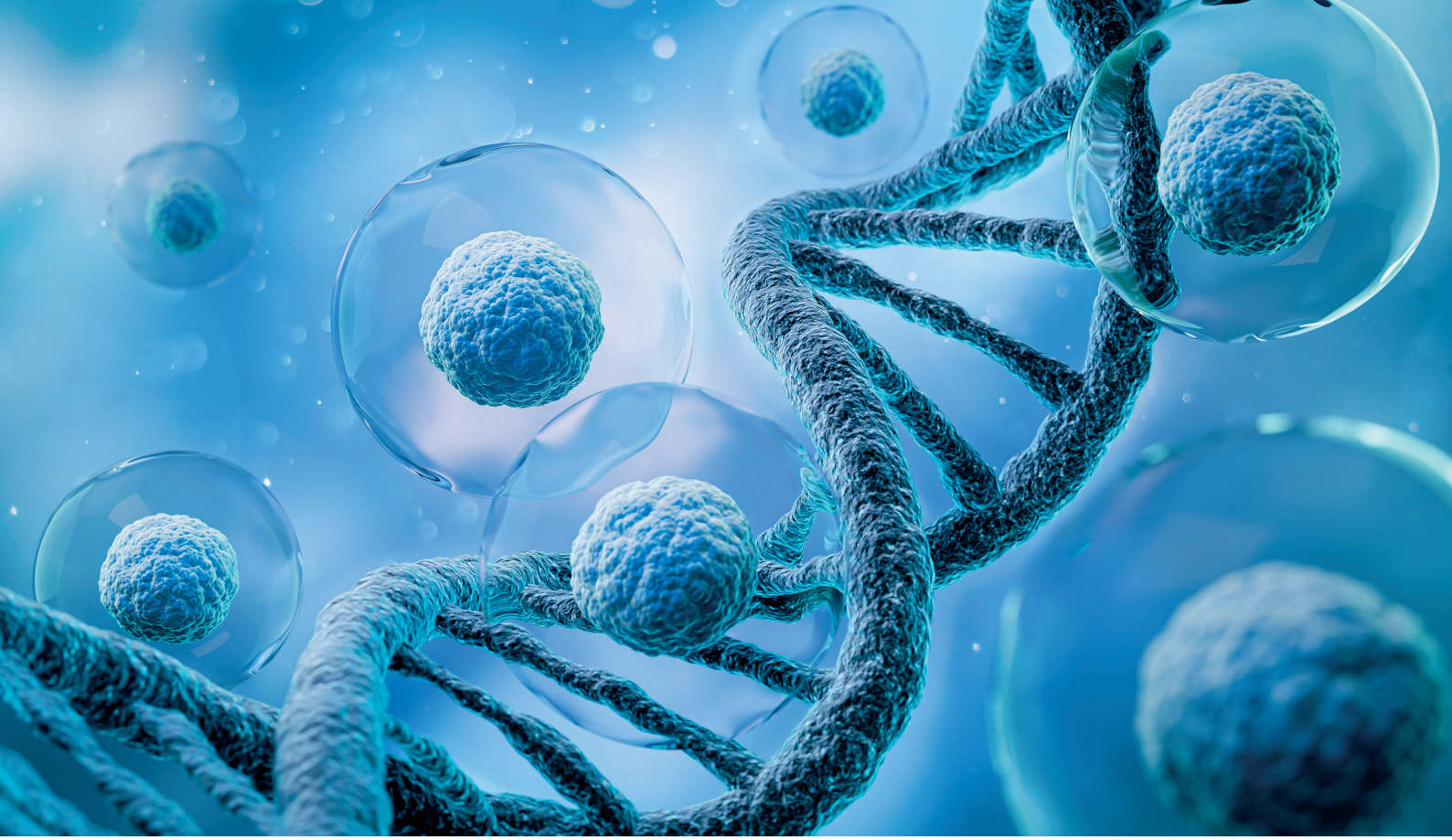

PRIMARY PACKAGING AND ADMINISTRATION OF CELL THERAPIES: CURRENT TRENDS AND CHALLENGES

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.

"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."

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® by Novartis (Basel, Switzerland) and Yescarta® by 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

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.

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