fibrosis transmembrane conductance regulator (CFTR) mRNA developed for treating CF and delivered by nebulisation – is generally safe and well tolerated in adults with two severe Class I and/or II CFTR mutations.[1]

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MESH NEBULISERS ARE A PREFERRED CHOICE FOR TREATING SEVERE RESPIRATORY DISEASES

Nebulisation of mRNA formulations encapsulated in LNPs presents several technical and biological challenges, including physical stability of mRNA molecules after nebulisation, fill volume and delivery efficiency, which need to be considered when selecting the appropriate nebuliser. Today, mesh nebulisers are the preferred choice when treating severe respiratory diseases,[5] and this also applies for nebulisation of mRNA.

The gentle aerosolisation mechanism of mesh nebulisers compared with other nebuliser technologies, such as ultrasonic or jet nebulisers, and the associated high delivery efficiency, favour mesh technology. The ability to better accommodate low-concentration drug formulations due to a large reservoir is an additional advantage, specifically over soft mist inhalers. This is because the latter allow only a few microlitres per puff and therefore require higher concentrations, which could limit formulation development and stability of the API. Another benefit is the ability of mesh nebulisers to deliver aerosolised formulations during normal tidal breathing, which helps to enhance patient comfort and ease of use.

Recent advances in mesh nebuliser technology have also significantly enhanced drug delivery precision and efficiency. Breath-triggered systems enable aerosol generation exclusively during stages of the inspiratory phase, thereby optimising dosing accuracy and minimising drug loss. Historically, these systems were limited by prolonged nebulisation times. However, innovations in mesh design have substantially increased aerosol output rates and, along with an innovative breath-guiding concept,[6] effectively overcome this limitation.

"NEBULISATION OF mRNA FORMULATIONS ENCAPSULATED IN LNPs PRESENTS SEVERAL TECHNICAL AND BIOLOGICAL CHALLENGES, INCLUDING PHYSICAL STABILITY OF mRNA MOLECULES AFTER NEBULISATION, FILL VOLUME AND DELIVERY EFFICIENCY, WHICH NEED TO BE CONSIDERED WHEN SELECTING THE APPROPRIATE NEBULISER."

As the following study demonstrates, the customisation of nebulisers for ideal drug delivery is an essential process. Customisation enables the correct amount of the intact API to be delivered, resulting in levels of cellular uptake and bioavailability sufficient for therapeutic efficacy.

mRNA DELIVERY PERFORMANCE OF DIFFERENT MESH NEBULISERS

A recent study compared the performance of different mesh nebulisers in the delivery of LNP-encapsulated mRNA, analysing the preservation of mRNA integrity in an indirect method, degree of drug delivery and resulting lung deposition for each device.[7]

Five vibrating mesh nebulisers were evaluated, including the drug-specific nebulisers eFlow® Integrated[6] and eFlow® Open System Type A and B (eFlow OS A/B) as well as two general-purpose devices; eFlow® rapid and Aerogen® (Galway, Ireland) Solo (Table 1). The eFlow OS A and B differ in hole geometry and the number of holes laser-drilled into the mesh. For drug-specific nebulisers, the laser-drilling parameters and therefore the hole geometry can be adapted to the drug, which is crucial for complex formulations such as LNP suspensions.

Intracellular protein expression was measured *in vitro* for both pre- and post-nebulised mRNA-LNP formulations. Device performance was evaluated using 2.5 mL of Sultanol® (salbutamol) forte (GSK) and lung deposition was analysed through multiple-path particle dosimetry (MPPD) modelling.[8]

Nebuliser	MMAD (µm)	TOR (mg/min)	GSD	DD (%)
eFlow Integrated	5.2 ± 0.2	1568 ± 31	1.8 ± 0.0	96.4 ± 2.1
eFlow OS A	5.4 ± 0.2	1223 ± 66	1.9 ± 0.0	50.9 ± 1.6
eFlow OS B	3.9 ± 0.1	1057 ± 16	1.5 ± 0.1	65.6 ± 2.5
eFlow rapid	4.8 ± 0.1	1168 ± 76	1.6 ± 0.1	28.2 ± 1.0
Aerogen Solo	4.3 ± 0.3	356 ± 27	1.9 ± 0.1	38.9 ± 1.3

DD = delivered dose; GSD = geometric standard deviation; MMAD = mass median aerodynamic diameter; TOR = total output rate.

Table 1: Nebulisers used in the study including aerosol and performance data (ISO 24724).

The eFlow Integrated Device Demonstrates Superior Drug Delivery

The analysis of delivered dose (DD) – the first hurdle of the delivery cascade – showed that the breath-triggered eFlow Integrated device was clearly superior with a DD of 96.4% compared with the other four continuous nebulisation devices, whose DD ranged from 28.2% to 65.6% (Figure 1a & Table 1).

Importantly, the difference in DD observed between the general-purpose eFlow rapid and customisable eFlow OS devices was driven not only by differences in mass median aerodynamic diameter but also by other device customisation. For example, the smaller aerosol chamber and the residual volume in the reservoir of eFlow rapid deliberately reduces the DD to prevent overdosing of drug products developed for administration in general-purpose nebulisers, thus reiterating the importance of device customisation to maximise performance for delivery of novel inhaled drug products.

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Measures of Lung Deposition are Comparable Across Devices

The second hurdle of the delivery cascade depends on the fraction actually delivered to the lung. While the degree of lung deposition estimated by the MPPD model did not vary greatly among devices (Figure 1a), ranging from 44% (eFlow OS A) to 50% (eFlow OS B, eFlow rapid), it should be noted that lung doses for the eFlow devices are likely to be underestimated. For example, for both the eFlow OS A/B and eFlow rapid, the aerosol bolus generated by the aerosol chamber led to transient aerosol output, which reduces exhalation losses and increases lung deposition.[9] Similarly, the trigger algorithm of the eFlow Integrated device halts nebulisation before the end of inspiration to minimise exhalation losses.[6] These effects are not accounted for in the MPPD model and can therefore result in underestimated lung doses.

The eFlow OS A and eFlow Integrated Nebulisers Elicit Higher Levels of Protein Expression

The third hurdle of the delivery cascade assessed the drug's intracellular activity, quantified by mean fluorescence intensity (MFI) of transfected cells. This analysis of protein expression served as an indicator of mRNA-LNP integrity following nebulisation and was compared with a pre-nebulisation sample across all five devices.

The lowest levels of protein expression (all <25% MFI compared with the non-nebulised sample) were observed with the Aerogen Solo, eFlow OS B and eFlow rapid (Figure 1a), indicating that a substantial portion of the nebulised mRNA failed to induce protein expression. In contrast, the highest expression values were obtained for eFlow OS A and eFlow Integrated (42% and 50% MFI, respectively), demonstrating greater post-nebulisation mRNA-LNP integrity and thus more effective nebulisation with these devices.

The *in vitro* protein expression analysis was selected since it offers greater insight into therapeutic efficacy than other parameters such as hydrodynamic diameter or encapsulation efficiency, capturing intracellular activity rather than just LNP characteristics.

Figure 1: (a) Fraction of drug passing each of the three hurdles of the delivery cascade (b) Cascade of usable mRNA throughout the delivery process.

In Vitro Cellular Protein Expression is Greatest with the eFlow Integrated Device

Considering all three hurdles of the delivery cascade, the delivery efficiency in terms of *in vitro* cellular protein expression can be determined (Figure 1b). The eFlow Integrated nebuliser emerged as superior, achieving levels of cellular protein expression (22%) that were over double the degree of expression achieved by the other devices. Of all the nebulisers tested, the eFlow Integrated was therefore the most effective for delivering LNP-encapsulated mRNA, followed by eFlow OS A and B. The general-purpose devices eFlow rapid and Aerogen Solo achieved the lowest levels of cell expression (3%), a finding that was also observed by van Rijn *et al* (2023).[10] In the present study, tailoring the nebuliser to the drug led to a seven-fold increase in cell expression. This finding emphasises the importance of customisation.

The eFlow Integrated Nebuliser Exhibits Rapid Drug Delivery Times

With the results of protein expression (equivalent to 1,000 mg of drug product in the lung cell) and total output rate (TOR), drug delivery times can be calculated. When comparing all five devices, the eFlow Integrated achieved the shortest delivery time of just 5.8 minutes, achieved due to high efficiency and high TOR. The longest delivery time of 90.3 minutes was found for the Aerogen Solo, reflecting low efficiency and TOR (Table 2).

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	eFlow Integrated	eFlow OS A	eFlow OS B	eFlow rapid	Aerogen Solo
TOR (mg/min)	1568	1223	1057	1168	356
Cell Expression	22%	10%	6%	3%	3%
Delivery Time (min)	5.8	8.6	15.6	25.0	90.3

Table 2: Calculated nebulisation time for an identical cell dose (1,000 mg drug product) for each nebuliser. For the triggered device the theoretical maximum duty cycle (head-on:head-off time) of 50% for the standard breathing pattern was assumed.

CONCLUSION

These findings suggest that it is crucial to select an appropriate nebuliser and configuration to achieve effective nebulisation of LNP-encapsulated mRNA and a resulting optimal cellular response.

While the performance of general-purpose nebulisers not intended for mRNAs is suboptimal, customisable drug-specific product platforms, including the eFlow OS and eFlow Integrated, demonstrate superior performance for mRNA-based inhalation therapies, resulting in highly efficient drug delivery and mRNA preservation.

The eFlow OS A and the breath-triggered eFlow Integrated nebuliser are effective for the delivery of LNP-encapsulated mRNA, indicating potential therapeutic efficacy. Nebulisation with the eFlow Integrated resulted in the highest levels of DD and *in vitro* cellular protein expression, along with displaying the fastest drug delivery time compared with the other nebulisers.

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REFERENCES

1. *Rowe SM et al, "Inhaled mRNA therapy for treatment of cystic fibrosis: Interim results of a randomized, double-blind, placebo-controlled phase ½ clinical study". J Cyst Fibros, 2023, Vol 22(4), pp 656–664.*
2. *Hu B et al, "Modulating tumor collagen fiber alignment for enhanced lung cancer immunotherapy via inhaled RNA". Nat Comm, 2025, Vol 16, art 8120.*
3. *Hennig M et al, "Inhaled DNAI1 mRNA therapy for treatment of primary ciliary dyskinesia". Proc Natl Acad Sci USA, 2025, Vol 122(18), art e2421915122.*
4. *Sarode A et al, "Inhalable dry powder product (DPP) of mRNA lipid nanoparticles". Drug Deliv Trans Res, 2024, Vol 14(2), pp 360–372.*
5. *Pritchard J et al, "Mesh nebulizers have become the first choice for new nebulized pharmaceutical drug developments". Ther Deliv, 2018, Vol 9(2), pp 121–136.*
6. *Braeunlich G, Hahn M, "Deep Breaths, Deep Dives: The New eFlow Integrated Nebuliser". ONdrugDelivery, Issue 158 (Apr 2024), pp 16–19.*
7. *Beike H et al, "Analysis of mRNA Delivery Performance via Vibrating Mesh Nebulization". DDL Conference Proceedings, 2025, Vol 36, pp 328–331.*
8. *Miller F et al, "Improvements and additions to the Multiple Path Particle Dosimetry model". J Aerosol Sci, 2016, Vol 99(13), pp 14–26.*
9. *Grill M et al, "Steady or not? Using realistic, transient aerosol parameters to predict lung deposition". DDL Conference Proceedings, 2023, Vol 34, pp 53–57.*
10. *van Rijn C et al, "Low energy nebulization preserves integrity of SARS CoV 2 mRNA vaccines for respiratory delivery". Sci Rep, 2023, Vol 13(1), p 8851.*

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Expert View

PRECISION DELIVERY: THE MISSING LINK IN CELL & GENE THERAPY

Jessica Alzamora, **Dr Karla Sanchez** and **Emily Chang**, all of Cambridge Design Partnership, discuss the necessity for precision when delivering cell and gene therapies, explore how this precision can be designed and demonstrated, then go on to describe how a minimum viable product approach to device development can act as a strong predictor of a successful delivery device.

Cell and gene therapies (CGTs) are at the forefront of precision medicine, with the potential to repair or replace faulty genes and cells to treat disease at its biological source. Despite this promise, the success of CGTs depends on one defining factor: precision. Every stage, from designing a vector to delivering it in the body, demands careful control to ensure that the treatment reaches the targeted region and/or cells, at the right dose and with minimal off-target effects (Figure 1).

A clear example of this reliance on precision comes from a currently available gene therapy to help improve functional vision in patients with an inherited retinal disease due to a genetic mutation. The approved adeno-associated virus 2 (AAV2) gene therapy Luxturna® (voretigene neparvovec) from Spark Therapeutics (Philadelphia, PA, US) must be delivered via a highly targeted subretinal injection to ensure that the therapy reaches and acts on the exact layer of cells needed for vision. Even small variations in injection depth or placement can change how effectively it restores function, and incorrect placement can increase the risk of inflammation.[1] This shows that the success of a therapy depends as much on how it is delivered as what it delivers – the therapeutic effect is dependent on the accuracy of the delivery modality.

To unlock the full potential of CGTs, the industry must not only consider molecular innovation but also focus equally on the method of precision delivery to expand the pivotal link between discovery and patient benefit. Achieving reproducible precision will determine how effectively these breakthroughs translate from rare success stories into accessible, scalable therapies.

"THIS SHOWS THAT THE SUCCESS OF A THERAPY DEPENDS AS MUCH ON HOW IT IS DELIVERED AS WHAT IT DELIVERS – THE THERAPEUTIC EFFECT IS DEPENDENT ON THE ACCURACY OF THE DELIVERY MODALITY."

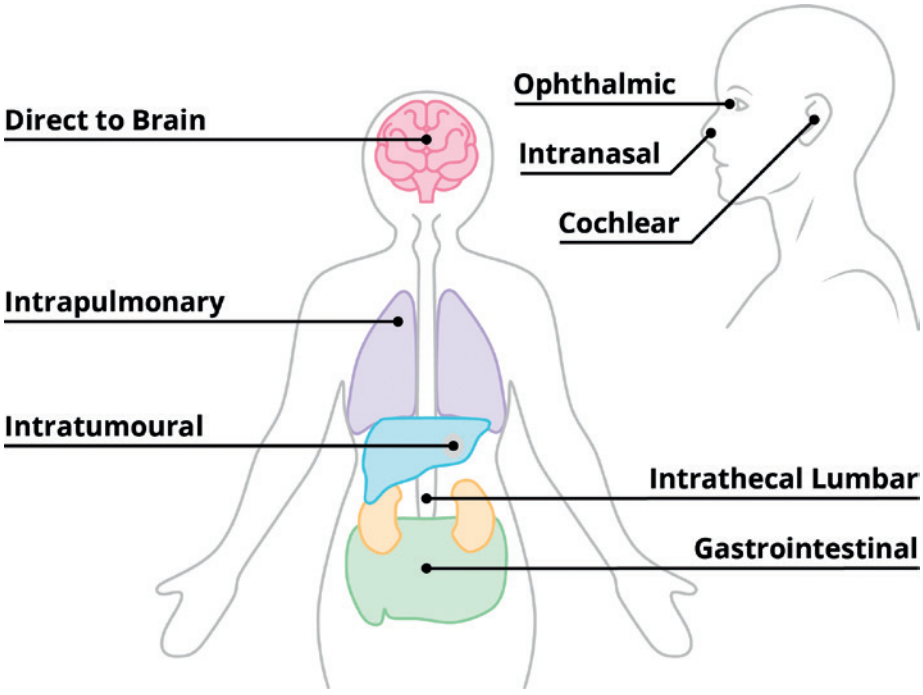

Figure 1: Commonly targeted delivery sites for CGTs.

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WHERE PRECISION MATTERS MOST IN CGTS

CGTs are not produced in the same way as small molecules or standard biologics. Many programmes are patient-specific or produced in small, labour-intensive batches, with customised biomanufacturing and strict cold chain to preserve vector integrity or cell viability. These constraints make products extremely costly: Luxturna®, for example, is priced at around US$850,000 (£650,000) per patient.[2] Given the resource-intensive nature of producing usable material, development teams must prioritise process efficiency and precision from the earliest stages of production.

Potency and safety are also tightly linked. Small deviations in target delivery or poor biodistribution control can provoke serious immune-mediated toxicities,[3] among other serious side effects, which is particularly true in gene therapies.[4] For instance, intrathecal delivery (administration into the cerebrospinal fluid, e.g. via lumbar injection, allowing direct access to the central nervous system) can have a biodistribution-associated risk that results in dorsal root ganglion inflammation and neuronal degeneration, particularly with higher doses, where neither the therapy's tropism (affinity with specific cells) nor cerebrospinal fluid dynamics have been fully characterised.[4]

Some therapies may only succeed when they are placed with millimetre-scale accuracy. For a rare neurological disorder called aromatic L-amino acid decarboxylase deficiency, the AAV2-based therapy Upstaza™ (eladocagene exuparvovec) from PTC Therapeutics (Warren, NJ, US), is delivered through stereotactic neurosurgery, which delivers four small infusions into the putamen in a single session (two per hemisphere).[5] The product label specifies the route, infusion sites and dosing parameters, as the efficacy of the therapy depends on reaching the correct brain region while avoiding wider systemic exposure. This is precision delivery built directly into the treatment's design. Furthermore, for one-off or single-administration gene therapies, re-delivery may not be possible (e.g. due to pre-existing antibodies to AAV) or may be considered too risky to conduct (e.g. direct-to-brain administration).

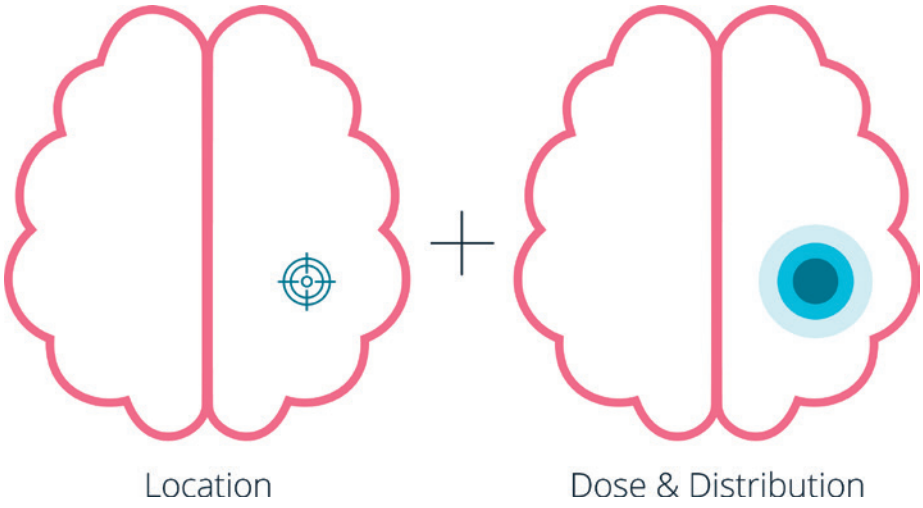

Figure 2: Achieving the correct location, dose and distribution.

Precision in where and how therapies are delivered determines how safely it can be dosed, how consistently it can be scaled and how much product is needed to achieve a therapeutic effect.

WHEN PRECISION BECOMES A MOVING TARGET

Precision is easy to define, in theory, but difficult to achieve in practice. For many CGTs, location, distribution and dose must be defined long before clinical trials begin, yet each is influenced by complex and patient-specific variables (Figure 2). Precision is less critical for *ex vivo* approaches, such as chimeric antigen receptor T-cell therapies, where cells are modified outside of the body prior to intravenous administration. These treatments have demonstrated success, as seen with Kymriah® (tisagenlecleucel) by Novartis and Yescarta® (axicabtagene ciloleucel) by Kite Pharma (Santa Monica, CA, US) in haematological malignancies. In contrast, precision becomes far more consequential for *in vivo* gene and stem cell therapies. What seems simple – such as targeting a specific organ for a rare disease – quickly becomes challenging when teams must decide what level of precision is sufficient in terms of which part of the organ and its diverse cell populations to target for the therapy to be effective.

Location

This challenge is clearly visible in liver-directed AAV therapies, where defining location goes beyond reaching the organ itself. The liver's intricate vasculature and cell diversity means that vector access and expression vary widely, while efficacy depends on transducing enough hepatocytes without excessive uptake by other cells that may trigger immune responses or reduce potency.[6] Achieving this balance relies on optimising the route of administration, delivery site and dose flow control.

Distribution

Parameters such as vector concentration, infusion rate and device (e.g. cannula) geometry determine how the therapy is distributed through the tissue and how reliably it reaches target cells. To manage these interdependencies, computational

"PRECISION IN WHERE AND HOW THERAPIES ARE DELIVERED DETERMINES HOW SAFELY IT CAN BE DOSED, HOW CONSISTENTLY IT CAN BE SCALED AND HOW MUCH PRODUCT IS NEEDED TO ACHIEVE A THERAPEUTIC EFFECT."

