Overcoming Challenges in Cell and Gene Therapy Containment

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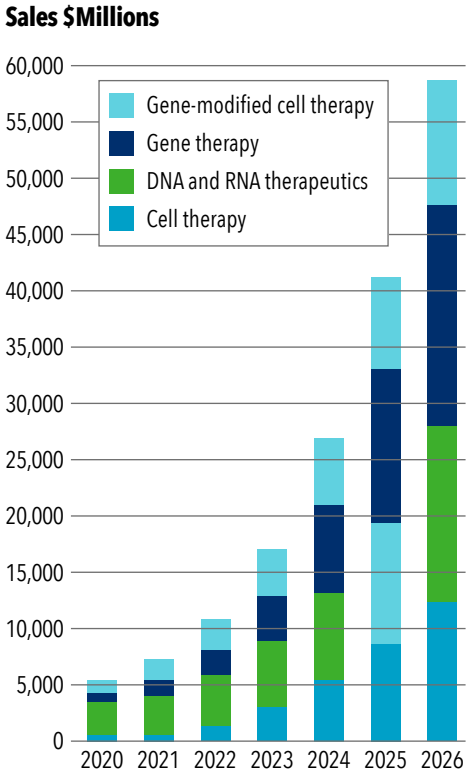
Executive Summary

Cell and gene therapies (CGTs) typically target genetic diseases or diseases with very high unmet needs and limited existing therapeutic options. Therefore, quickly getting these life-altering therapies to the market is critical for patients. This white paper will review some hurdles that can slow your time to market and proven West solutions to help you mitigate risk and simplify the journey.

Overcoming Challenges in Cell and Gene Therapy Containment

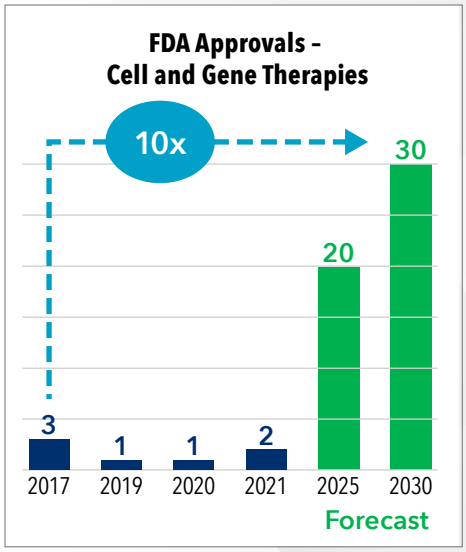
TRENDS IN THE CELL AND GENE THERAPY MARKET ARE DRIVING RAPID GROWTH

The cell and gene therapy market is growing rapidly, with sales expected to reach $59B by 2026, excluding vaccines.[1]



This growth is partly attributable to the fact that CGTs are increasingly important healthcare solutions, especially for rare diseases or those with limited treatment options. Across the global pipeline, small molecules are beginning to plateau, and monoclonal antibodies are starting to mature. New companies are emerging to develop cell, gene, and RNA therapeutics. There are currently more than 1,000 companies working on CGTs globally.[2] In addition, strong investor interest is leading to an influx of capital funding and regulatory pathways are opening to provide more opportunities for expedited approval.

These trends are contributing to a growing pipeline and shortening development timelines. On average, drugs designated as breakthrough therapies have shorter premarket development (nearly two years shorter than non-breakthrough therapies) and faster approval (nearly three months ahead of FDA deadlines). There were 2,093 trials ongoing globally at the end of June 2022.[2] As of December 2022, 23 CGTs have been approved,[3] and the FDA projects that they will be approving 10 to 20 CGTs per year by 2025[4] and 30 approved CGTs by 2030.