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and experimental modelling are integral throughout development of the therapy and delivery device. By modelling vector flow, convection and uptake in patient-specific anatomy, device developers can predict how a formulation or delivery approach will behave before starting animal studies, or they can refine it alongside these studies. These models enable the integrated team (composed of formulation/modality specialists, device developers and more) to optimise distribution patterns, reduce experimental uncertainty and accelerate iteration, allowing precise delivery to be engineered rather than inferred.

Dose

A clearer understanding of anatomical location and distribution also improves how the team defines and manages dose precision, which ultimately determines efficacy and safety. Dosing CGTs is about far more than volume; it reflects how much active vector or number/type of cells are needed to ensure the desired effect within the target tissue. Achieving precise dosages means controlling both potency and delivery conditions so that the administered quantity can translate into a safe and effective treatment. Advances in data analytics (e.g. vector analysis), flow-controlled infusion and real-time delivery monitoring are helping to define this relationship more accurately, enabling teams to move from empirical dose escalation to evidence-based dose design.

Although device design cannot completely negate biological variability, it can stabilise the physical conditions of delivery in terms of location flow and distribution, reducing the influence of external factors on therapeutic performance. In this sense, delivery systems are an integral and essential part of the therapy's design; the therapeutic without the device is useless. A minimum viable product (MVP) delivery device is essential even in early-stage therapy development, as it underpins both the predictability and scalability of clinical outcomes, as well as reducing risk to both the patient and therapy programme.

> "IS THE ISSUE WITH THE THERAPY ITSELF OR WITH HOW IT WAS DELIVERED?"

HOW TO DEMONSTRATE PRECISION

If defining precision is difficult, demonstrating it under clinical conditions is even harder. Many CGTs show encouraging results in modelling and *in vitro* studies, only to encounter unexpected variability once tested in animals or humans. Translating a theoretical understanding of location, dose and delivery pattern into reproducible, *in vivo* performance remains one of the toughest challenges in the field.

The difficulty often emerges during the transition from therapeutic discovery to device-specific preclinical testing. Early studies may demonstrate vector bioavailability or device function separately, focusing on establishing foundational performance characteristics; however, this separation can limit understanding of how the two interact under physiological conditions. As a result, the first time the full system is tested, typically in animal models, teams may struggle to interpret poor outcomes. The question being: is the issue with the therapy itself or with how it was delivered?

If the delivery device or route is not well characterised before entering *in vivo* preclinical work, study design, surgical procedures and even success criteria can become ambiguous or have a lack of reproducibility.

Study Design

Preclinical study design therefore becomes the first true test of precision. The chosen route of administration determines not only how the therapy will be delivered, but also which model is appropriate for advancing an MVP approach to device design that supports overall therapy development. For example, a device that matches the therapy development stage and its requirements allows for evidence gathering on the control of delivery – isolating results for therapeutic effectiveness.

Anatomical and physiological differences, particularly in vascular structure, tissue density or organ size, mean that delivery parameters optimised in animals may not translate directly to humans. Building these constraints into the study design early on can help teams interpret results with greater confidence.

Procedural Control

Demonstrating precision also depends on procedural control. Every step, from therapy preparation and handling to administration and post-delivery care, can influence efficacy. For cell therapies, cell sedimentation during preparation or delays between thawing and delivery can alter dose consistency and viability. For gene therapies, infusion rate, device placement and user variability can all shift distribution patterns. Integrating human factors engineering into device and protocol design using procedural expertise helps to standardise these steps, thus improving reproducibility and safety.

Regulatory Scrutiny

Ultimately, preclinical and clinical studies are where precision delivery meets regulatory scrutiny. Demonstrating that a therapy and its delivery system consistently achieve targeted exposure is essential for proving both safety and efficacy. Without an early integrated approach to development of the device, formulation and route of administration, teams risk employing complex and expensive animal models or clinical studies only to discover that the delivery method itself limits their ability to assess therapeutic potential.

Incorporating delivery design and evaluation early in development is therefore not just good engineering – it is a strategic safeguard. Precision that is defined, engineered and tested in parallel with the therapy dramatically increases the chances of reproducible success in the clinic.

CONCLUSION: PRECISION DELIVERY IS THE NEXT FRONTIER

The future of CGTs will not be defined solely by novel vectors or manufacturing breakthroughs, but by the industry's ability to deliver these therapies with accuracy and consistency at scale. As CGTs move towards broader indications, the need for predictable, accessible delivery will only

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intensify. Achieving precision demands earlier integration of biological, engineering and human factors design, alongside continued investment in modelling and device innovation. Precision delivery bridges the gap between discovery and patient impact, turning theoretical efficacy into real-world benefit.

The lesson is clear: precision delivery is not a supporting technology, but the missing link that will connect scientific ingenuity with clinical and commercial success. Those who master it will define the next era of CGTs.

ABOUT THE COMPANY

Cambridge Design Partnership (CDP) is a design and engineering consultancy with R&D centres in the UK and US. The company creates breakthrough products and services for global brands and ambitious start-ups across the healthcare, consumer and industrial sectors. The drug delivery team innovates solutions for parenteral, respiratory, nasal, sublingual, transdermal and novel delivery routes, such as ocular, brain and direct-to-organ delivery.

"THE FUTURE OF CGTS WILL NOT BE DEFINED SOLELY BY NOVEL VECTORS OR MANUFACTURING BREAKTHROUGHS, BUT BY THE INDUSTRY'S ABILITY TO DELIVER THESE THERAPIES WITH ACCURACY AND CONSISTENCY AT SCALE."

REFERENCES

1. *Patel MJ et al, "Surgical Approaches to Retinal Gene Therapy: 2025 Update". Bioengineering, 2025, Vol 12(10), art 1122.*
2. *"Spark's gene therapy price tag: $850,000". News Article, Nat Biotechnol, 2018.*
3. *Morris EC, Neelapu SS, Giavridis T & Sadelain M, "Cytokine release syndrome and associated neurotoxicity in cancer immunotherapy". Nat Rev Immunol, 2022, Vol 22(2), pp 85–96.*
4. *Perez BA et al, "Management of Neuroinflammatory Responses to AAV-Mediated Gene Therapies for Neurodegenerative Diseases". Brain Sci, 2020, Vol 10(2), art 119.*
5. *"Upstaza (eladocagene exuparvovec)". Web Page, European Medicines Agency, accessed November 2025.*
6. *Cao D et al, "Innate Immune Sensing of Adeno-Associated Virus Vectors". Hum Gene Ther, 2024, Vol 35(13–14), pp 451–463.*

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MAPPING INNOVATION IN mRNA DELIVERY THROUGH PATENT TRENDS

Dr Elodie Bovier of KnowMade, considers the evolution of messenger RNA therapeutics in biotechnology, examining patent trends and exploring how they have triggered litigation in the field, demonstrating the growth and maturity of this sector.

"ACROSS ALL TECHNOLOGICAL SEGMENTS OF mRNA THERAPEUTICS, DELIVERY REMAINS ONE OF THE MOST ACTIVELY PATENTED AND STRATEGICALLY PROTECTED AREAS."

Messenger RNA (mRNA) therapeutics have evolved from a research concept to a central pillar of modern biotechnology, redefining the landscape of gene and cell therapies. One critical factor lies at the core of this transformation: the delivery system that determines not only therapeutic efficacy but also the feasibility of scaling these approaches across diverse indications.

THE CENTRAL ROLE OF DELIVERY IN mRNA THERAPEUTICS

Mechanistic Basis of mRNA Delivery

After administration, mRNA must survive in circulation, reach the correct tissue and enter target cells – impossible steps without a delivery system. Naked mRNA is rapidly degraded by serum nucleases and cleared by the liver and spleen. Effective carriers therefore protect the molecule, promote cellular uptake and enable endosomal escape – the crucial step that releases mRNA into the cytoplasm for translation. Each stage – protection, biodistribution and cellular entry – depends on the delivery system, making delivery design the true determinant of therapeutic success.[1–4]

LNPs: Established But Evolving

Among non-viral systems, lipid nanoparticles (LNPs) are the most clinically validated vehicles. They combine ionisable lipids, phospholipids, cholesterol and polyethylene glycol (PEG) lipids to condense and protect RNA in circulation. Ionisable lipids bind mRNA at a low pH and trigger release inside endosomes, while helper phospholipids stabilise membranes. Cholesterol adds rigidity, and PEG-lipids reduce aggregation and immune recognition – although excessive PEGylation can hinder uptake if desorption is delayed.[2,4–6]

Despite the success of LNPs, challenges remain – hepatic tropism, immunogenicity and limitations on repeated dosing. These constraints drive innovation in lipid chemistry, such as new ionisable scaffolds, biodegradable PEG substitutes and ligand–lipid conjugates for tissue targeting.

Innovation also extends beyond lipids to polymeric carriers and biological vesicles. As many advances precede clinical validation, patent activity functions as the earliest and most quantifiable signal of progress. Monitoring these dynamics provides a direct measure of how rapidly mRNA delivery is evolving.

PATENT ACTIVITY AS AN INNOVATION BAROMETER

Patent Trends in mRNA Delivery

Intellectual property (IP) analysis provides a powerful lens through which to trace the technological evolution of mRNA therapeutics. The data presented in this article focus on a timeline from Q1 2024 to Q3 2025, reflecting the most recent dynamics within the delivery segment.

During this period, about 1,450 mRNA-related patent families were published worldwide, of which nearly half (~49%) addressed delivery. The quarterly share ranged from 42% to 59%, peaking in Q2 2024 (59%) and Q2 2025 (54%). Even in quarters with slightly lower total publication volumes (e.g. Q3 2024 and Q4 2024), delivery maintained a consistent presence of above 45% of all filings. This persistence highlights that, across all technological segments of mRNA therapeutics (design, manufacturing, storage or application), delivery remains one of the most actively patented and strategically protected areas (Figure 1).

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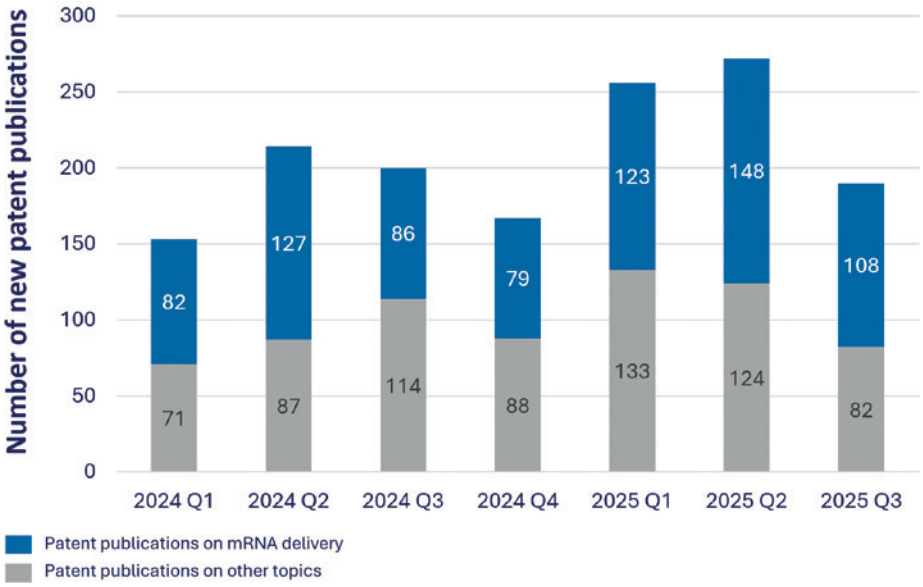

Figure 1: Quarterly proportion of delivery-related patent families, Q1 2024–Q3 2025.

This trend is further reflected within the profiles of the leading assignees in this field (Figure 2). The University of Pennsylvania (PA, US) leads delivery-related patenting, with 20 new publications in 2025 compared with nine the previous year, followed by BioNTech (Mainz, Germany), with a similar trajectory (17 versus eight new delivery patents year-on-year). In contrast, Moderna (Cambridge, MA, US) and Abogen (Suzhou, China), which dominated the 2024 landscape, have not yet appeared in 2025, likely due to pending disclosures.

Other prominent players – including Sanofi (Paris, France), CanSino (Tianjin, China) and Pfizer (Manhattan, NY, US) – maintained stable levels of new patenting activity, while companies such as Jitai Pharmaceutics (Shaanxi, China), Orna Therapeutics (Watertown, MA, US), Fujifilm (Tokyo, Japan), Nanovation (Vancouver, BC, Canada) and Beam Therapeutics (Cambridge, MA, US) showed a slight decline. Conversely, a new wave of academic and research organisations, MIT (Cambridge, MA, US), Samyang Biopharmaceuticals (Seoul, South Korea), Acuitas Therapeutics (Vancouver, BC, Canada), KIST (Seoul, South Korea) and the University of Texas (Austin, TX, US), demonstrated higher activity in 2025 compared with 2024, underscoring academia's growing role in advancing delivery platforms and broadening the innovation base of the field.

These shifts illustrate how patent dynamics act as an innovation radar, capturing both the speed and direction of technological changes. Data confirm that delivery is not only a scientific challenge but also a strategic axis defining competitiveness in the mRNA sector (Figure 2).

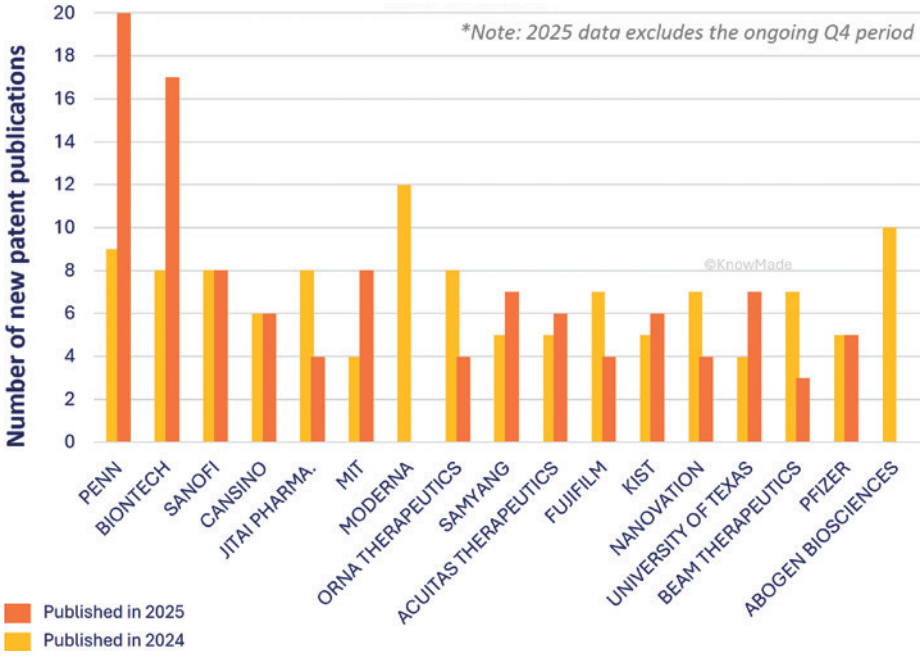

Figure 2: New patent publications for delivery by main assignees in 2024 and 2025*.

BEYOND LNPs: INNOVATION FROM NEWCOMERS

While LNPs remain the cornerstone of mRNA therapeutics, the field is rapidly diversifying. A new generation of companies is reimagining RNA transport to overcome immunogenicity, tissue-targeting and scalability barriers. Their work demonstrates how delivery innovation has evolved from a domain dominated by major pharmaceutical players into a multidisciplinary frontier, with academic institutions and emerging companies playing an increasingly decisive role.

Among them, three companies illustrate how innovation in the post-LNP era is being driven by novel concepts that expand the possibilities of mRNA transport beyond conventional lipid-based architectures: Parcel Bio (San Francisco, CA, US), AGS Therapeutics (Paris, France) and CILA Therapeutics (Boston, MA, US).

"A NEW GENERATION OF COMPANIES IS REIMAGINING RNA TRANSPORT TO OVERCOME IMMUNOGENICITY, TISSUE-TARGETING AND SCALABILITY BARRIERS."

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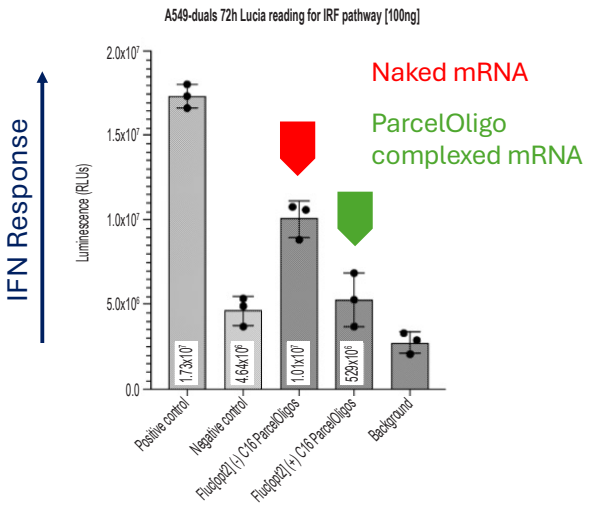
(A)



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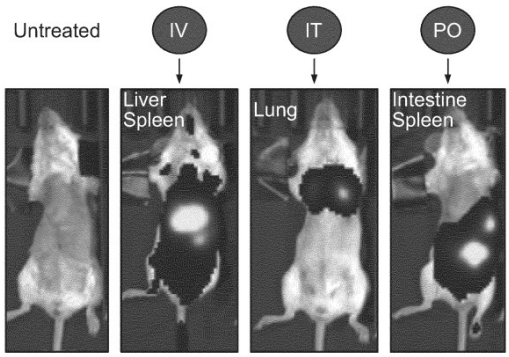
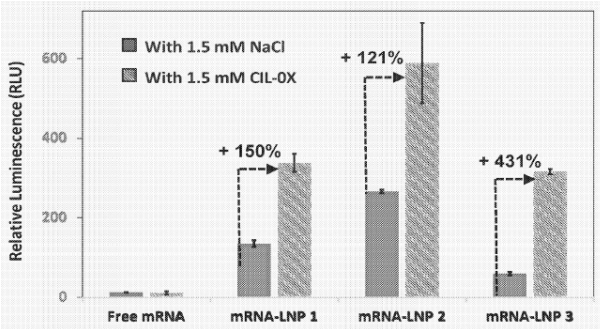


IV: Intravenous; IT: Intratracheal; PO: Per Os

(C)



mRNA transfection in Primary Human Bronchial Epithelial Cells

Innovation from 3 newcomers in the delivery segment since 2024

- Parcel Bi's STAmP™ Immunogenicity from the patent application WO 2024/166052
- AGS MEVs delivery routes from the patent application WO 2024/194423
- CILA transfection-enhancing agent CIL-0X efficiency from the patent application WO 2025/101704

Figure 3: Representative newcomer delivery platforms disclosed in recent patents: (A) Parcel Bio STAmP™, (B) AGS Therapeutics MEVs, (C) CILA Therapeutics aerosol lipids.

Case Study 1: Parcel Bio – Molecularly Encoded Delivery

Parcel Bio (founded 2023) has introduced STAmP™ (Structured Trans-Assembly of mRNA Precursors), a nanoparticle-free delivery in which oligo-tiled, ligand-targeted mRNA forms stable molecular complexes without lipids. Patent WO 2025/166052 reports strong serum stability, protection from nuclease degradation and low innate-immune activation, while maintaining robust protein expression comparable with lipid-based formulations. By removing the lipid component, STAmP aims to support repeat dosing and broaden biodistribution to muscle and central nervous system targets, pointing to a shift towards molecularly encoded delivery, where the RNA architecture contributes to both stability and targeting (Figure 3a).

Case Study 2: AGS Therapeutics – Microalgae Vesicles

In Europe, AGS Therapeutics (founded 2020) has developed a biologically inspired alternative using microalgae extracellular vesicles (MEVs) derived from *Chlorella vulgaris*. These vesicles are inherently non-immunogenic, biodegradable and scalable, capable of transporting RNA, DNA and proteins. Their natural origin and sustainable production process make them an attractive and eco-friendly alternative to synthetic nanocarriers. Patent WO 2024/194423 demonstrates that MEVs can cross mucosal and blood-brain barriers to deliver RNA and protein cargos *in vivo* (Figure 3b). Administered via oral, nasal or ocular routes, they achieved their functional objectives. Reported outcomes include antigen-specific immune responses and cytokine modulation without interferon activation or detectable toxicity, supporting repeatable administration.

Case Study 3: CILA Therapeutics – Pulmonary Delivery

Another emerging company, CILA Therapeutics (founded 2018) focuses on the pulmonary route – one of the most challenging targets for mRNA drug delivery. Its international patent application (WO 2025/101704) details a lipid-based aerosol formulation optimised for nebulisation, combining cationic and helper lipids to preserve RNA integrity and promote expression in airway cells. In addition, co-formulation with thiol compounds, such as MESNA or CIL-OX, improves uptake under oxidative conditions while maintaining cell viability, demonstrating that aerosolised lipid systems can achieve efficient, repeatable RNA delivery directly to the lung (Figure 3c). This approach is particularly relevant for diseases such as cystic fibrosis and primary ciliary dyskinesia.

Summary

Together, these newcomers illustrate a clear post-LNP diversification from LNP optimisation and alternatives such as molecular self-assembly, to biological vesicles and aerosol delivery. Such transitions, visible first in patent data, redefine the boundaries of mRNA pharmacology and suggest new paths for systemic and local delivery.

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Year	Plaintiff	Defendant	Delivery Tech Focus
2020–2025 (appeal)	**Moderna**	**Pfizer/BioNTech**	**Partly delivery (5' UTR & LNP claim overlap)**
	Cause of Action: Infringement Jurisdiction/Case: UK Court of Appeal Subject/Patent Family: mRNA construct & delivery patents EP3 719 565 B1 et al. Status*: Pfizer/BioNTech lost appeal Aug 2025		
2021–2025	**Arbutus Biopharma/ Genevant Sciences**	**Moderna**	**Ionisable lipids & LNP formulation composition & manufacture**
	Cause of Action: Infringement Jurisdiction/Case: US District Court, Case 1:22-cv-00252 + Global fillings Subject/Patent Family: LNP delivery patents (Arbutus/Genevant portfolio) Status*: Active; trial set for Sep 2025		
2022–2025	**Alnylam**	**Moderna**	**Cationic/ionisable lipids for mRNA delivery**
	Alnylam	**Pfizer**	
	Cause of Action: Infringement Jurisdiction/Case: US District Court, Case. 1:23-cv-00580 (Alnylam v. Moderna) & 1:23-cv-00578 (Alnylam v. Pfizer) Subject/Patent Family: Cationic-lipid patents (Alnylam) used in mRNA vaccine LNPs Status*: Non-infringement in favour of Moderna (currently on appeal) & still pending for the other case		
2022–2025	**CureVac/GSK**	**BioNTech & Pfizer**	**LNPs & ionisable lipid formulations**
	Cause of Action: Infringement & EPO Opposition Jurisdiction/Case: US District Court, Case 2:23-cv-00222 Subject/Patent Family: CureVac's mRNA + delivery patents ('493 Family & others) Status*: Settled (Aug 2025) – Pfizer/BioNTech paid $740 M + royalties; granted non-exclusive US licence, BioNTech's deal to buy CureVac		
2023–2024	**Acuitas Therapeutics**	**CureVac SE**	**LNPs – cationic lipid ALC-0315 for mRNA delivery**
	Cause of Action: Inventorship Jurisdiction/Case: US District Court, Case 3:23-cv-00764 Subject/Patent Family: US Patents 11,241,493 et al. ('493 Family) Status*: Settled (Apr 25, 2024); inventorship dispute resolved, CureVac withdrew three patents; Acuitas licensed use rights		
2024	**GSK**	**Moderna**	**LNP & self-amplifying mRNA delivery systems**
	Cause of Action: Infringement Jurisdiction/Case: US District Court, case 1:24-cv-01136 and 1:24-cv-01135 Subject/Patent Family: GSK mRNA/LNP platform patents (Moderna's Spikevax & mRESVIA) Status*: Early stage		
2025	**Arcturus Therapeutics**	**AbbVie (Capstan Therapeutics)**	**LNP formulation know-how for mRNA delivery**
	Cause of Action: Trade-secret suit Jurisdiction/Case: US District Court, case 3:25-cv-02494 Subject/Patent Family: Alleged misappropriation of LNP delivery tech Status*: Early stage		

*As of October 2025.

Table 1: Summary of the six main litigations in the mRNA delivery field.

WHERE CONTENT MEETS INTELLIGENCE ON drugDELIVERY

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STRATEGIC LITIGATION AND THE CONSOLIDATION OF mRNA DELIVERY TECHNOLOGIES

Overview of Major Legal Disputes

The growing commercial value of LNP and delivery patents has triggered extensive litigation, reflecting the field's maturity. Between 2020 and 2025, six major disputes shaped the LNP IP landscape, ranging from inventorship claims to infringement and trade-secret actions, as illustrated in Table 1.

These cases underline how ownership of delivery IP has become a decisive competitive determinant. Cross-licensing outcomes define royalty baselines, while ongoing suits will likely establish precedents for global mRNA patent enforcement.

From Conflict to Collaboration

The settlements in Acuitas versus CureVac (Tübingen, Germany) and CureVac/GSK versus BioNTech and Pfizer illustrate a shift from defensive litigation to cross-licensing aimed at stabilising access to LNP technology. The Acuitas–CureVac dispute revolved around the patent family, covering mRNA–LNP formulations, incorporating the cationic lipid ALC-0315, used in Comirnaty®. Acuitas claimed CureVac excluded its scientists from inventorship; the case was settled in April 2024, with CureVac withdrawing disputed patents and granting Acuitas licences. In parallel, CureVac (with GSK) and BioNTech/Pfizer contested patents relating to mRNA sequence optimisation and LNP delivery. BioNTech and Pfizer sought declaratory judgements of non-infringement, while CureVac countered with infringement claims. The proceedings concluded in August 2025 through a global settlement of roughly US$740 million (£568 million) plus royalties, granting BioNTech and Pfizer non-exclusive US licences. Together, these cases exemplify how major players now employ IP negotiation to secure technological and market stability.

The Arbutus/Genevant Versus Moderna Precedent

In contrast, the ongoing Arbutus (Warminster, PA, US) and Genevant (Vancouver, Canada) versus Moderna proceedings, spanning more than 30 jurisdictions, represent the consolidation of foundational LNP patents as globally strategic assets and one of the most extensive global disputes to date concerning the IP on LNPs. Indeed, this case was filed initially in the US in 2021 and subsequently in five international lawsuits (in Canada, Japan and Switzerland, and two filed in the Unified Patent Court). Beyond its commercial scale, the case can be viewed as a potential precedent-setter for the valuation and licensing of core LNP technologies, as its outcome may establish the royalty structures and ownership boundaries that will govern future mRNA delivery partnerships across the industry.

CONCLUSION: THE MATURATION OF DELIVERY AS A COMPETITIVE AXIS

The analysis of patent dynamics and litigation trends offers a unique vantage point on how mRNA delivery is evolving. Patent activity quantifies innovation momentum, identifies new entrants and captures the diversification of materials long before clinical validation. Litigation patterns, in turn, reveal where technology ownership and value are consolidating. For scientists, these developments expand the possibilities of nucleic-acid pharmacology; for analysts, they map the competition of tomorrow's mRNA therapeutics market.

Delivery remains the decisive enabler of mRNA therapeutics — and the pulse of that innovation is written first in its patents.

ABOUT THE COMPANY

KnowMade is a technology intelligence and intellectual property (IP) strategy consulting company specialising in patent analysis and scientific publications. The company helps companies, investors and R&D organisations to understand competitive landscapes, follow technological evolutions, reduce uncertainties and identify opportunities and risks in terms of technology and IP. KnowMade's analysts combine strong technology expertise and in-depth knowledge of patents with powerful analytics tools and methodologies to turn patent information and scientific literature into actionable insights, providing reports with high added value for decision makers working in R&D, innovation strategy, IP and marketing. The company's experts provide prior art search, patent landscape analysis, freedom-to-operate analysis, IP due diligence and monitoring services. KnowMade has expertise in medical devices, medical imaging, microfluidics, biotechnology, pharmaceutics and agri-food, compound semiconductors, power electronics, batteries, radio-frequency technologies and wireless communications, solid-state lighting and display, photonics, memories, microelectromechanical systems and sensors, and semiconductor packaging.

> "PATENT ACTIVITY QUANTIFIES INNOVATION MOMENTUM, IDENTIFIES NEW ENTRANTS AND CAPTURES THE DIVERSIFICATION OF MATERIALS LONG BEFORE CLINICAL VALIDATION."

BRAND NEW TITLE
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ON diagnostics

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REFERENCES

1. *Hamilton AG, Swingle KL, Mitchell MJ, "Biotechnology: Overcoming biological barriers to nucleic acid delivery using lipid nanoparticles". PLoS Biol, 2023, Vol 21(4), art e3002105.*
2. *Monique CP et al, "Design of lipid-based nanoparticles for delivery of therapeutic nucleic acids". Drug Discov Today, 2023, Vol 28(3), art 103505.*
3. *Moon S, Lee JB, "Lipid nanocarriers for RNA and DNA therapeutics: Next-generation delivery strategies in precision medicine". J Ind Eng Chem, 2025, available online.*
4. *Xu S et al, "Lipid nanoparticles: Composition, formulation, and application". Mol Ther Methods Clin Dev, 2025, Vol 33(2), art 101463.*
5. *Chowdhury CR, Hoover EC, Day ES, "Membrane-modified lipid nanoparticles for RNA delivery". Mol Ther Methods Clin Dev, 2025, Vol 33(3), art 101505.*
6. *Zhang T et al, "Optimized lipid nanoparticles (LNPs) for organ-selective nucleic acids delivery in vivo". iScience, 2024, Vol 27(6), art 109804.*

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SHEAR RELIEF: MINIMISING SHEAR STRESS IN CGT PRODUCTION

Dr Ethan Miller of Sanner examines the manufacturing of cell and gene therapies where shear stress can impact cells and explores strategies to mitigate such damage, helping to ensure that therapies retain their viability, functionality and therapeutic potency from production through to administration.

Cell and gene therapies (CGTs) are a rapidly developing area of technology, and therapies using chimeric antigen receptor (CAR) T-cells, stem cell and other gene-edited cell products are transforming the pharmaceutical landscape. These new therapies essentially exploit cells as living drugs, capable of proliferating and generating a sustained, targeted immune response to treat disease sites in the patient's body.

CAR T-cell therapy involves engineering a patient's T-cells to expand in number and generate sustained immune responses, targeting tumours and diseased tissue. Similarly, stem cell therapies use multipotent or pluripotent cells that proliferate and help regenerate damaged tissues. CAR T-cell therapies, such as tisagenlecleucel and axicabtagene ciloleucel, engineer a patient's T-cells to attack tumours. Viral gene therapies, such as RGX-314 for neovascular age-related macular degeneration, show potential for durable disease control with a single administration. Despite these advances, CGTs face critical challenges during manufacturing, transport and delivery, where maintaining cell viability, phenotype and function remains essential.

Despite advances in CGT delivery and manufacturing, an often-overlooked challenge comes from the mechanical stress experienced by cells during handling. Therapeutic cells are highly mechanosensitive, and exposure to shear forces from fluid flow, tubing, bioreactors, microfluidic devices or injectors can reduce viability, alter phenotype and compromise functional performance, potentially impacting efficacy and safety.

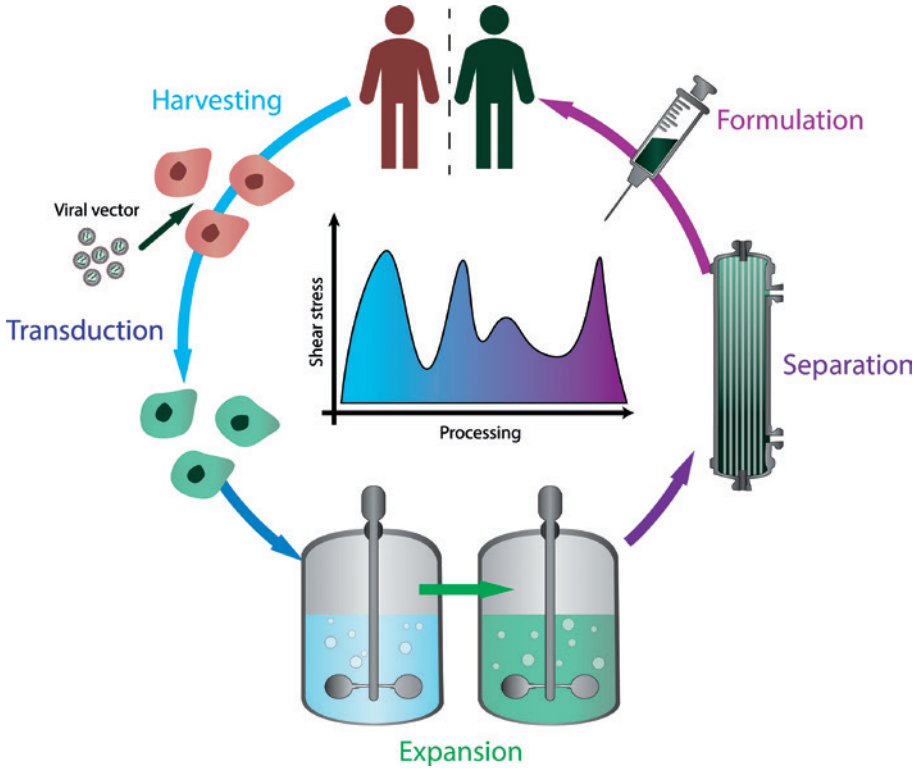

Figure 1: This schematic outlines some major workflow stages in CGT manufacture: harvest and transduction, expansion, separation and final formulation for patient delivery. When unmanaged, shear stress can fluctuate sharply across CGT manufacturing at any of these stages.

WHY SHEAR STRESS MATTERS FOR CGTs

In fluid-mechanical terms, shear stress (τ) arises when layers of fluid move relative to one another or to adjacent surfaces and can be expressed as the product of fluid viscosity (μ) and shear rate ($\dot{\gamma}$); that is, $\tau = \mu \times \dot{\gamma}$. In cellular systems, exposure to shear can have profound biological consequences, including morphological deformation, cytoskeletal disruption, membrane perturbation, altered gene expression and reduced viability. Even modest shear rates can produce measurable drift in membrane-bound proteins,[1,2] indicating that fluid forces acting near membranes can mechanically perturb membrane-bound entities and thereby impose mechanical stress on the cell surface.

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During the manufacture and delivery of CGTs, therapeutic cells are exposed to a variety of fluid-mechanical environments that can impose shear stress at multiple stages of processing (Figure 1), potentially impacting viability, phenotype and functional potency. In the initial cell harvest and processing stage, cells are typically collected, subjected to centrifugation and resuspended in media. Here, shear arises during pipetting, aspiration and passage through narrow tubing, with high flow rates generating localised high shear that can deform membranes or disrupt fragile cytoskeletal structures.

During transduction or gene-editing in bioreactors, viral vectors or gene-editing complexes are introduced under mixing conditions; here, even gentle agitation can create gradients of fluid velocity, exposing cells to non-uniform shear. During expansion in stirred-tank or perfusion bioreactors, cells are exposed to varying shear stresses generated by impellers, perfusion flows and sparging (i.e. when oxygen is bubbled through media). These shear stresses can alter cytoskeletal integrity, trigger apoptosis or induce subtle phenotypic drift.

The separation and washing steps, commonly conducted via tubing, pumps and filtration devices, similarly produce localised shear, particularly at constrictions, bends or membrane surfaces, where fluid velocity gradients can be high. Finally, during formulation and delivery, cells are transferred into infusion media; pass through tubing, connectors and injectors; and, ultimately, are administered via catheters or syringes – the high pressures at needle tips or microfluidic sorting channels can produce transient but intense shear spikes.

Collectively, these mechanical exposures can reduce cell viability, alter functional markers and induce apoptotic or stress signalling, potentially reducing the therapeutic potency of the final product, increasing batch-to-batch variability and raising regulatory concerns under GMP and International Council for Harmonisation guidelines.

Figure 2: Understanding shear is essential to protect sensitive CGT products, preserving their integrity and therapeutic potency during delivery.

METHODS OF SHEAR STRESS MITIGATION

As CGTs scale to more complex processes, systems and formulations, their exposure to shear stress rises, increasing risks to product quality. Larger bioreactors, higher throughput microfluidic devices and more complex formulations all increase the frequency of shear stress exposure, compounding potential damage on cultured cells (Figure 2). This growing mechanical challenge underscores the need for robust mitigation strategies. Strategies such as optimised flow geometries, controlled infusion rates and protective formulations can help to preserve the functional characteristics of these living therapeutic agents throughout manufacturing and delivery workflows.

For expansion and harvest, platform choice matters. A review of microcarrier and bioreactor strategies by Tsai *et al* (2021) showed that rocking and fixed-bed platforms produced substantially gentler hydrodynamic environments than conventional stirred-tank reactors, making these low-shear systems attractive for the scale-up of adherent mesenchymal stromal cells (MSCs).[3]

Sparging during expansion can be another major source of localised high shear, with studies showing that aeration and agitation can depress yields or viability of shear-sensitive viral vectors via and bubble-induced damage.[4] Minimising active sparging where possible by using head-space aeration, membrane oxygenation or low-shear mass-transfer strategies can mitigate some of these damaging effects. Alternatively, the use of shear protectants such as Pluronic® F-68 or albumin can be beneficial in processes where bubbles or agitation are unavoidable. Grein *et al* (2019) document that these surfactant/protein additives can protect cells from interfacial stresses in serum-free processes; but caution is required, as any excipient must be validated for downstream effects on potency and regulatory acceptability.[4]

Innovation in reactor geometry can deliver low shear without sacrificing scale. Burns *et al* (2021) describe a 3D-printed lattice, fixed-bed bioreactor that achieves ultra-low wall shear, with computational

"AS CGTS SCALE TO MORE COMPLEX PROCESSES, SYSTEMS AND FORMULATIONS, THEIR EXPOSURE TO SHEAR STRESS RISES, INCREASING RISKS TO PRODUCT QUALITY."

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fluid dynamics (CFD)-predicted shear stresses in the 10^{-3}–10^{-2} Pa range;[5] this was much lower than the shear forces that cells are typically exposed to.[2] Such low-shear conditions yielded much higher purity and viability MSCs compared with stirred cultures. Their work underscores that structural, fixed-bed or structured-matrix solutions can substantially reduce cumulative shear exposure during expansion and improve downstream product quality.

MARKET-READY MITIGATIONS: REACTORS DESIGNED TO MINIMISE SHEAR

Translating these academic insights into practical solutions, several commercial developers are now introducing next generation, low-shear bioreactors that combine innovative fluidic and structural designs to minimise mechanical stress while maintaining scalability and process control. For example, BioThrust (Aachen, Germany) has introduced a "bionic" bioreactor architecture that replaces conventional sparging with a membrane-based gas transfer and mixing system, enabling bubble-free aeration and gently circulating flow fields even at higher oxygen demands. By decoupling oxygen transfer from impeller speed, the platform enables operators to dial in extremely low-shear conditions without compromising volumetric oxygen transfer. This feature is particularly attractive for induced pluripotent stem cells (iPSCs), which can differentiate into any cell type, and mesenchymal stromal stem cells (MSCs), multipotent cells that support tissue repair, as well as other shear sensitive CGT substrates.

Other companies are pursuing equally innovative, but mechanically distinct, strategies. PBS Biotech (Camarillo, CA, US) has advanced its well-established Vertical-Wheel™ technology, which produces uniform, low-turbulence mixing through a rotating paddle-like wheel; this geometry reduces shear gradients and dead zones while supporting expansion of large aggregates, as demonstrated in numerous iPSC and viral-vector manufacturing programmes. Univercells Technologies (now part of Quantoom Biosciences, Nivelles, Belgium) has taken a different approach with its scale-X™ structured fixed-bed bioreactors, using tightly controlled laminar flow through high-surface-area carriers to achieve high volumetric productivity with minimal fluid shear.

> "BY EMBEDDING LOW-SHEAR HYDRODYNAMICS INTO BOTH HARDWARE AND CONTROL SYSTEMS, NEW PLATFORMS ALLOW CGT DEVELOPERS TO EFFECTIVELY SCALE PROCESSES WHILE PRESERVING CELL VIABILITY, PHENOTYPE AND POTENCY."

Cytiva (Marlborough, MA, US) and Sartorius (Göttingen, Germany) have re-engineered their single-use stirred-tank bioreactors to accommodate the mechanical sensitivity of CGTs. Cytiva's XDR and ReadyToProcess platforms incorporate axial-flow impellers with widened blades, magnetically coupled low-shear drives and controlled agitation profiles that maintain mixing while reducing turbulence. Their integrated fluid paths and perfusion modules minimise pulsatile flow, protecting cells during media exchanges and wash steps. Sartorius's BIOSTAT STR and Univessel SU systems employ low-aspect-ratio impellers, streamlined baffles and films engineered to reduce drag, while automated control of agitation ramps and perfusion rates further limits localised high shear.

By embedding low-shear hydrodynamics into both hardware and control systems, new platforms allow CGT developers to effectively scale processes while preserving cell viability, phenotype and potency. Optimising familiar stirred-tank formats, balancing operational efficiency and overall gentler processes come together to further preserve cell viability, phenotype and potency.