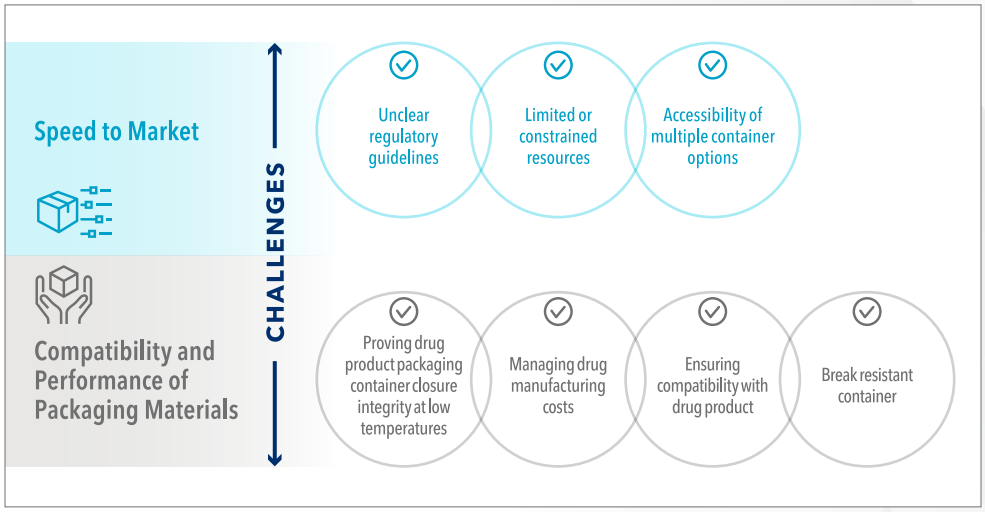


Each of these drugs has a high value, reaching hundreds of dollars per dose. For this reason, robust packaging is of utmost importance. CGTs often involve the use of delicate biological materials, such as live cells or genetic material, which must be carefully protected during transport and storage. Inadequate packaging can result in the degradation or contamination of these materials.

The following sections consider the challenges in packaging these high-value therapies and how West containment solutions can help.

CHALLENGES RELATED TO PACKAGING OF CGT PRODUCTS

Challenges related to packaging of CGTs fall under two major themes. Addressing the challenges of speed to market and packaging compatibility is essential for the successful development and delivery of new CGTs.



Speed to Market

Speed to market refers to the need for packaging solutions that can be developed and implemented quickly. This requires packaging solutions that can be tailored to the specific needs of individual therapies and that can be brought to market quickly to keep pace with the rapid development of new treatments.

Regulatory Guidelines/Complexity

The first challenge for getting products approved and to market fast is unclear regulatory guidelines. CGTs are a new and emerging field, and the developing regulatory guidelines are often unclear to companies working in the field. While agencies are continuing to look at and issue guidance, regulatory clarity is still lacking.

Limited or Constrained Resources

Allocation of available resources can significantly impact the development of new CGTs. Mid-to-small emerging pharmaceutical companies have limited in-house expertise and resources for timely drug development. In contrast, larger companies may have sufficient resources but may elect to outsource areas outside their wheelhouse, including packaging. All businesses may look for an outsourcing partner to handle workload fluctuations.

Accessibility of Multiple Container Options

CGTs encompass an extensive range of technologies and demand more than a one-size-fits-all container. Companies may need different container sizes depending on the type of drug. Selecting a container that can support different fill volumes and quantities along a drug development timeline is a challenge.

Compatibility and Performance of Packaging Materials

CGTs require compatible packaging materials that maintain their stability and potency throughout the journey from the manufacturer to the patient. Finding packaging materials that meet these requirements can be challenging and time-consuming and requires careful consideration and testing to ensure compatibility and performance.

Low-temperature Container-Closure Integrity (CCI)

Low-temperature container-closure integrity (CCI) is critical for CGTs that are stored at ultra-low (-80°C) or cryogenic (-180°C) temperatures. There is a need to maintain CCI throughout the life of the therapeutic, including potential freeze and thaw cycles.

High Drug Manufacturing Costs

CGT manufacturers demand high-yield maximization due to the cost of manufacturing and currently limited manufacturing yields. Therefore, containers that facilitate a high recovery and maximize yields are critical.

Ensuring Compatibility with Drug Product

A significant challenge in package selection is selecting a container compatible with the therapeutic. Packaging should be inert and not introduce particulate quality issues. In addition, the packaging system chosen should be available in multiple sizes to support scaling.

Break-resistant Containers Able to Withstand Low Temperatures

Due to the demands of CGTs, containers must be selected that are not only break-resistant, but also retain this ability at low and cryogenic temperatures.

SOLUTIONS FOR CHALLENGES RELATED TO PACKAGING OF CGT PRODUCTS

The successful development and delivery of CGTs depend on working with a component supplier who:

- Understands the regulatory guidelines
- Offers fully integrated vial solutions robust enough for CGT applications
- Provides support in extractables and leachables (E&L), CCI, performance and functionality, and particle analysis
- Performs and demonstrates integrated vial-stopper-seal combinationtesting
- Can demonstrate their success with FDA-approved CGTs

West has a range of products and services that solve each of these challenges and mitigate the risk of bringing a CGT product to the market.