Overall, these commercial systems reflect a broader shift in CGT bioprocess engineering – rather than treating shear stress as an unavoidable consequence of scale, manufacturers are now embedding shear-minimising fluid mechanics directly into their reactor architecture, offering platforms that combine gentle handling, closed-system operation and GMP readiness. This convergence of engineering innovation and regulatory alignment is enabling developers to scale shear-sensitive cell products more confidently while maintaining viability, phenotype and long-term functionality.

MITIGATING SHEAR STRESS DURING DELIVERY

Delivery is a critical – and often overlooked – opportunity to minimise shear-related cell loss. Studies show that slower ejection rates, larger-gauge needles and smoothed infusion pulses improve viability and reduce apoptosis in MSCs.[6,7] Beyond needle and pump optimisation, innovations such as damped or microfluidic infusion devices, protective formulations, wide-bore tubing and adaptive flow control can further mitigate shear, and are making delivery an active step in preserving CGT viability, phenotype and potency.

Manufacturers can build upon such insights into flow dynamics and needle geometry when engineering novel delivery systems, using CFD and finite element analysis simulation to characterise flow fields, mechanical stresses and formulation–tissue interactions during injection and infusion, allowing for precise understanding of where damaging shear forces arise. This modelling capability is paired with extensive hands-on experience in the design and development of advanced drug delivery systems, from respiratory platforms to autoinjectors and ambulatory infusion pumps, providing a practical understanding of how geometry, actuation, flow control and material choices all influence cell integrity. Combining simulation-led insights with evidence-based device design can help to develop delivery solutions that preserve potency, viability and functional efficacy.

Delivery systems should no longer be considered a passive step but a critical aspect of maintaining CGT product quality. By combining careful device

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design and controlled infusion protocols, manufacturers can significantly mitigate shear-induced apoptosis, preserve phenotype and improve the functional potency of therapeutic cells at the point of administration.

FUTURE PERSPECTIVES: SHEAR CONTROL AS A KEY TO CGT SUCCESS

Shear forces represent a critical, often underappreciated, factor in the manufacturing and delivery of CGTs. Mechanistic studies have revealed how cells respond to fluid stresses at each stage of development and highlight the importance of integrating process monitoring and controlled handling to mitigate risk. The accelerated adoption of CFD-driven reactor design, "digital-twin" models and artificial intelligence/machine learning for process control will likely emphasise the importance of considering shear effects when optimising critical CGT processes.

Manufacturers should proactively evaluate shear exposure across their workflows, implement monitoring and diagnostic tools, redesign processes and equipment where needed, and embed these considerations within their quality frameworks to ensure consistent product potency. As CGTs scale, controlling shear will likely be key to preserving viability, function and safe delivery. Success demands a holistic approach, including engineering, biology and process control in balance to keep living therapies intact in the turbulent world of CGT manufacturing.

Dr Ethan Miller

Ethan Miller, PhD, Senior Biophysicist, is an experimental biophysicist with a background in developing synthetic biological systems and high-resolution imaging. He can quickly grasp new concepts and break down complicated problems, enabling him to discover creative solutions. His experience includes medical device development, manipulation of synthetic bio-membranes with microfluidics and nanoscale surface characterisation.

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ABOUT THE COMPANY

Springboard, Sanner's Design Centre of Excellence since 2024, is an engineering company that specialises in the design and development of new products and technologies in the field of medtech and drug delivery devices, resolving technical challenges and decreasing time to market.

REFERENCES

1. *Ratajczak AM et al, "Measuring flow-mediated protein drift across stationary supported lipid bilayers". Biophys J, 2023, Vol 122(9), pp 1720–1731.*
2. *Sasidharan S et al, "Microfluidic measurement of the size and shape of lipid-anchored proteins". Biophys J, 2024, Vol 123(19), pp 3478–3489.*
3. *Tsai A-C, Pacak CA, "Bioprocessing of Human Mesenchymal Stem Cells: From Planar Culture to Microcarrier-Based Bioreactors". Bioengineering, 2021, Vol 8(7), p 96.*
4. *Grein TA et al, "Aeration and Shear Stress Are Critical Process Parameters for the Production of Oncolytic Measles Virus". Front Bioeng Biotechnol, 2019, Vol 7, p78.*
5. *Burns AB et al, "Novel low shear 3D bioreactor for high purity mesenchymal stem cell production". PLoS ONE, 2021, Vol 16(6), art e0252575.*
6. *Amer M et al, "A Detailed Assessment of Varying Ejection Rate on Delivery Efficiency of Mesenchymal Stem Cells Using Narrow-Bore Needles". Stem Cells Transl Med, 2016, Vol 5(3), pp 366–378.*
7. *Walker P et al, "Effect of Needle Diameter and Flow Rate on Rat and Human Mesenchymal Stromal Cell Characterization and Viability". Tissue Eng Part C Methods, 2010, Vol 16(5), pp 989–97.*

"SHEAR FORCES REPRESENT A CRITICAL, OFTEN UNDERAPPRECIATED, FACTOR IN THE MANUFACTURING AND DELIVERY OF CGTs."

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Expert View

CELL AND GENE THERAPY DIGITAL INFRASTRUCTURE: REPLACING FRAGMENTATION WITH STANDARDISATION

Dr Akshay Peer examines why bespoke digital systems for cell and gene therapies are reaching a saturation point, how clinicians experience this fragmentation on the ground and why a shift towards standardisation is becoming essential for enabling safe, scalable and sustainable delivery of these innovative treatments.

Cell and gene therapies (CGTs) are highly personalised treatments that are redefining what is possible in modern medicine. By transforming patient cells into living therapeutics or using targeted genetic modifications to correct diseases at their molecular roots, CGTs can offer curative possibilities for conditions previously considered untreatable. However, this promise comes with intense operational complexity. A single therapy's journey can involve collecting patient materials, transporting them under strict temperature controls, manufacturing the product, co-ordinating data across multiple teams and maintaining a tight chain of identity and custody at every step.

Managing these processes requires an ecosystem of digital infrastructure capable of supporting precision, transparency and speed. This contrasts with today's CGT operating model, which remains fragmented and slow. Most treatment centres must juggle multiple digital portals, each built independently by individual therapy developers, to order therapies, co-ordinate manufacturing slots, track logistics and manage patient journeys. The resulting digital landscape is inefficient and increasingly unsustainable as the number of approved therapies grows.

FRAGMENTATION AT CGT TREATMENT CENTRES

The CGT digital environment has evolved to be fragmented. In the earliest days of commercial autologous therapies, when few CGTs were in production, individual developers built customised portals to manage their proprietary processes. These first platforms were logical and necessary innovations at the time – purpose-built tools to manage a new class of therapies with unprecedented supply chain constraints.

However, with the number of therapies having multiplied and major regulatory bodies anticipating a significant wave of novel CGT approvals, the problems with this "portal per product" model are more evident. Clinical and operational teams are now required to manage a patchwork of systems, each with its own nomenclature, its own workflow and its own login credentials. In many centres, staff rely on binders full of URLs, passwords, process guides and technical contacts simply to treat patients across different therapies.

Healthcare professionals consistently express frustration with the practical challenges created by today's fragmented digital landscape. Although each therapy manufacturer promotes its portal as cutting-edge, extra features matter far less in a clinical environment than having a system that is fast, intuitive and easy to use. What staff ultimately need is the ability to log in quickly, place an order, complete essential tasks and move on to the next patient without disruption.

Teams often have to manage purchase orders through a mix of inconsistent processes – some fully digital and others still dependent on paper forms, faxing or third-party systems. This lack of uniformity complicates training and creates frequent opportunities for error, particularly when new staff join or when multiple therapies are in play.

These issues are only intensifying as treatment centres expand their CGT programmes and as interest grows in

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"EACH ADDITIONAL THERAPY TYPICALLY BRINGS ANOTHER PORTAL, WORKFLOW AND TERMINOLOGY SET, ADDING TO AN ALREADY HEAVY COGNITIVE LOAD."

delivering certain cell-based therapies beyond major academic hospitals, especially in the case of administration at local- and community-level healthcare centres. Each additional therapy typically brings another portal, workflow and terminology set, adding to an already heavy cognitive load. The sheer number of IT platforms and communication channels required has the potential to overwhelm site staff. With care teams already stretched thin, layering more digital complexity onto their daily workflow is neither sustainable nor scalable. This phenomenon is now widely known in the community as "portal fatigue".

THE CHALLENGES OF BESPOKE PORTALS IN A SCALING CGT INDUSTRY

High Development Costs and Long Timelines

Custom systems require extensive engineering effort, including:

- Requirements gathering
- User experience (UX) design
- Back-end development
- Integrations
- Testing
- Validation
- Hosting
- Cybersecurity
- Ongoing maintenance.

When regulations evolve or supply chain models shift, these portals must be updated, revalidated and redeployed. This creates perpetual cost and technical debt for therapy developers.

What begins as a tool to support a single product often evolves into a long-term software commitment that requires ongoing investment. As more CGT products enter the market, duplication of these costs across dozens of companies has become economically inefficient for the entire sector.

User Experience Shortcomings That Risk Patient Safety

Most bespoke portals were designed for a single therapy workflow and do not incorporate universal UX principles or broad user input from diverse clinical settings. As a result, they often include:

- Inconsistent navigation
- Unclear labelling or terminology
- Unintuitive use steps
- Redundant data entry
- Interfaces that do not reflect real-world clinical scenarios.

Under clinical pressure, these inconsistencies can slow staff or lead to mistakes. Each additional interface compounds cognitive load, increasing the risk of miscommunication or error – issues that can directly affect treatment timelines and outcomes.

Integration Bottlenecks Across the Multi-Stakeholder CGT Network

The CGT network requires seamless co-ordination across:

- Hospitals and authorised treatment centres (ATCs)
- Community clinics
- Apheresis centres
- Manufacturing facilities
- CDMOs
- Quality assurance and quality control labs
- Distributors and depots
- Logistics providers
- Payers.

Each bespoke portal must integrate separately with these partners, resulting in dozens of redundant point-to-point integrations across the industry. Maintaining these connections is costly and slow.

Limited Flexibility as CGT Science Evolves

The pace of innovation in CGT development requires digital systems that evolve just as quickly. Bespoke portals often cannot adapt fast enough, especially when new clinical or operational workflows are introduced.

PORTAL FATIGUE: A BARRIER TO ACCESS, QUALITY AND EQUITY

The most significant consequences of portal fatigue are felt directly in the care setting. The need to navigate multiple systems introduces substantial administrative burden, consuming time that clinicians could otherwise devote to patients. Staff often have to juggle different login processes, unique terminology, various methods for requesting manufacturing slots, multiple documentation upload procedures and separate points of contact for troubleshooting. In some cases, clinicians report managing well over 10 systems at once, relying on physical lists of credentials – an approach that creates both operational inefficiency and security concerns.

This complexity also creates a significant training burden. Each new therapy brings its own portal and workflow, requiring dedicated training for every staff member involved. Treatment centres already face high turnover rates, so the constant need to onboard new personnel into a growing number of platforms only amplifies the challenge.

The impact extends beyond workflow efficiency. Fragmented data, manual transcription and inconsistent processes create opportunities for missteps or delays, which is particularly problematic given the time-sensitive nature of many autologous treatment journeys. Even small errors in scheduling, documentation or communication can have meaningful consequences for patient care.

These issues become even more pronounced as the industry seeks to expand CGT delivery into community settings.

"TREATMENT CENTRES ALREADY FACE HIGH TURNOVER RATES, SO THE CONSTANT NEED TO ONBOARD NEW PERSONNEL INTO A GROWING NUMBER OF PLATFORMS ONLY AMPLIFIES THE CHALLENGE."

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While this shift is critical for improving access, many community clinics have limited IT resources and cannot feasibly manage a proliferation of portals. Without greater standardisation, the push towards broader, more equitable access to CGTs risks slowing down or stalling altogether.

STANDARDISATION AND BUILDING A SUSTAINABLE DIGITAL ECOSYSTEM

For CGTs to scale responsibly, the sector must shift from bespoke, siloed portals towards standardised, interoperable orchestration frameworks that support multiple therapies across diverse sites.

Interoperability by Design

Rather than building one-off integrations for each therapy, a standardised architecture could enable "plug-and-play" connections through open application programming interfaces, shared data models and harmonised process steps. A successful standardised platform would be able to exchange data seamlessly with:

- Electronic health records (EHRs)
- Laboratory information systems
- Logistics platforms
- Manufacturing execution systems
- Regulatory documentation workflows.

Reduced Cognitive Load for Clinicians

A consistent user experience can reduce training time, minimise errors and give clinical teams confidence navigating workflows. When multiple therapies share similar digital touchpoints, clinicians can focus on patient care rather than portal management.

Scalability for Expanding Global Networks

Standardised systems can help therapy developers to onboard new ATCs, regions, distributors and manufacturing partners with rapid, repeatable deployment methods.

Sustainable Economic Models

Shared digital infrastructure can reduce the duplication of effort across therapy developers and improve cost predictability. In so doing, investments can be shifted from maintaining proprietary systems to enhancing shared, industry-aligned platforms.

Support for Community-Based Delivery

If, rather than bespoke portals, CGTs used standardised systems with intuitive interfaces and unified workflows, community clinics with limited digital support would be able to participate in CGT delivery more confidently and safely.

KEY CONSIDERATIONS FOR FUTURE-READY ORCHESTRATION SYSTEMS

Whether developed internally or implemented through commercial vendors, orchestration systems must be built on a set of foundational principles that ensure that they can support the evolving needs of the CGT ecosystem. Central to this is user-centric design – interfaces should be shaped by continuous input from the people who interact with them every day, both in major treatment centres and community settings. Their insights reflect the real operational pressures of CGT workflows and can help to ensure that digital tools align with practical needs, rather than abstract IT assumptions.

These systems must also offer configurable, modular architectures. As new therapies, technologies and manufacturing methods emerge, digital platforms need to be able to adapt without requiring extensive redevelopment. Flexibility and modularity can help future-proof the infrastructure and support rapid iteration as the field progresses.

Interoperability is another essential requirement. Open integration frameworks allow systems to connect smoothly with EHRs, manufacturing systems, logistics platforms and other critical components of the healthcare and supply chain ecosystem. An interoperable approach would eliminate the need for repeated bespoke integrations and reduce the risk of data silos.

Security and compliance must also be embedded at every level of system design. Given the sensitivity of patient data and the strict chain-of-identity and chain-of-custody requirements in CGT workflows, platforms must meet rigorous global standards for cybersecurity, privacy and auditability.

Finally, long-term stability matters. Therapy developers and treatment centres depend on reliable digital infrastructure, so clear visibility into product roadmaps, update cycles and ongoing support is essential. A system's value is not just in what it delivers today but in the assurance that it will continue to evolve and remain dependable as the CGT landscape continues to grow over the coming years.

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A COLLABORATIVE FUTURE: THE PATH TOWARDS INDUSTRY-WIDE STANDARDISATION

No single stakeholder can solve the fragmentation challenges facing the CGT ecosystem. Meaningful progress depends on a co-ordinated effort among therapy developers, technology providers, clinical centres, logistics partners, regulatory bodies and standards organisations. Each plays a distinct role in shaping a digital environment capable of supporting safe, scalable and efficient therapy delivery.

"MEANINGFUL PROGRESS DEPENDS ON A CO-ORDINATED EFFORT AMONG THERAPY DEVELOPERS, TECHNOLOGY PROVIDERS, CLINICAL CENTRES, LOGISTICS PARTNERS, REGULATORY BODIES AND STANDARDS ORGANISATIONS."

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To accelerate momentum towards a more unified infrastructure, several collaborative actions will be particularly important, including:

- Harmonising terminology and workflow definitions to reduce variability across platforms, particularly for steps such as slot reservation, product release and chain-of-identity confirmation.
- Strengthening participation in industry boards and cross-stakeholder working groups, ensuring that platform capabilities reflect real-world clinical needs, regulators have insight into operational pain points and manufacturers remain aligned on best practices.
- Adopting and contributing to interoperability standards, such as emerging extensions for CGTs, to support secure, efficient data exchange at scale.
- Shifting from proprietary to compatible infrastructure, recognising that the goal is not uniformity but seamless collaboration among systems developed by different organisations.

Through shared effort, the industry can move closer to a cohesive digital foundation that supports the next generation of CGT therapies.

SECURING THE FUTURE OF CGTS THROUGH DIGITAL MATURITY

CGTs are on a trajectory towards broader indications, larger patient populations and more diverse treatment settings. However, without a fundamental shift in digital strategy, fragmentation will continue to strain clinical teams, inflate operational costs and limit patient access. The industry now stands at an inflection point:

- Bespoke portals supported the first wave of CGT commercialisation, but their limitations are now clear
- Standardised, collaborative and interoperable platforms are essential for the next wave – one defined by scale, sustainability and global reach.

By embracing shared digital infrastructure and prioritising user-centric, interconnected systems, the CGT ecosystem can support the safe, efficient and equitable delivery of life-changing therapies to the patients who need them most.

ABOUT THE COMPANY

TrakCel is a provider of integrated cell and gene therapy software solutions for the orchestration and precise management, control and tracking of cell and gene therapy products. With deployments supporting a wide variety of therapy classes in industry, TrakCel has built a deep understanding of the unique challenges faced by advanced therapy developers globally.

Dr Akshay Peer

Akshay Peer, PhD, is Chief Product Officer at TrakCel. He has many years of experience in creating technology-based solutions for the cell and gene therapy industry. His long-standing tenure in the field reflects a dedicated commitment to advancing innovation and contributing to the industry's growth.

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Expert View

DRUG DELIVERY IN CELL AND GENE THERAPY: WHY EARLY DEVICE DEVELOPMENT MATTERS

Bharat Arora, Director of Global Product Quality, Cell & Gene Therapies at Vertex Pharmaceuticals, discusses how the delivery method for a cell and gene therapy is an integral part of the overall product, inextricable from the therapy itself, and how properly synchronising drug and delivery device development can greatly benefit the overall development programme.

A NEW ERA, NEW DELIVERY CHALLENGES

Cell and gene therapies (CGTs) are reshaping modern medicine; from chimeric antigen receptor T-cell (CAR-T) therapies to *in vivo* CRISPR treatments, these products offer a curative potential once considered impossible. However, alongside their promise lies a less glamorous, yet absolutely critical, reality – no matter how advanced the science, the therapy is only as effective as its delivery system.

In CGTs, the delivery system is often more than a container or conduit – it is a determinant of efficacy, safety and usability. Be it the infusion system that keeps CAR-T viable, the intrathecal catheter that precisely delivers an adeno-associated virus (AAV) vector or the prefilled syringe that ensures accurate dosing, each of these devices is inseparable from the therapy's clinical outcome.

However, in many development programmes, delivery systems are treated as an afterthought. The drug or cell product drives early-stage attention, while device integration is deferred until the later clinical phases. This imbalance creates major risks, including delays in clinical trials, increased regulatory scrutiny, the need for redesigns and even post-approval issues.

THE ASYMMETRY OF DRUG AND DEVICE DEVELOPMENT

One reason delivery systems lag is that drugs and devices live in different development universes:

- Drugs and biologics follow a well-trodden path of preclinical toxicology, clinical phases and chemistry, manufacturing and controls (CMC)
- Devices are governed by engineering principles, design controls and iterative usability testing.

A level of integration between drug development and device development teams is crucial during early-stage development. When teams are integrated correctly, drug development efforts provide desirable inputs to design control elements for the device (Figure 1).

However, drug and device timelines rarely align; a gene therapy vector may be ready for Phase I trials long

"IN CGTs, THE DELIVERY SYSTEM IS OFTEN MORE THAN A CONTAINER OR CONDUIT – IT IS A DETERMINANT OF EFFICACY, SAFETY AND USABILITY."

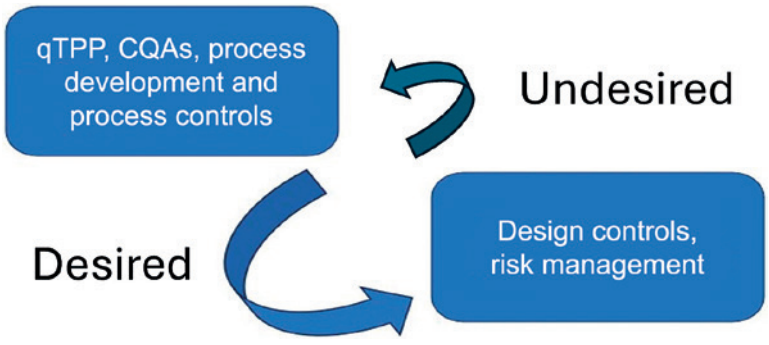

Figure 1: Desired and undesired information flow between drug and device development. (qTPP: Quality Target Product Profile, CQA: Critical Quality Attribute)

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Drug Development	Device Development
Formulation Development (Target Product Profile)	Design Inputs (User Needs, Device Requirements, Use/Hazard Analysis)
Process Development (Critical Quality Attributes, Critical Process Parameters, Stability)	Design Outputs (Specifications, Prototypes, Essential Requirements)
Process Qualification (Engineering Runs, Characterisation Studies)	Design Verification and Validation
Process Risk Assessment	Risk Management File (Risk Plan, Design/Use/Process Risk Analysis, Risk Report)

Table 1: Side by side comparison of early-stage drug and device development activities.

before the catheter or infusion set is fully characterised. Conversely, a proven device may not meet the unique needs of fragile biologics. For small molecules, late device integration can sometimes be tolerated, but, for CGTs, the delivery interface defines whether or not the product works at all.

Table 1 shows a high-level side-by-side comparison of drug and device development activities during early development. The US FDA's guidance "Current Good Manufacturing Practice Requirements for Combination Products" provides guidance on how cGMP requirements apply to combination products, and how device and drug regulations overlap.

"DRUG AND DEVICE TIMELINES RARELY ALIGN; A GENE THERAPY VECTOR MAY BE READY FOR PHASE I TRIALS LONG BEFORE THE CATHETER OR INFUSION SET IS FULLY CHARACTERISED. CONVERSELY, A PROVEN DEVICE MAY NOT MEET THE UNIQUE NEEDS OF FRAGILE BIOLOGICS."

WHY EARLY DEVICE DEVELOPMENT IS NON-NEGOTIABLE

A more pragmatic, risk-based approach is to treat drug and device as co-equal from day one. The FDA guidance "Early Development Considerations for Innovative Combination Products" provides valuable insights on scientific, technical and regulatory issues when combining drugs, biologics and devices early in development. Delaying device development can trigger cascading problems:

- **Regulatory Delays:** Agencies expect evidence of drug-device compatibility before pivotal trials. The FDA's Center for Biologics Evaluation and Research (CBER) and Center for Devices and Radiological Health (CDRH), as well as the EMA's Committee for Advanced Therapies (CAT), all emphasise early alignment
- **Clinical Risk:** Suboptimal devices can compromise cell viability, affect biodistribution or alter pharmacokinetics
- **Manufacturing Disruption:** Device-related variability (e.g. shear forces, adsorption, extractables and leachables) can invalidate batches
- **User Failure:** Poorly designed systems can increase dosing errors or reduce adherence, especially in outpatient or home settings
- **Cost Escalation:** Redesigns late in development often require bridging studies or new stability data, adding millions to programme costs.

When the investigational product is a gene therapy, the FDA's guidance "CMC Information for Human Gene Therapy IND Applications" offers recommendations on how to include device or delivery aspects.

FIT-FOR-PURPOSE DEVICES: ENGINEERING FOR BIOLOGY

During early development stages, developers should characterise the device not as a commodity but as an enabler of the therapy. Critical considerations include:

- **Physical Forces:** Shear stress in tubing or pumps can rupture cells or destabilise viral capsids
- **Volume and Viscosity:** Many gene therapy formulations are highly viscous, requiring specialised syringes or autoinjectors
- **Container Closure Integrity:** AAV vectors or messenger RNA (mRNA) are sensitive to oxygen and moisture, so their primary packaging must protect their integrity
- **Delivery Accuracy:** Variability in residual volume can alter the delivered dose by clinically meaningful margins
- **Temperature Control:** Cryopreserved cell therapies demand devices that are compatible with cold chain workflows.

The concept of essential performance requirements or essential drug delivery outputs, borrowed from device regulations, should be generally applied to biologics. For example, in a prefilled syringe, break-loose and glide forces are not just ergonomic metrics; they determine whether or not a fragile biologic is delivered intact. The article "Opportunities and Challenges in Biologic Drug Delivery" provides useful information on delivery challenges (e.g. viscosity, stability, adsorption) for biologics that parallel those for CGTs.[1]

LESSONS FROM REAL-WORLD EXAMPLES

The following examples highlight that the challenges of delivery do not have a universal solution – it must be engineered to suit the specific biology of each therapy. The article "Watershed Year of Cell and Gene Therapy (CGT): A Review" provides additional examples on the evolving landscape and momentum of CGTs to supplement those presented here.[2]

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CAR-T Therapies

Approved CAR-T therapies, such as Kymriah (tisagenlecleucel, Novartis) and Yescarta (axicabtagene ciloleucel, Kite Pharma, Santa Monica, CA, US), rely on infusion bags and transfer sets designed to preserve cell viability. Early development challenges included cell loss due to adsorption on tubing surfaces and viability drops linked to pump systems. These issues underscored the importance of testing device-cell interactions before scaling manufacturing.[3]

Spinal Delivery of AAV Gene Therapies

Intrathecal delivery of AAV vectors, as in Zolgensma (onasemnogene abeparvovec-xioi, Novartis) clinical programmes, required specialised catheters to ensure accurate placement and flow rates. Regulatory agencies scrutinised these delivery systems closely, recognising that off-target dosing could create severe risks.

Prefilled Syringes for mRNA Vaccines

While not CGTs, mRNA vaccines highlighted the importance of syringe compatibility, where adsorption of lipid nanoparticles to syringe surfaces was a critical risk, necessitating material-specific testing. This lesson can be directly applied to future *in vivo* gene therapies.

GLOBAL REGULATORY COMPLEXITY

Combination products straddle regulatory silos. For example, in the US:

- CBER/CDER regulate the biologic component
- CDRH governs device performance
- Final jurisdiction depends on the "primary mode of action".

In Europe, the EMA's CAT evaluates advanced therapy medicinal products (ATMPs), with device conformity assessed under the Medical Device Regulation (MDR). Japan, China and other regions apply their own hybrids of drug and device frameworks.

The 21st Century Cures Act in the US and the MDR in the EU both elevate the importance of early drug-device integration. Global developers must plan for divergent but overlapping requirements.

> "ENGAGING REGULATORS EARLY ISN'T OPTIONAL – IT IS A SURVIVAL STRATEGY FOR CGT DEVELOPERS."

The article "A Regulatory Risk-Based Approach to ATMP/CGT" discusses regulatory strategies for both the EU and the US, as well as risk-based planning for advanced therapies.[4]

KEY TESTING PRIORITIES FOR CGT COMBINATION PRODUCTS

Engaging regulators early is not optional – it is a survival strategy for CGT developers. Some key priorities include:

- **Extractables and Leachables**: Detecting impurities that migrate from device materials into biologics
- **Drug-Device Interactions**: Adsorption of proteins, viral vectors or cells onto device surfaces
- **Stability Under Delivery Conditions**: Ensuring that biologics remain intact during infusion, injection and storage
- **Performance Testing**: Residual volume, dose accuracy, injection forces and flow rates
- **Usability and Human Factors**: Validating device operation under real-world conditions.

LIFECYCLE PLANNING: BEYOND FIRST APPROVAL

Delivery challenges do not end with approval. Lifecycle changes – new manufacturing sites, material substitutions and production scale-up – can all impact product quality. Regulators increasingly require "line of sight" planning that anticipates post-approval changes.

Smart developers use a total product lifecycle model, embedding feedback loops from clinical trials, supply chains and post-market surveillance back into design. By implementing transparency across suppliers and CDMOs, drug developers can ensure continuity throughout product development and commercialisation.

FUTURE HORIZONS: DIGITIAL, CONNECTED AND SUSTAINABLE DELIVERY

The CGT market is continually growing. While these therapies are currently focused on managing monogenic disorders produced by a mutation in a single gene, such as severe combined immunodeficiency, muscular dystrophy and haemophilia, the scope of CGTs is increasing to target more complicated multigenic diseases, such as tumours, cardiac disease and diabetes, by changing the expression of multiple genes instantaneously.

According to Nova One Advisor (Pune, India), the global CGT market size is expected to be worth around US$119.30 billion (£90.78 billion) by 2034, increasing from $25.89 billion in 2025, representing a healthy compound annual growth rate of 18.5% from 2025 to 2034.[5] And the future of CGT delivery will not stop at syringes and catheters – emerging trends include:

- Connected devices that track dosing, flow rates and patient adherence
- Digital twins for device-drug systems, enabling predictive modelling of performance
- Sustainable materials, driven by a push from regulators and patients for greener supply chains
- Platform devices, where a single delivery system supports multiple therapies, reducing redundancy.

For CGTs, these innovations could be game-changers – but only if planned early.

CONCLUSION: DELIVERY DEFINES SUCCESS

The message is simple – in CGT, the delivery system is not a separate component; it is the therapy's partner. Treating drug and device as co-equal from the outset reduces risk, accelerates approvals and ensures that patients receive therapies that are both safe and effective. By merging quality by design with design controls, embracing risk-based integration and effectively planning the development lifecycle, developers can transform delivery from a bottleneck into a differentiator.

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In the race to bring curative therapies to patients, those who master delivery will define the future of CGTs.

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REFERENCES

1. *Hooven MD, "Opportunities and Challenges in Biologic Drug Delivery". American Pharmaceutical Review, Dec 2017.*
2. *Jian A et al, "Watershed year of cell and gene therapy (CGT): A review of 2024 CGT approvals". Cancer Lett, 2025, Vol 632, art 217980.*
3. *Awasthi R et al, "Kymriah® (tisagenlecleucel) - An overview of the clinical development journey of the first approved CAR-T therapy". Hum Vaccin Immunother, 2023, Vol 19, art 2210046.*
4. *Salazar-Fontana LI, "A Regulatory Risk-Based Approach to ATMP/CGT Development: Integrating Scientific Challenges With Current Regulatory Expectations". Front Med (Lausanne), 2022, Vol 9, art 855100.*
5. *"Cell and Gene Therapy Market Size Expected to Hit USD 119.30 Billion by 2034". Press Release, BioSpace, Sep 2025.*

"TREATING DRUG AND DEVICE AS CO-EQUAL FROM THE OUTSET REDUCES RISK, ACCELERATES APPROVALS AND ENSURES THAT PATIENTS RECEIVE THERAPIES THAT ARE BOTH SAFE AND EFFECTIVE."

Bharat Arora

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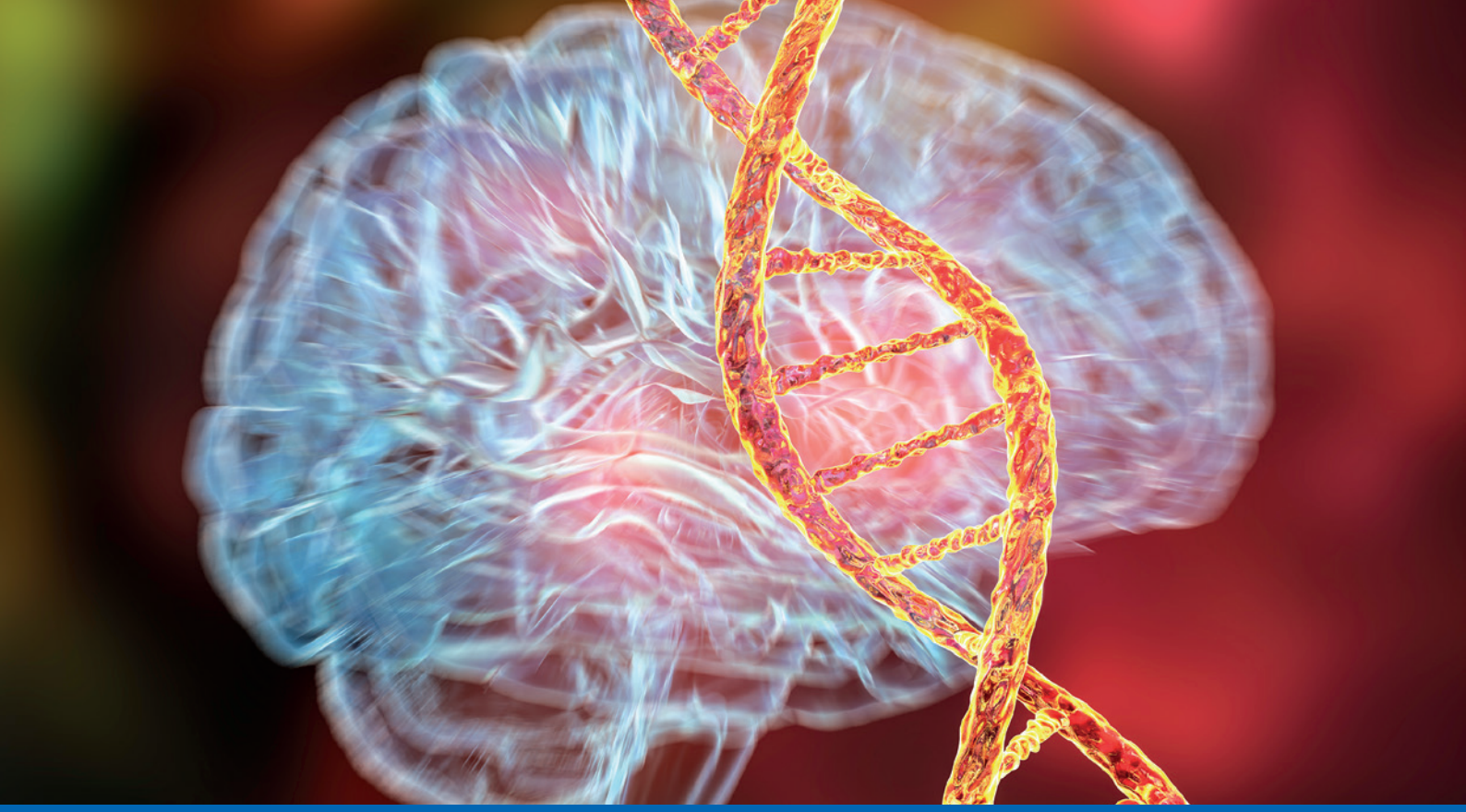

Early Insight

PRECISION DELIVERY: SEAMLESS COLLABORATION FOR DELIVERING NEURO-THERAPEUTICS

neurochase
Next generation CNS delivery

Fearsome

Professor Steven Gill of **Neurochase** and **Alan Suttie** of **Fearsome** provide insight into the unique collaboration and design philosophy behind their novel scalable interventional delivery system for gene and cell therapies – the Neurochase Acute Drug Delivery System.

A NEW PARADIGM FOR INTRAPARENCHYMAL DRUG DELIVERY

In the rapidly evolving landscape of gene and cell therapies, the challenge of safely and effectively delivering treatments directly to the brain in a scalable manner remains a critical hurdle. For therapies targeting neurological conditions, systemic administration is often ineffective – and potentially toxic – with less than 1% of the dose reaching the target.

Whilst existing intraparenchymal delivery methods are effective, they involve lengthy and complex surgeries that will make them challenging to roll out for more common indications. Instead, meeting this need will demand a precision-guided approach that needs to be faster and provide better target coverage than the currently available options. Together, Neurochase and Fearsome, have developed the Neurochase Acute Drug Delivery System (Figure 1) – an innovative approach that emphasises a tight synergy between deep clinical expertise and engineering to overcome fundamental physiological and logistical challenges.

The foundation of the project's success arises from a single point of inspiration. Neurochase's unique combination of decades of surgical leadership in intraparenchymal drug delivery together with an intuitive understanding of physiology and engineering, provided the Fearsome team with an unparalleled starting point. This vision was not just about

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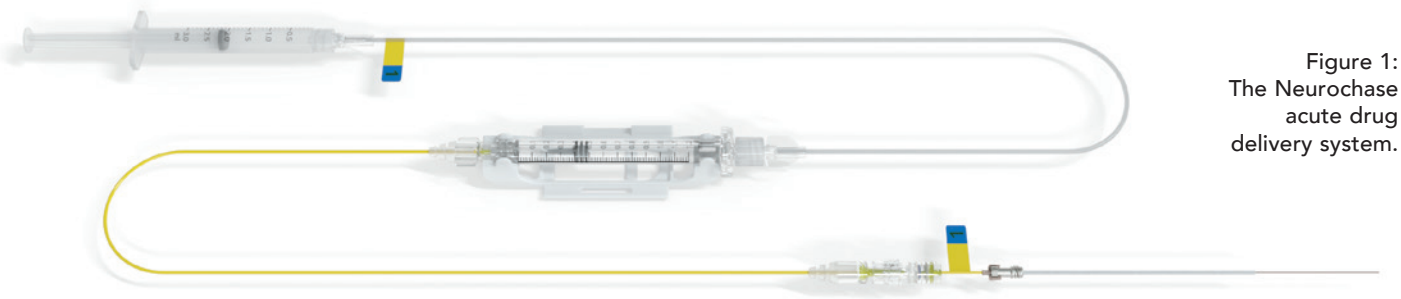

Figure 1: The Neurochase acute drug delivery system.

the device, but rather the critical interface between the synthetic device, therapeutic agent and delicate brain physiology.

PRIORITISING THE END RESULT: CONTROLLED INFUSION

The Neurochase Acute Drug Delivery System was developed from a singular focal point – the ultimate delivery of the therapeutic. The key objective of the system is that it has to produce a certain shape of infused volume within the brain at the end of the procedure. Achieving this required mastering an extraordinarily complex technical problem: controlled volume infusion. As an analogy, imagine trying to blow up a balloon without there actually being a skin on the balloon. The team needed to model fluid behaviour influenced by precise flow rates and cannula tip pressure to design unique features into the system.

The necessity of direct delivery is driven by the biology of gene therapy. For most gene therapies, it is critical that sufficient numbers of viral particles penetrate each cell to ensure that the therapy actually works. If the therapy is administered systemically by intravenous infusion, only about 0.1% of the given dose enters the brain – the rest of it goes to the liver and is quite toxic. As such, it is important to have tight control of the dose and make sure that it ends up in the right place.

"IF THE THERAPY IS ADMINISTERED SYSTEMICALLY, ONLY ABOUT 0.1% OF THE DOSE GIVEN ENTERS THE BRAIN – THE REST OF IT GOES TO THE LIVER AND IS QUITE TOXIC. AS SUCH, IT IS IMPORTANT TO HAVE TIGHT CONTROL OF THE DOSE AND MAKE SURE THAT IT ENDS UP IN THE RIGHT PLACE."

TACKLING TECHNICAL HURDLES: REFLUX CONTROL

One of the most persistent technical challenges in intraparenchymal drug delivery is managing reflux – the backwards flow of infusate along the cannula track, which can lead to insufficient dosing at the target and potentially toxic dose accumulation outside the target area. The development team's solution diverges from traditional "point source" delivery, where a very fine rigid tube passed into the brain tissue creates a tissue seal. This produces a spherical volume, but creates a source of very high pressure at a single point, which may cause tissue damage.

To overcome this, the final design of the Neurochase Acute Drug Delivery System focuses on distributing the infusate along the exposed length of the cannula to maintain lower pressure at any single point, minimising tissue damage and maximising distribution (Figure 2). The result is a system designed to control reflux, while achieving more than 70% coverage of the target structure.

The Neurochase Acute Drug Delivery System has a unique proprietary cannula design that allows the fluid to run back along the exposed length of the cannula up to the step. Furthermore, it has a soft, coated outer guide-tube design

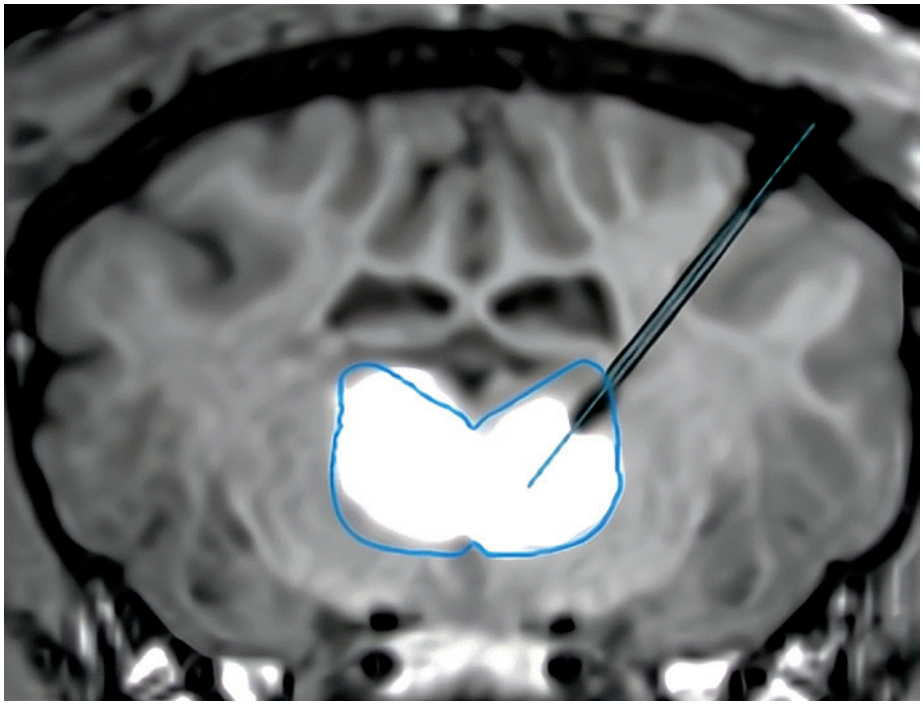

Figure 2: Magnetic resonance imaging (MRI) showing a real-time infusion into the thalamus using the Neurochase Acute Drug Delivery System of a gene therapy co-labelled with MRI contrast agent gadolinium to enhance visibility.

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that prevents the fluid from travelling any further. This innovative approach is critical for achieving the intended distribution of volume deep within the brain tissue.

DESIGNING OUT HUMAN ERROR: CLINICAL WORKFLOW FIRST

A core principle of the collaboration between Neurochase and Fearsome was ensuring that the device is intuitive and robust in the stressful environment of an operating room. Both partners emphasised the importance of designing the clinical workflow to be human-error-proof.

For the infusion phase, the system removes the necessity for manual programming of multiple pumps. Instead, a patented "dispenser" concept ensures that the drug is prepared and checked by the hospital pharmacist, enabling the technician or nurse to simply connect pre-labelled components (Catheter #1 to Dispenser #1, and so on) and start the infusions. This workflow-led design ensures that precision is baked into the system, reducing dependence on the surgeon's real-time calculations and minimising human error.

THE OPERATING ROOM VERSUS THE DRAWING BOARD

Designing novel drug delivery systems forces a meeting between rigid engineering requirements and the dynamic realities of surgical practice. That meeting often produces productive, albeit challenging, tension. Developing highly complex medical devices requires rigorous documentation and controlled processes. Even small changes may need extensive paperwork, sign-offs and re-testing to meet the necessary regulatory and internal standards.

Creating innovative and useful solutions, in contrast, requires rapid and agile iteration – identify what failed, understand why and fix it. This is especially important when working without precedent and pushing into true innovation. Developers will always want to keep refining the device, but there is a process to go through and that is where the challenge lies. From an engineering perspective, there is a huge amount of work done to document progress, which can make quick pivots difficult.

At its heart, the friction is simple: surgical practice demands speed and adaptability; patient safety and regulators demand process and evidence. Resolving that tension requires a deliberate compromise. The Fearsome team balanced responsiveness with rigour by batching and gating changes. Surgical feedback was collected comprehensively but implemented only at defined design-review points and scheduled development cycles. This approach preserved iterative learning while producing the coherent, traceable body of evidence regulators require. By clearly defining when the drawing board could adapt to the operating room, the team kept their innovative momentum alive without sacrificing the discipline necessary for safe, compliant medical device development.

"BOTH PARTNERS EMPHASISED THE IMPORTANCE OF DESIGNING THE CLINICAL WORKFLOW TO BE HUMAN-ERROR-PROOF."

Figure 3: A subset of the joint Fearsome and Neurochase innovation team.

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PRECLINICAL IMPERATIVE: THE COST OF NOVELTY

Because the Neurochase Acute Drug Delivery System represents a significant advance in the field of direct brain drug delivery, the team could not rely on existing benchmarks. Determining the performance bar for this novel device hinged on rigorous *in vivo* preclinical validation. The team had to scrutinise why the device concept did or did not work and try to understand what was going on throughout the development process.

This constant feedback loop, which involved Fearsome engineers observing hundreds of live procedures, provided the essential physiological data needed to refine the system's mechanics. The success of the system is a function of the mechanics being subservient to the physiology, ensuring that the device enables the desired clinical effect without causing harm. Unlike traditional models, where medical device engineers might meet with end users once or twice a year, the Neurochase and Fearsome collaboration enabled near-daily iteration. The engineering team observed and scrutinised every preclinical procedure, immediately feeding data back into the design process.

Professor Steven Gill

Professor Steven Gill, Founder and Chief Scientific Officer of Neurochase, is an expert in drug delivery strategies for the central nervous system (CNS). An eminent neurosurgeon with over 30 years of experience, he has led multiple preclinical and clinical trials proving out the potential of convection-enhanced delivery and gene therapies. Professor Gill is also a prolific inventor of medical technology, including the Prestige Cervical joint (Medtronic), and has pioneered deep brain stimulation of novel targets in the brain. He is an industry-leading expert on the delivery of novel therapeutics to the CNS and frequently consults with key decision-makers from many of the world's biggest pharmaceutical and biotech organisations.

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> "UNLIKE TRADITIONAL MODELS, WHERE MEDICAL DEVICE ENGINEERS MIGHT MEET WITH END USERS ONCE OR TWICE A YEAR, THE NEUROCHASE AND FEARSOME COLLABORATION ENABLED NEAR-DAILY ITERATION."

Alan Suttie

Alan Suttie is founder and managing director of Fearsome, with two decades of experience bridging clinical practice and device engineering, leading multidisciplinary teams to deliver practical solutions for complex procedural challenges. He is an advocate for clinician-engineer collaboration, exposing engineers to the clinical environment, and vice versa, to accelerate patient-impacting innovation. Since 2015, Mr Suttie has been increasingly focused on solving the intricate challenges that arise where physiology, device and drug must come together harmoniously in a novel drug delivery system.

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The collaboration between Neurochase and Fearsome is best described as a seamless, high-velocity fusion of deep clinical expertise and responsive, innovative engineering (Figure 3). The partnership's unique structure is successfully tackling a novel and complex medical device challenge and is accelerating the path to life-changing neurological therapies.

ABOUT THE COMPANIES

Neurochase is a UK-based biotechnology company focused on developing innovative medical devices and delivering consulting services for central nervous system drug delivery. Founded in 2020, it is dedicated to developing efficient, effective and scalable solutions to deliver targeted treatments for a wide range of neurological disorders currently impacting hundreds of millions of people globally.

Fearsome is a contract design and development company working with leading clinicians and med-tech and biopharma clients to realise innovative medical devices. Established in 2002, the company provides comprehensive, end-to-end services focusing on high-risk devices and targeted drug delivery systems. Its multi-disciplinary team is experienced in ocular and neurological programmes.

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Expert View

IMPROVING RNA THERAPEUTIC TARGETING BEYOND DELIVERY

Dr Fiona McLaughlin and **Dr Mark Edbrooke** of N4 Pharma discuss the possibilities for developing novel cancer treatments using functionalised nanoparticles, in order to transport a variety of therapies into the tumour microenvironment.

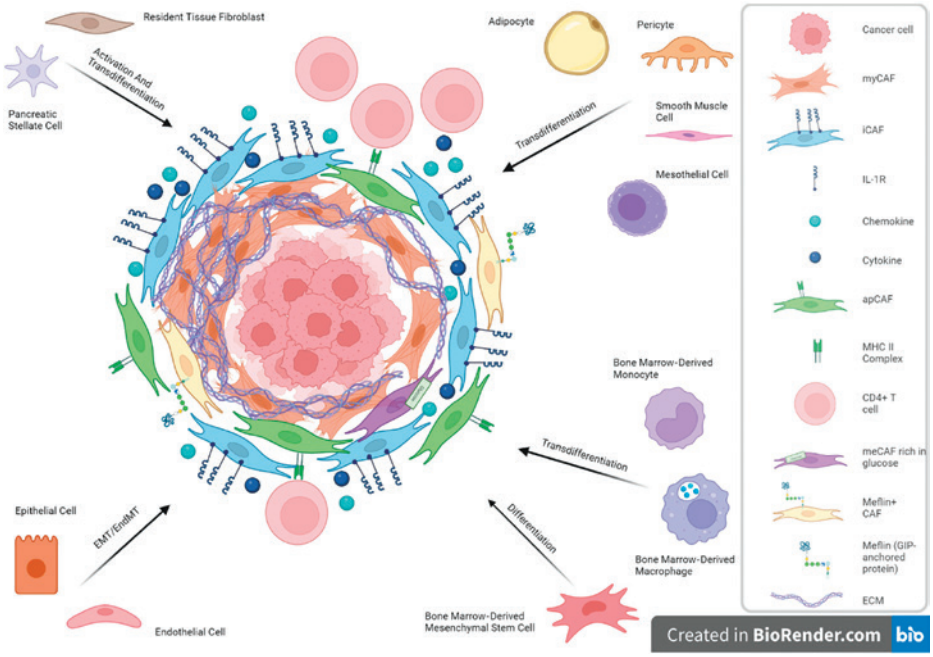
In oncology, the low therapeutic index of traditional chemotherapy drugs poses a persistent barrier – achieving cytotoxic concentrations in tumour cells often results in systemic toxicity that limits efficacy. The rise of ribonucleic acid (RNA) therapeutics, comprising antisense oligonucleotides (ASOs), small interfering RNA (siRNA) and microRNA, offers a route to greater precision. Over the past five years, the number of US FDA-approved RNA therapeutics has risen sharply, yet all currently approved drugs of this class involve either "local" delivery to the central nervous system or only target a single organ – the liver – because no clinically validated platform has yet achieved safe, targeted delivery elsewhere in the body.[1]

The "genome era" has enabled researchers to map disease-causing mutations, spurring the development of personalised nucleic acid drugs capable of silencing or modulating these mutations. The challenge now is to direct these powerful molecules accurately to their intended cellular targets beyond the liver, particularly in complex solid tumours.

BEYOND SINGLE-TARGET DELIVERY

Recent research emphasises that multi-targeting and dual loading are the next transformative steps in cancer treatment.[2,3] If RNA therapeutics can be delivered selectively not only to tumour cells, but also to the cells of the surrounding tumour microenvironment (TME), such as

"THE CHALLENGE NOW IS TO DIRECT THESE POWERFUL MOLECULES ACCURATELY TO THEIR INTENDED CELLULAR TARGETS BEYOND THE LIVER, PARTICULARLY IN COMPLEX SOLID TUMOURS."



Epithelial-mesenchymal transition / endothelial-mesenchymal transition (EMT/EndMT), myofibroblastic CAF (myCAF), inflammatory CAF (iCAF), interleukin-1 receptor (IL-1R), antigen-presenting CAF (apCAF), major histocompatibility complex Class II (MHC II), metabolic CAF (meCAF), extracellular matrix (ECM).

Figure 1: A diagram illustrating CAFs and cellular origin heterogeneity in pancreatic ductal adenocarcinoma.[4]

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fibroblasts, macrophages or T-cells, then multiple disease pathways could be modulated simultaneously. Furthermore, co-delivering two distinct cargos (for example dual siRNAs or an siRNA with a chemotherapeutic) could notably increase therapeutic precision and overcome resistance mechanisms.

Nanoparticle-mediated active targeting strategies, such as arginyl-glycyl-aspartic acid (RGD)-functionalised particles that recognise integrins overexpressed in the TME, offer substantial improvements to therapeutic index and delivery accuracy. These targeted systems overcome the limitations of relying on passive accumulation via the enhanced permeability and retention effect, and enable selective delivery to stromal and immune cells within tumours. Functionalised nanoparticles also exhibit stimuli-responsive features, such as pH-triggered release in the acidic TME, enhancing localised cargo delivery and minimising systemic exposure.

OVERCOMING CURRENT CHALLENGES

An example of the challenge of drug delivery is illustrated by pancreatic carcinoma where up to 90% of the tumour mass consists of cancer-associated fibroblasts (CAFs) and only 10% of malignant epithelial cells (Figure 1).[5] The dense extracellular matrix produced by activated CAFs acts as a physical barrier to conventional drug penetration, whether they are small molecules or biologics. Similarly, immunotherapies struggle because the fibrotic and hypoxic microenvironment restricts immune cell infiltration. Overcoming this requires systems that can target both tumour cells and stromal elements, ideally delivering distinct but complementary cargos.

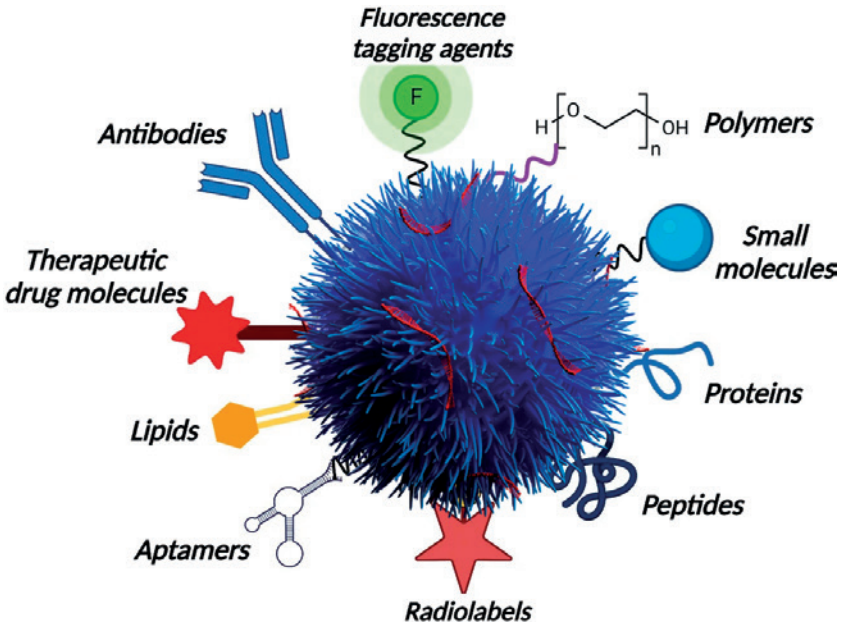

Figure 2: A diagram illustrating how Nuvec® (N4 Pharma) silica nanoparticles can be functionalised to deliver multiple therapeutic and diagnostic agents.

Beyond chemical modifications to improve nanoparticle stability, the use of bispecific ligands targeting both CAF-associated proteins and integrins significantly enhances tumour uptake and therapeutic efficacy. This dual-targeting approach is central to tackling stromal barriers, which traditional drugs cannot cross efficiently. Early preclinical platforms such as silica-based nanoparticles are now being engineered specifically for this multifaceted targeting, providing a sophisticated bridge between nanotechnology and tumour biology.

ONE PAYLOAD IS NOT ENOUGH

Tumour heterogeneity and adaptive resistance limit the long-term efficacy of single-agent therapies. Combination or multi-drug delivery systems allow simultaneous modulation of different cancer pathways and phenotypes.[3]

> "EARLY PRECLINICAL PLATFORMS SUCH AS SILICA-BASED NANOPARTICLES ARE NOW BEING ENGINEERED SPECIFICALLY FOR THIS MULTIFACETED TARGETING, PROVIDING A SOPHISTICATED BRIDGE BETWEEN NANOTECHNOLOGY AND TUMOUR BIOLOGY."

For instance, systems that can carry multiple cargos, such as siRNAs targeting both epidermal growth factor receptor and polo-like kinase 1 in non-small cell lung cancer, have demonstrated improved inhibition and reduced compensatory resistance.[6] Similarly, co-loading chemotherapeutic and RNA agents within a single carrier enables synergistic control of tumour growth and immune modulation. PEGylation and surface functionalisation further improve circulation and protect therapeutic cargo from proteolytic degradation en route to their targets.

DIFFERENTIATING TARGETS IN ONCOLOGY

Recent studies using silica nanoparticle-based delivery systems demonstrate how scalable, precision-engineered platforms can be fine-tuned for multi-target approaches. Advances in surface functionalisation, including the attachment of antibodies, ligands or aptamers, enable nanoparticles to recognise specific receptor patterns across tumour and non-tumour cells in the TME (Figure 2).

A mesoporous silica-based nanoparticle can deliver siRNAs or small molecules to multiple cell types simultaneously, ensuring deeper tissue penetration and balanced modulation of tumour biology.

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For example, functionalisation with an αvβ6 ligand achieved precise RNA delivery into epithelial tumour cells, including lung, breast, prostate and pancreatic adenocarcinomas. These targeted systems can achieve selective uptake, confirming that they can be steered to specific cancer subtypes, a major advance over non-functionalised platforms. This multi-receptor approach offers a translational pathway to address tumour heterogeneity, validated by significant progress in the development of preclinical lung and pancreatic models.

AMPLIFYING SUCCESS

The promise of dual-cargo, multi-target nanoparticle therapies lies in their modularity. In principle, delivery platforms can:

- Load different modalities (small molecules, oligonucleotides or peptides) tuned for specific release profiles
- Target multiple cell types, whether malignant, stromal or immune, by incorporating diverse ligands on its surface
- Exhibit environment-sensitive release, responding to the acidity, redox conditions or enzyme composition of the TME to ensure localised administration for systemic use.

These attributes align directly with the evolving commercial need for precision RNA therapeutics. With scalable manufacturing and predictable safety profiles, silica nanoparticle carriers could enable precise delivery of siRNA or ASO drugs to previously inaccessible tissues, extending the use of RNA therapeutics beyond hepatic models to complex cancers. Notably, studies from Lorenzoni *et al* stress the need for harmonised physico-chemical characterisation, toxicity evaluation and manufacturing standards to ensure clinical translation of such advanced nanoparticles.[2] Collaborative frameworks between researchers, clinicians and regulatory bodies will be vital for success.

CONCLUSION

The convergence of dual loading and multi-targeting provide a practical pathway towards overcoming the two greatest obstacles in oncology therapeutics: tumour heterogeneity and microenvironmental resistance. As highlighted by the emerging literature on RGD-functionalised systems, precision nanoparticle delivery can orchestrate simultaneous engagement of multiple pathways across the tumour ecosystem, transforming how efficacy, safety and resistance of these therapies are balanced.

Silica nanoparticle carriers exemplify the next evolutionary step towards

"SILICA NANOPARTICLE CARRIERS EXEMPLIFY THE NEXT EVOLUTIONARY STEP TOWARDS SCALABLE, PRECISE AND ADAPTABLE DELIVERY SYSTEMS FOR RNA AND COMBINATION ONCOLOGY THERAPEUTICS."

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scalable, precise and adaptable delivery systems for RNA and combination oncology therapeutics. While technical and translational challenges remain, such as protein corona formation and patient-specific microenvironment variability, the strategic integration of targeting ligands and multiplexed cargos offers a roadmap towards more effective, less toxic cancer treatments, redefining the therapeutic landscape for complex malignancies such as pancreatic and lung cancer.

By integrating adaptive design principles from nanotechnology with precision targets derived from molecular oncology, silica nanoparticle systems can transform how RNA and combination therapies are deployed.

"BY INTEGRATING ADAPTIVE DESIGN PRINCIPLES FROM NANOTECHNOLOGY WITH PRECISION TARGETS DERIVED FROM MOLECULAR ONCOLOGY, SILICA NANOPARTICLE SYSTEMS CAN TRANSFORM HOW RNA AND COMBINATION THERAPIES ARE DEPLOYED."

Dr Fiona McLaughlin

Fiona McLaughlin, PhD, Head of Research and Development at N4 Pharma, is an experienced oncology drug developer and independent consultant, bringing over 25 years of experience in research and translational drug development in the pharmaceutical and biotech sectors, having led teams from early research through to clinical development. Dr McLaughlin started her career at GSK and has held leadership positions in biotech companies including Avacta Therapeutics, Algeta ASA (now Bayer), Antisoma plc and BTG plc (now part of Boston Scientific). She is also a non-executive director of Hox Therapeutics. Dr McLaughlin received a PhD from the Haematology Department at Cambridge University (UK) and has a BSc in Biochemistry from Glasgow University (UK).

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Mark Edbrooke, PhD, Head of Strategy at N4 Pharma, is an independent scientific consultant with broad experience in pharmaceutical R&D. During 25 years at GSK, he ran a transnational functional genomics department, then set up and led GSK's therapeutic nucleic acid unit. Dr Edbrooke then joined AstraZeneca's Oncology Division for three years, working with Ionis and Moderna. He currently has a portfolio of clients including UK- and US-based investment companies, UK- and European-based universities, and small biotech companies including being Head of Translational Research at Argonaute RNA and on the scientific advisory board for Deep Genomics.

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ABOUT THE COMPANY

N4 Pharma is a preclinical biotech company developing Nuvec®, its proprietary gene delivery system, to enable advanced therapies for cancer and other diseases. RNA therapeutics are set to impact the treatment of a wide range of diseases and Nuvec® has several key advantages for RNA gene delivery, including the ability to deliver multiple RNA therapies in a single particle, ease of manufacturing, protection of the RNA payload to allow for oral delivery, no unwanted immune response and excellent stability and storage.

REFERENCES

1. *Jo SJ et al, "Clinical pharmacokinetics of approved RNA therapeutics". Int J Mol Sci, 2023, Vol 24(1), p 746.*
2. *Lorenzoni S, Rodríguez-Nogales C, Blanco-Prieto MJ, "Targeting tumor microenvironment with RGD-functionalized nanoparticles for precision cancer therapy". Cancer Lett, 2025, Vol 614, art 217536.*
3. *Imtiaz S et al, "Mechanistic study of cancer drug delivery: current techniques, limitations, and future prospects". Eur J Med Chem, 2025, Vol 290, art 117535.*
4. *Saúde-Conde R et al, "Cancer-associated fibroblasts in pancreatic ductal adenocarcinoma or ametaphor for heterogeneity: from single-cell analysis to whole-body imaging". Biomedicines, 2024, Vol 12(3), p 591.*
5. *Domen A et al, "Cancer-associated fibroblasts as a common orchestrator of therapy resistance in lung and pancreatic cancer". Cancers, 2021, Vol 13(5), p 987.*
6. *Chai M et al, "Targeted and intelligent nano-drug delivery systems for colorectal cancer treatment". Front Bioeng Biotechnol, 2025, Vol 13, art 1582659.*

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Expert View

REVEALING THE FRONTIER: DRUG DELIVERY CHALLENGES AND INNOVATIONS IN OCULAR GENE THERAPY

Dr Max Chambers of Team Consulting discusses novel approaches for delivering ocular gene therapies, summarising the challenges and benefits of various delivery routes and exploring the devices used to successfully improve vision.

"DELIVERY VECTORS MUST DIFFUSE OVER A CONSIDERABLE DISTANCE THROUGH THE VITREOUS HUMOUR TO REACH THE THERAPEUTIC SITE – WHILE AVOIDING NEUTRALISATION BY ANTIBODIES, TRAVERSING THE INNER LIMITING MEMBRANE AND SUCCESSFULLY DELIVERING A TRANSGENE TO THE NUCLEUS OF EACH TARGET CELL."

Eyesight is precious and taking care of it is crucially important, not just to patients, but also to the healthcare systems that support it. The eye presents a number of advantages for the administration of drugs. It is an immune-privileged environment, having no lymphatic vessels, which results in a lower rate of adverse responses compared with systemic administration, while providing a good therapeutic effect from relatively low drug doses.

Gene therapy has emerged as one of the most promising frontiers in ophthalmology as a treatment modality for inherited or acquired diseases, from inherited retinal disorders (IRDs) to age-related macular degeneration (AMD) and diabetic retinopathy. Current treatments for these diseases often involve periodic intravitreal injections, which places a burden on both patients and clinics. As such, opportunities for "one-and-done" treatments for ocular diseases have attracted considerable investment due to their potential to bring transformative benefits for patients. However, the success of these therapies hinges not only on the genetic payload but, critically, on how and where it is delivered.

OPHTHALMIC GENE THERAPIES

Gene therapies in ophthalmology can be broadly categorised into two types:

- **Gene Replacement Therapies:** These aim to correct defective genes in IRDs, such as RPE65-related retinal dystrophy.
- **Therapeutic Gene Therapies:** These transform the eye into a bio-factory to produce therapeutic proteins, such as anti-vascular endothelial growth factor (VEGF) agents for wet AMD.

"THE SUCCESS OF THESE THERAPIES HINGES NOT ONLY ON THE GENETIC PAYLOAD BUT, CRITICALLY, ON HOW AND WHERE IT IS DELIVERED."

While IRDs often involve small patient populations and severe outcomes such as blindness, AMD affects millions of people and requires scalable solutions. The delivery method must be tailored to the disease, the patient and the therapeutic goal. Vectors to deliver genetic material to cells are most often viruses, such as adeno-associated virus (AAV) or lentivirus, but lipid nanoparticles (LNPs) are currently the subject of increasing investigations due to their association with lower immune reactions and potentially improved targeting – the design of gene therapy vectors alone is challenging and huge in scope.

DELIVERY ROUTES FOR OPHTHALMIC GENE THERAPIES – THE TRADE-OFFS AND TECHNICAL BARRIERS

Many people have, at some point, used an eye treatment in the form of eye drops or an ocular spray. However, vectors for gene therapies are too large to traverse the sclera and reach the deep structures of the eye, so more invasive delivery methods are required. There are four main approaches

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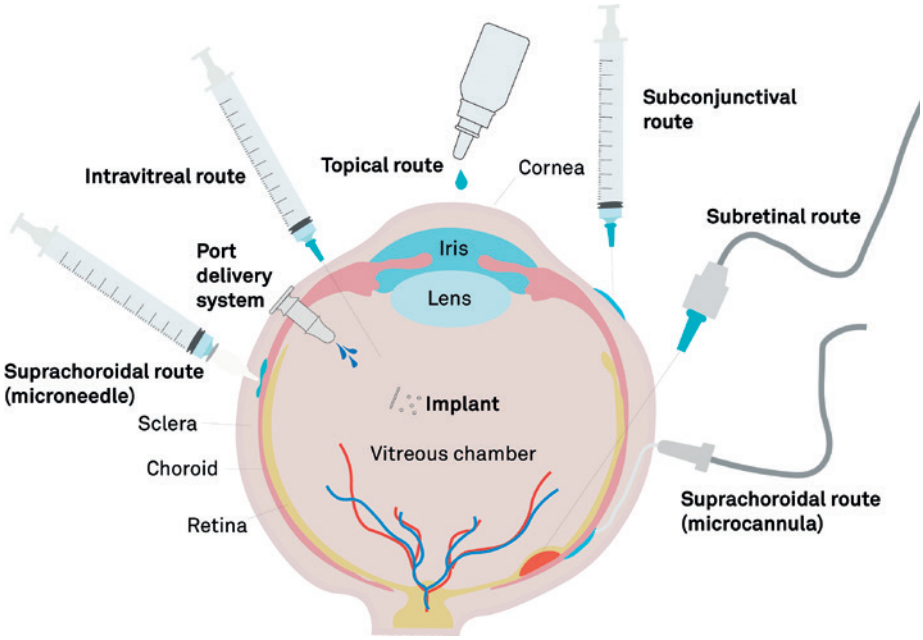

Figure 1: Drug delivery to the eye.

for delivering ocular gene therapies: intravitreal therapy (IVT), subretinal (SR) delivery, implants and suprachoroidal (SC) delivery (Figure 1).

Intravitreal Therapy

IVT has been the common choice for ocular delivery for decades and is widely used for delivering biologics such as anti-VEGF agents to treat AMD. It is minimally invasive, can be performed in outpatient settings and has a good safety profile historically. An IVT delivery device may be as simple as a needle and syringe, making the procedure easily accessible. However, there are challenges with the efficacy of gene therapies delivered by IVT.[1] Delivery vectors must diffuse over a considerable distance through the vitreous humour to reach the therapeutic site – while avoiding neutralisation by antibodies, traversing the inner limiting membrane and successfully delivering a transgene to the nucleus of each target cell.

These challenges can pose a barrier to successful development of ocular gene therapies. For example, a Phase I trial of the drug AAV2-sFLT01, an IVT-delivered therapy for neovascular AMD, originally under development by Sanofi Genzyme (Cambridge, MA, US), showed a good safety profile at all doses, but development was halted due to poor efficacy.[2]

The work has been done to design vectors that improve performance in IVT-delivered gene therapies by engineering vectors with enhanced immune resistance and membrane penetration, but the challenges are still significant. Currently, it appears that there are no IVT therapies that can match the efficacy of SR or SC delivery.

Subretinal Injection

SR delivery is the gold standard for the precise targeting of retinal cells to deliver gene therapies. The technique is performed with a specialist cannula via a transscleral, transvitreous route or by passing a cannula through the SC space, delivering a bolus between the neurosensory retina (NR) and the retinal pigment epithelium (RPE). The procedure must be performed in-theatre, requiring a vitrectomy prior to the injection, however, it presents some distinct advantages over the less complex IVT approach. Direct injection to the retina provides a high drug load at the target site, ensuring high transduction efficiency and localised gene expression limited to the neighbourhood of the bolus, thereby providing superb precision for targeted therapies.

However, SR injection carries a higher risk of retinal detachment than other delivery techniques. Injecting a fluid bolus into delicate organic structures subjects them to mechanical stress and this technique necessitates some degree of detachment between the NR and RPE. This separation is usually transient, as the bolus is absorbed over time, but it still represents a real risk to patient vision. There are also logistical challenges with SR injection, since its surgical requirements are resource-intensive and non-scalable. The issue with scalability is outlined by an industry specialist: "For large gene therapy products [for IRDs], if the total population is 2000 patients worldwide, you do two surgeries a week. Compare that to something like AMD and you're doing 75,000 procedures a year, then is there enough operating room capacity?"

Suprachoroidal Injection

SC delivery presents a compromise between the procedurally simple but less efficacious IVT, and the more complex but targeted SR delivery. The key distinguishing feature of this approach is the delivery of a bolus into the SC space – a virtual space between the sclera and the choroid. Once inside the SC space, the therapy flows around the eye, contacting anatomical structures adjacent to the choroid. The technique may be less invasive than IVT or SR delivery, while providing access to deep structures of the eye and a broader distribution of the therapy across those structures.

There is great potential in this approach, but the devices designed for consistent success are still relatively new, and SC delivery is still undergoing thorough investigation in clinical trials. While clinical

"DIRECT INJECTION TO THE RETINA PROVIDES A HIGH DRUG LOAD AT THE TARGET SITE, ENSURING HIGH TRANSDUCTION EFFICIENCY AND LOCALISED GENE EXPRESSION LIMITED TO THE NEIGHBOURHOOD OF THE BOLUS, THEREBY PROVIDING SUPERB PRECISION FOR TARGETED THERAPIES."

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data is still emerging, companies have paused SC programmes due to concerns of immune reactions. The route's success will depend on reproducibility, safety and clinician familiarity. Andrew Osbourne of Ikarovec (Norwich, UK) describes SC delivery by saying: "If the SC approach can combine the precise cell targeting of an SR injection with the ease of administration of an intravitreal one, that's the sweet spot where it truly stands out".

FORMULATION AND DOSING STRATEGIES

All successful drug deliveries must holistically consider technique, formulation and delivery device, and gene therapies are no different. Gene therapy formulations are complex – they must balance manufacturability, biological efficacy, stability for cold-chain storage, transport and deliverability for the chosen approach. Understanding how formulation rheology affects deliverability and dosing is essential. For example, viscous formulations are inappropriate for IVT, as they slow diffusion and mixing in the vitreous humour, but viscous formulations are preferable for SC delivery, as they offer better control over injectate spread in the SC space and are associated with lower interference with vision after the procedure.

Viruses and LNPs also require additional considerations due to their large size relative to biologics and small molecules. These vectors require high multiplicity of infection to ensure transduction, which often necessitates bolus dosing; however, high viral or LNP loads are more likely to induce an immune response. They are also sensitive to shear forces and will degrade if subjected to excess stress. This places limits on formulation viscosity, injection rate and delivery time, all of which impact the patient experience.

DEVICE DESIGN

The success of ocular gene therapies heavily depends on the devices used for delivery. Devices for IVT are conceptually simple – a syringe and narrow-gauge needle is used, typically 30G for injections of non-colloidal drugs or 27G for suspensions.[3] There are also commercially available accessory devices to aid positioning, such as Precivia® from Veni Vidi Medical (Halifax, UK).[4]

SR injections require specialised devices consisting of cannulas that are sufficiently long to traverse the vitreous cavity or pass through the SC space, and are very narrow to limit procedural trauma – often 38G to 41G – with even narrower tips to aid retinal penetration. These cannulas are connected to a syringe or extension line for manual delivery, or may be incorporated into a vitrectomy machine for automated pneumatic control. There is some overlap between devices for SR and SC delivery, such as the Orbit® Subretinal Delivery System by Gyroscope Therapeutics (London, UK), where flexible cannulas can be deployed to traverse the SC space and puncture the retina from the rear side.

In principle, SC delivery devices can be similar to those used for IVT, and common needle and syringe systems are still used. However, accurate freehand positioning of a needle within a few tens of micrometres of a sensitive organ is a considerable challenge and requires highly trained clinicians to execute correctly. Catheter-based devices have been developed to address this, such as a new device developed by Everads Therapy (Tel Aviv, Israel).[5] Advanced microneedle systems are also under development for SC delivery, such as the Bella-Vue from Uneedle (Enschede, The Netherlands),[6] which uses very short narrow-gauge needles to control penetration depth through the sclera. Laura Vaux of Ikarovec says: "If the suprachoroidal approach can reach the posterior segment and achieve broad transduction across the RPE and surrounding sclera, it delivers both the reach and precision needed for effective gene therapy".

Many of these devices share similar challenges for gene therapy delivery, foremost of which is the requirement for accurate placement and drug spread. There is little distribution control during IVT delivery, but for SR and SC delivery, ensuring that the devices are suited to the rheological characteristics of the formulation is crucial for effective treatment.

PATIENT AND CLINICIAN CONSIDERATIONS

The patient experience is central to the success of any therapy. Patients prefer low-risk, low-pain procedures, but are willing to accept more invasive methods if the vision outcomes are significantly better. The balance to strike is between continuous but less invasive treatments and a single treatment that carries greater risk of complications, but could provide enormous benefit across a patient's expected lifetime. In either case, an understanding of patient needs and timescales is critical. To summarise from an industry specialist, "Ideally, you want to do a gene therapy to help preserve the retina before it is destroyed. Once the cells are dead, gene therapy is not going to help".

Clinicians, meanwhile, prefer well-understood procedures with low complication rates. IVT is widely accepted because of its procedural simplicity, with expert clinicians able to perform multiple IVT injections per hour. SR and SC injections require additional training and confidence with the technology, so device usability and reproducibility are key to bridging the gap towards adoption for these more advanced techniques. Andrew Osborne of Ikarovec observes that: "From a technical perspective and to enable widespread adoption, clinicians are likely to prefer an office-based delivery approach that is familiar, consistent and reliable".

"THE BALANCE TO STRIKE IS BETWEEN CONTINUOUS BUT LESS INVASIVE TREATMENTS AND A SINGLE TREATMENT THAT CARRIES GREATER RISK OF COMPLICATIONS, BUT COULD PROVIDE ENORMOUS BENEFIT ACROSS A PATIENT'S EXPECTED LIFETIME."

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FUTURE DIRECTIONS FOR INNOVATION

The future of ocular gene therapy lies in technological convergence. Artificial intelligence (AI) is already being used to design synthetic vectors with reduced immunogenicity. Non-viral delivery methods, such as optimised LNPs and naked DNA or RNA fragments, offer alternatives to traditional viral vectors. New AI, augmented reality and virtual reality tools, such as the EyeSi Simulator at the Royal College of Ophthalmologists in London (UK), are also providing a platform to train clinicians without the need for theatre time or expensive drugs.[7]

Inducible gene therapies, which allow for on/off control and dose modulation, are a similar exciting innovation, where the dose can be modulated by systemically delivered excipients. This level of control may increase efficacy, reduce the rate of immunological adverse events and reduce long-term stress on retinal cells, while also providing a dose at an optimal rate for transduction efficiency. However, such treatments are early in development and have not yet made the transition into ophthalmology. They also require the patient to make additional clinic visits, which may dampen some of the benefits of "one-and-done" treatments.

CONCLUSION

Drug delivery is the linchpin of ocular gene therapy. The choice of route, formulation and delivery device determines not only the efficacy but also scalability, safety and patient experience. Andrew Osbourne of Ikarovec summarises this experience: "Patients will want treatments that work as effectively as possible, while minimising procedural risk and off-target complications. SC delivery offers a potential advantage in achieving that balance compared with intravitreal or SR approaches". The techniques of IVT, SR delivery and SC delivery require differing devices. With the latter two being the more novel approaches, additional training will be required for clinicians, as well as hospitals that are willing to adopt these approaches.

These challenges are not insurmountable, but device and therapy development demand a holistic approach. As ophthalmic gene therapies mature, collaboration between biotech innovators, clinicians, regulators and device manufacturers will be essential. The goal is not just to deliver gene therapies but to deliver clear vision, safely and effectively, to millions of patients worldwide.

ABOUT THE COMPANY

Team Consulting is a fee-for-service consultancy that works with pharma and medtech clients to design and develop medical devices, in particular drug delivery devices. In the field of drug delivery, Team Consulting's focus is in administration via the respiratory and parenteral routes.

"PATIENTS WILL WANT TREATMENTS THAT WORK AS EFFECTIVELY AS POSSIBLE, WHILE MINIMISING PROCEDURAL RISK AND OFF-TARGET COMPLICATIONS. SC DELIVERY OFFERS A POTENTIAL ADVANTAGE IN ACHIEVING THAT BALANCE COMPARED WITH INTRAVITREAL OR SR APPROACHES."

Dr Max Chambers

Max Chambers, PhD, is Applied Scientist at Team Consulting. He focuses on translating complex scientific problems into functional medical technology and devices. His work often sits at the intersection of many distinct fields, to which he brings a broad multidisciplinary background, including surface chemistry, functional materials and microfluidics. Dr Chambers' PhD is in molecular scale engineering; he worked on the fabrication of arrays of plasmonic aluminium nanostructures and their use as biosensors. He has previously worked on enzymatic DNA synthesis technology and its incorporation into microfluidic bioreactors.

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REFERENCES

1. *Ross M & Ofri R, "The future of retinal gene therapy: Evolving from subretinal to intravitreal vector delivery". Neural Regeneration Research, 2021, Vol 16(9), pp 1751–1759.*
2. *Heier JS et al, "Intravitreous injection of AAV2-sFLT01 in patients with advanced neovascular age-related macular degeneration: A phase 1, open-label trial". Lancet, 2017, Vol 390(10089), pp 50–61.*
3. *"Intravitreal injection therapy". Ophthalmic Service Guidance, Royal College of Ophthalmologists, Aug 2018.*
4. *"Precivia® Device". Company Web Page, Veni Vidi Medical, accessed Nov 2025.*
5. *"Our technology". Company Web Page, Everads Therapy, accessed Nov 2025.*
6. *"Suprachoroidal injection". Company Web Page, Uneedle, accessed Nov 2025.*
7. *"EYESi ophthalmic surgical simulators". Web Page, Royal College of Ophthalmologists, accessed Nov 2025.*

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USING OXYCAPT™ MULTILAYER PLASTIC VIAL FOR GENE AND CELL THERAPIES STORED IN DRY ICE AND LIQUID NITROGEN

This article was originally published in ONdrugDelivery, Issue 178 (Oct 2025), pp 134–139.

MITSUBISHI GAS CHEMICAL

Masashi Miura and **Tomohiro Suzuki** of **Mitsubishi Gas Chemical** consider the various challenges presented by cold-chain logistics to both traditional glass vials and many cyclo-olefin polymer alternatives, and how the company's OXYCAPT™ vials offer significant advantages for maintaining container closure integrity compared with other materials on the market.

OXYCAPT OVERVIEW

OXYCAPT™ is a multilayer plastic vial and syringe developed by Mitsubishi Gas Chemical (MGC), offering a number of advantageous qualities as a primary drug container, including:

- Excellent oxygen and ultraviolet (UV) light barrier
- Strong water vapour barrier
- Very low extractables
- High pH stability
- Low protein adsorption and aggregation
- High transparency
- High break resistance
- Easy disposability
- Lightweight material.

MGC continuously conducts studies to confirm these properties. The latest results of these are shared in the later part of the article. Before that, the first half of this article provides an overview of the OXYCAPT multilayer plastic vial (Figure 1). The material consists of three layers – the drug contact layer and the outer layer are made of cyclo-olefin polymer (COP) and the oxygen barrier layer is made of MGC's novel polyester (Figure 2).

MGC recently obtained a report on the environmental impact of glass and plastic containers for medical use from a Japanese research company. The report shows that plastic containers for medical use are much more environmentally friendly compared with glass containers. For example, the carbon footprint, nitrogen oxide emissions,

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Figure 1: OXYCAPT multilayer plastic vial.

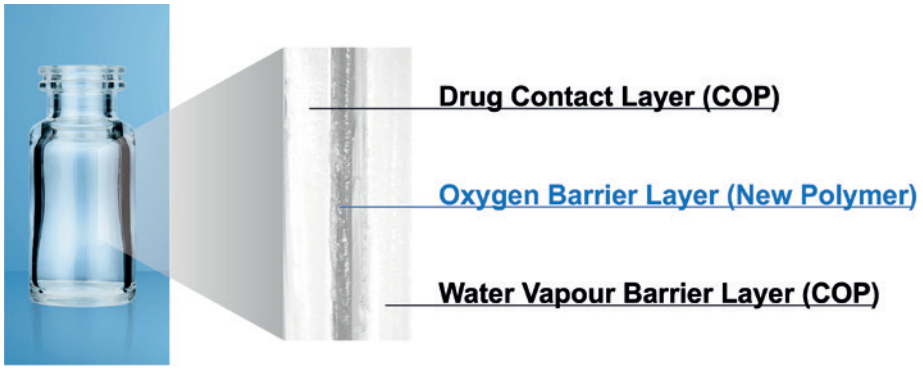

Figure 2: Multilayer structure of OXYCAPT.

"OXYCAPT PROVIDES AN EXCELLENT OXYGEN BARRIER – FOR EXAMPLE, THE OXYGEN BARRIER OF AN OXYCAPT VIAL IS ABOUT 20 TIMES BETTER THAN THAT OF A COP MONOLAYER VIAL."

sulphur oxide emissions and water consumption associated with plastic containers for medical use are several times smaller than those of their glass equivalents.

OXYCAPT provides an excellent oxygen barrier – for example, the oxygen barrier of an OXYCAPT vial is about 20 times better than that of a COP monolayer vial. Furthermore, OXYCAPT provides an excellent UV barrier. While about 70% of 300 nm UV light transmits through glass and COP, only 1.7% transmits through OXYCAPT. MGC has confirmed that this feature contributes to the stability of biologics.

While OXYCAPT cannot reach the performance of glass with respect to acting as a water vapour barrier, its properties are similar to those of COP, which has been used for injectable drugs for a long time. This means that OXYCAPT easily meets the requirements of a water vapour barrier set out by the ICH guidelines.

Studies have shown an extremely low level of extractables from OXYCAPT. One study was conducted to confirm the levels of volatile, semi-volatile and non-volatile impurities from OXYCAPT. Water and four solutions (50% ethanol, sodium chloride, sodium hydroxide and phosphoric acid) were selected, and impurities were measured by gas chromatography mass spectrometry (GC-MS) and liquid chromatography-UV spectroscopy-mass spectrometry (LC-UV-MS) after 70 days at 40°C. Compared with the control, impurities were not detected in the OXYCAPT containers. A second study confirmed that inorganic extractables levels from OXYCAPT were similar to those from COP, which is well known for being an extremely pure polymer with a better extractables profile than Type 1 glass. Lower levels of inorganic extractables are known to contribute to better pH stability in drug products.

The OXYCAPT vial is produced by co-injection blow-moulding technology. MGC has also developed inspection methods for testing the oxygen barrier layer. All the containers are fully inspected by state-of-the-art inspection machinery.

MGC can offer bulk vials and ready-to-use (RTU) vials, with its RTU products provided in standard nest-and-tub or tray formats. The nest and tub are mainly sterilised using gamma rays. There are 2, 6, 10 and 20 mL variants for vials. MGC is willing to provide samples for initial testing free of charge.

Each polymer meets the requirements of US Pharmacopeia (USP) regulations USP <661>, USP <87> and USP <88>, as well as those of the European Pharmacopoeia, and has been filed in the US FDA's drug master file (DMF). The vials are also compliant with each pharmacopoeia and have been filed in the DMF.

The primary target market for OXYCAPT is the therapeutic application of biologics. As mentioned in ICH Q5C (Stability of Biotechnological/Biological Products), oxidation is one of the causes of protein instability. As such, the oxygen and UV barrier properties of OXYCAPT contribute to the stability of biologics stored within. Furthermore, some drug developers have recently started evaluating OXYCAPT vials for their gene and cell therapies; the RTU vial is sterilised by gamma radiation, making it ideal for protein-based drugs.

OXYCAPT AT ULTRA-LOW TEMPERATURES

Plastic vials generally exhibit greater toughness at ultra-low temperatures compared with glass, markedly mitigating the risk of breakage during transportation and under thermal stress. For example,

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Vial	Total Number of Breakages					Total Number of Layer-Separations				
	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5
OXYCAPT™-P V10 RT	0/20	0/20	0/20	0/20	0/20	0/20	0/20	0/20	0/20	0/20
Competitor's Glass Vial(10R)	5/20	10/20	14/20	20/20	–	N/A				

Table 1: Heat cycling stress test performed with mannitol aqueous solution.

OXYCAPT vials demonstrated excellent performance in a heat cycling test designed to evaluate resistance to physical stresses such as material contraction and expansion, as well as the volumetric expansion of aqueous drug formulations. In this study, 8 mL of a 10 w/v% mannitol aqueous solution was filled into 20 10R OXYCAPT vials and 20 conventional glass vials, which were then sealed with rubber stoppers. The vials were alternately placed in constant-temperature chambers set at -80°C and 40°C, with each cycle consisting of storage at both temperatures for three to four consecutive days. This alternating process was repeated for a total of five cycles. By the end of the fifth cycle, all 20 glass vials were broken, whereas none of the 20 OXYCAPT™ vials exhibited any visible defects, such as cracks or layer separation (Table 1).

Container Closure Integrity

State-of-the-art drug products, including messenger RNA (mRNA)-based drugs and gene and cell therapies, are typically transported and stored at ultra-low temperature conditions (-78°C) using dry ice or at cryogenic temperature (-180°C) in the vapour phase of liquid nitrogen. Under these circumstances, there is a risk of losing container closure integrity (CCI), particularly for glass vials. This risk arises from the remarkable difference in the coefficients of thermal expansion between the vial's glass flange and the elastomeric closure.

"OXYCAPT VIALS DEMONSTRATED EXCELLENT PERFORMANCE IN A HEAT CYCLING TEST DESIGNED TO EVALUATE RESISTANCE TO PHYSICAL STRESSES SUCH AS MATERIAL CONTRACTION AND EXPANSION, AS WELL AS THE VOLUMETRIC EXPANSION OF AQUEOUS DRUG FORMULATIONS."

To simulate the conditions under which gene and cell therapy products are transported and stored, MGC conducted a CCI study using OXYCAPT vials. In this study, OXYCAPT vials and conventional glass vials were prepared, sealed under ambient air with non-laminated bromobutyl rubber stoppers and aluminium caps, after which their initial oxygen concentration was measured using an FMS-760, a headspace oxygen analyser (LIGHTHOUSE Instruments, Charlottesville, VA, US).

The vials were then stored in the vapour phase of liquid nitrogen within a dry shipper for up to three months. During storage, the oxygen concentration inside the vials was periodically measured to verify whether or not it remained at approximately 20.9%. The results showed that all of the conventional glass vials lost CCI within seven days, whereas the OXYCAPT vials maintained CCI even after three months (Figure 3). These findings demonstrate that OXYCAPT vials effectively prevent the ingress of air, moisture and contaminants, even under cryogenic conditions.

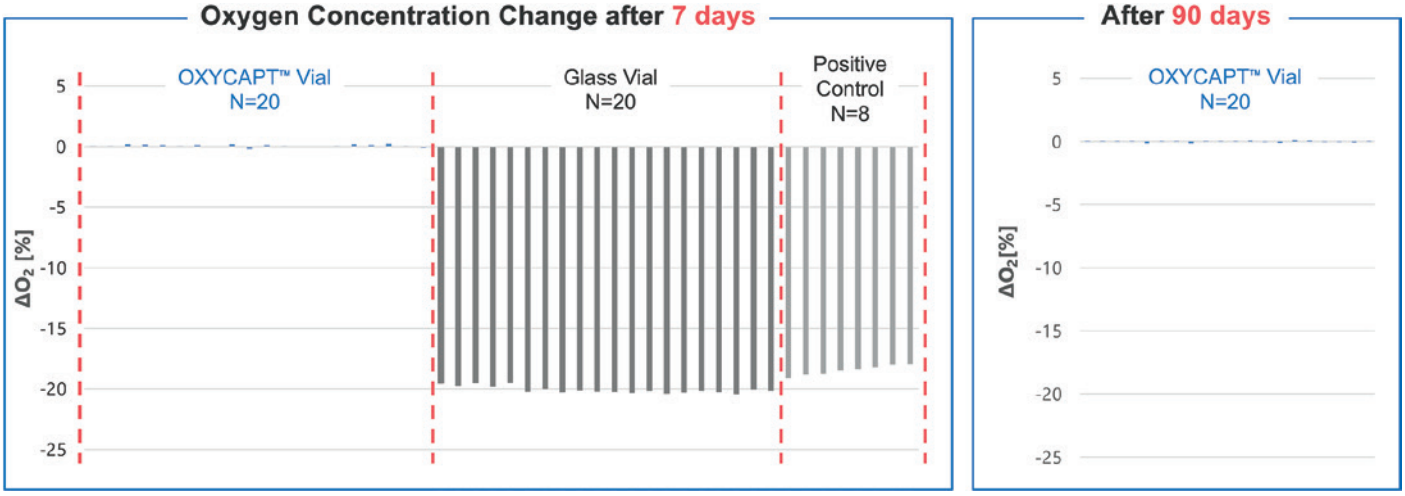

Figure 3: CCI test results in vapour phase of liquid nitrogen.

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Risk of Carbon Dioxide Ingress

While plastic vials are capable of markedly mitigating the risk of loss of CCI, conventional plastic vials present an alternative inherent risk under conditions of coexisting dry ice – the permeation of carbon dioxide (CO_2). To elucidate this latent risk, a simulated study was conducted using dry ice, as illustrated in Figure 4.

Five 10R OXYCAPT vials and five conventional COP vials were used as test samples. The vials were sealed with commercially available bromobutyl rubber closures and aluminium caps under a 100% nitrogen atmosphere. The vials were placed in an insulated container filled with dry ice and stored for seven days. Immediately upon removal (T_0), the CO_2 partial pressure in the vial headspaces was measured using FMS-CO_2 (LIGHTHOUSE Instruments). The vials were then stored under ambient conditions at either 5°C or 23°C, and the CO_2 partial pressure was measured again after one day, with subsequent periodic measurements performed over time.

As shown in Figure 5, no CO_2 was detected in the headspaces of either the COP or OXYCAPT vials at T_0, demonstrating excellent CCI at -78°C. However, when subsequently stored at 23°C for one day, the COP vials exhibited a CO_2 partial pressure of approximately 1.5 Torr (Figure 6). This phenomenon was also observed when the COP vials were stored at 5°C. In contrast, the OXYCAPT vials maintained a CO_2 concentration of 0% over a period of 70 days, even under continuous storage at 23°C (Figure 7).

This time-dependent permeation phenomenon of CO_2 can be attributed to the inherent physical properties of CO_2, which exhibits relatively high solubility coefficients at ultra-low temperatures and is readily soluble even in plastics. During cold storage, the CO_2 generated through the sublimation of dry ice dissolves into the near-surface region of the polymer layer. Under ultra-low temperature conditions, gas molecules scarcely diffuse through the polymer layer, meaning that, even when the headspace CO_2 partial pressure was measured immediately after removal from cold storage, no detection was observed (Figure 8). In contrast, upon subsequent storage under comparatively mild conditions, such as room temperature or

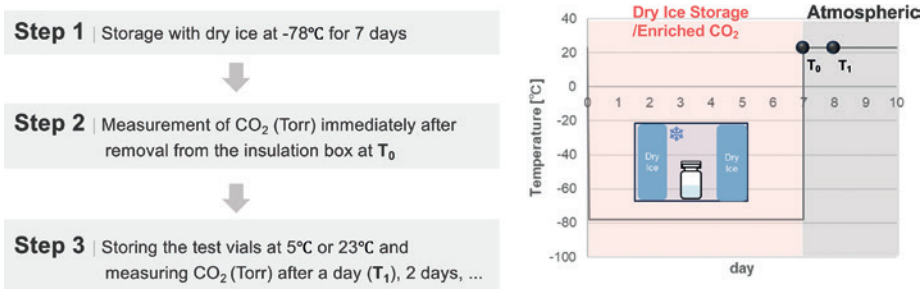

Figure 4: Environmental profile during CCI test with dry ice.

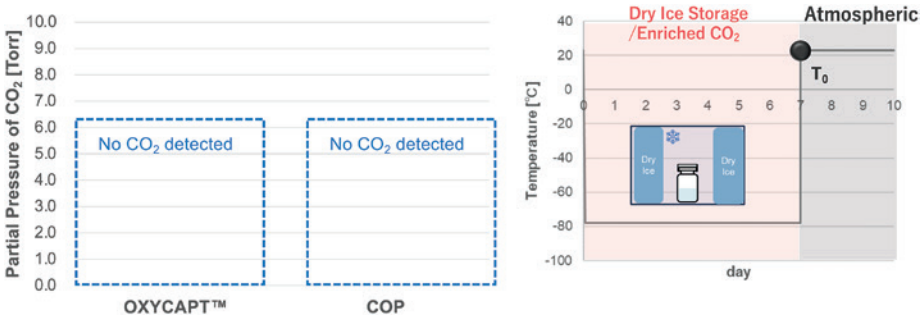

Figure 5: CO_2 measurements in vial headspace immediately after removal.

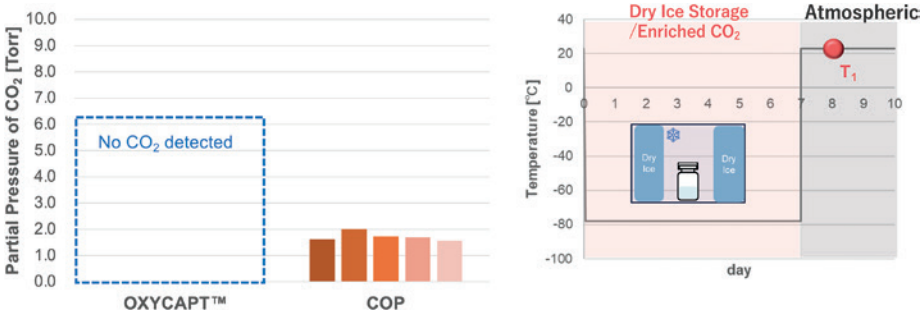

Figure 6: CO_2 measurements in vial headspace one day after removal.

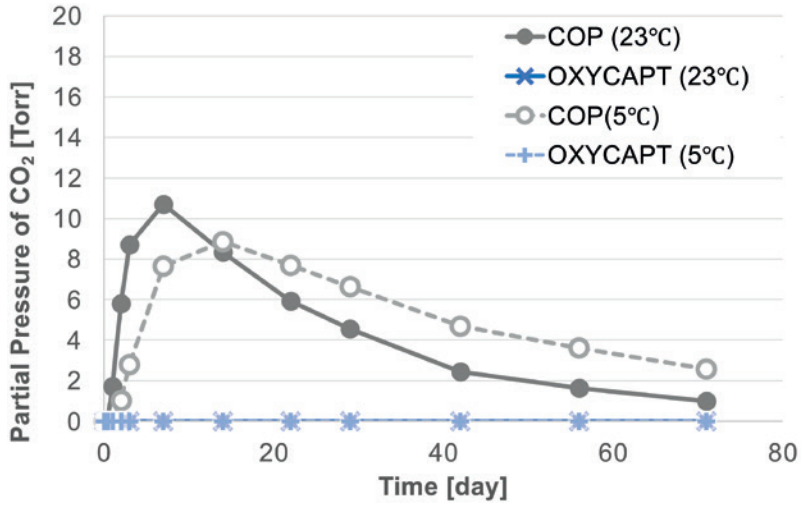

Figure 7: Changes in CO_2 partial pressure in vial headspaces after removal from insulated chamber.

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2–8°C, the dissolved CO_2 rapidly diffuses through the polymer and reaches the vial headspace (Figure 9).

An additional verification study was conducted using vials filled with distilled water, in which the pH was measured following storage with dry ice. Thirty samples were prepared for each vial type – 10R OXYCAPT, COP and glass. The vials were filled with distilled water under a nitrogen atmosphere and the initial pH value was measured at T_0 before sealing the vials with commercially available bromobutyl rubber stoppers (non-laminate). The samples were then divided into two groups – 15 vials were stored for seven days in the presence of dry ice and 15 vials were stored in a -80°C deep freezer. After storage, five vials from each group were thawed at 23°C for eight hours, after which the pH was measured again (T_7). Additional destructive testing was performed on independent sets of five vials each at one day (T_{7+1}) and four days (T_{7+4}) after thawing, with each vial discarded following measurement. The results showed that, in the COP vials stored with dry ice, the pH decreased beginning at T_{7+1}. In contrast, the OXYCAPT vials maintained their initial pH even at T_{7+4} (Figure 10).

In practice, upon delivery, pharmaceuticals transported with dry ice may be thawed or temporarily refrigerated at 2–8°C prior to administration. Under such conditions, exposure to ambient or refrigerated temperatures can result in the permeation of dissolved CO_2. Once present, CO_2 dissolves in aqueous drug formulations, generating protons and therefore posing a latent risk of detrimental pH shift in drug formulation.

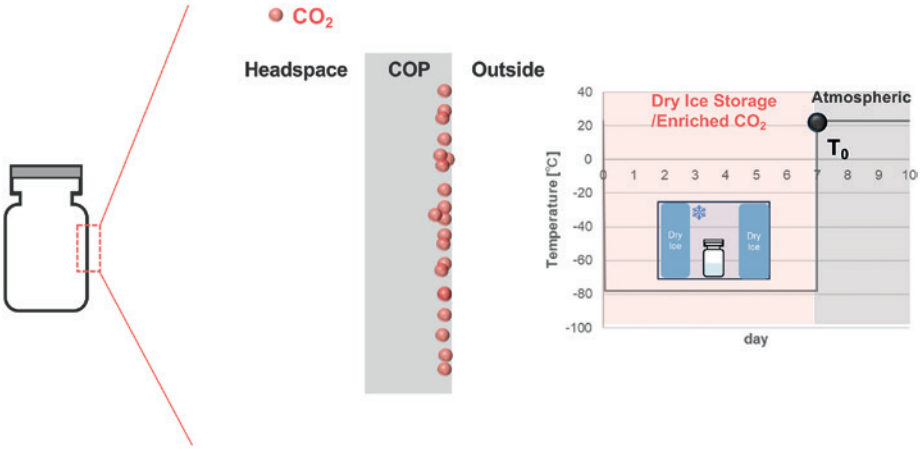

Figure 8: Schematic illustration of CO_2 dissolution in COP vials immediately after removal from dry ice.

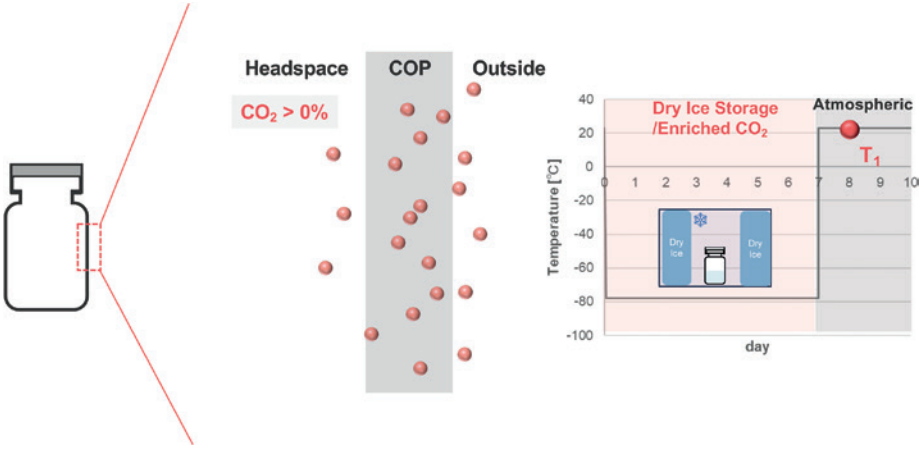

Figure 9: Schematic illustration of CO_2 diffusion through COP vials one day after removal.

To mitigate this "time-delayed" CO_2 permeation phenomenon, secondary packaging is sometimes used. However, secondary packaging introduces additional concerns, including the risk of physical damage, increased material and logistical costs and the necessity for packaging validation. In view of these challenges, OXYCAPT, which provides inherent gas-barrier properties at the level of the primary container, represents an optimal solution by ensuring CCI while simultaneously offering advantages in cost efficiency and environmental sustainability.

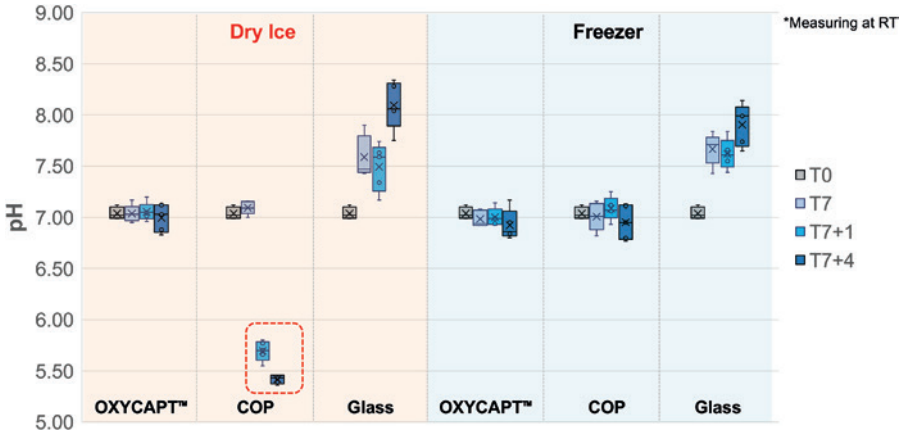

Figure 10: pH variation of distilled water after dry ice storage.

"OXYCAPT REPRESENTS AN OPTIMAL SOLUTION BY ENSURING CCI WHILE SIMULTANEOUSLY OFFERING ADVANTAGES IN COST EFFICIENCY AND ENVIRONMENTAL SUSTAINABILITY."

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Mitsubishi Gas Chemical (MGC) is a major chemical products manufacturer, operating across a wide range of fields, from basic chemicals to fine chemicals and functional materials. In 2012, MGC established a new division as a centre for continually creating new businesses. In the field of drug delivery, the company has developed the OXYCAPT plastic vial and syringe as an alternative to glass containers.

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