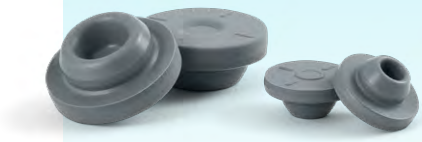
West and Daikyo Vial offerings for Low-Temperature and Cryogenic Applications

West and Daikyo offer the highquality components to protect, store, and deliver your drug products.

Vials

Daikyo Crystal Zenith® (CZ) Cyclic Olefin Polymer vials are formulated to limit chemical interactions between the container and the drug product over long-term storage. CZ is an engineered polymer vial with a low particle load and a favorable E&L profile.

- CZ vials are available in 2-, 5-, 10-, and 50-mL sizes.
- Vials are suitable for storage at -80°C and cryogenic temperatures to -180°C.
- Vials are break-resistant throughout the cold chain process: cold storage, thawing, and final handling.



Stoppers

Besides the polymer vials, West and Daikyo also offer vision-inspected, ready-to-use stoppers with FluroTec™ barrierfilm that reduce the interaction between the drug and base elastomer.

- Vision-verified to provide consistent, high-quality elastomer components.
- FluroTec barrier film protects against drug-closure interactions.
- Available in West or Daikyo designs and formulations.

Seals

Accompanying the vials and stoppers, clean-certified-sterilized seals complete the package and are available with various button colors (for drug product differentiation) and are suitable for crimping under an aseptic environment.

- Tamper-evident Flip-Off ® CCS (Clean, Certified, Sterilized) seals are available in a range of colors for product identification.
- Bioburden-controlled seals meet global guidelines for capping outside an isolator environment.

West Ready Pack™

The supply chain of the Ready Pack containment system has been designed to support you when you need it most. Stoppers, seals, and vials are held in stock within the region, allowing for convenient ordering and quick delivery to your site.

You get what you need, when you need it, while avoiding waste or the additional cost of processing.

West Ready Pack™

West solutions are available with easy ordering and quick delivery of small volumes.

West provides the flexibility to buy vial-stopper-seal combinationsor only the components that you need, thereby reducing waste associated with commercial volumes. This is particularly attractive for CGT applications, as batch sizes typically are smaller. Stoppers, seals, and vials are supplied directly from West, eliminating the need for you to work with multiple suppliers. Components are provided sterile and can be directly introduced into your filling operations, eliminating component preparation from your process.

West Analytical Services

Analytical Services has vast expertise and experience in extractables and leachables, particle analysis, container closure integrity, and performance and packaging/delivery systems. As a result of our understanding of materials and delivery systems and their compatibility with the drug product, we can assist our customers in designing studies and navigating the challenging and evolving regulatory landscape.

West team members sit on many of the standards organization groups, such as ISO,USP, AAMI and ASTM packaging committees. Therefore, we are able to understand where trends are heading, what we need to do to deliver best practices, and ultimately tie it all to the packaging and delivery system and risk associated with those products.

One good example is the introduction of the new USP <382> monograph, which focuses on systems testing for functionality and performance. West can provide customers with insights into the new requirements and how to approach system testing, particularly in accordance with some of the new ISO standards for performance testing.

Extractables and Leachables Analysis

Regulatory agencies are focusing on E&L in pharmaceuticals. Providing E&L information is expected. West Analytical Services partners with our customers to help navigate the challenging regulatory landscape. We offer a holistic approach for your container closure system, device, or combination product.

Packaging and Device / Combination Product Testing

A thorough understanding of current regulations enables West to create and execute robust study designs. These studies cover syringes, cartridges, vials, and all related components, devices, and combination products.

Particle Analysis

Due to the impact on patient safety, particles are a regulatory concern and a focal point of the pharmaceutical industry. West's Analytical Services Particle Laboratory provides testing with the ability to count and size sub-visible and visible particulate using technologies such as Light Obscuration (LO), microscopy, and light microscopy/ image analysis (LM/IA) for automated particle detection.

Container Closure Integrity

West has an extensive portfolio of CCI techniques and analysis for various packaging and delivery systems to meet the needs of pharmaceutical, biotech, and medical device manufacturers. We have the understanding and capabilities our customers need to ensure efficiency, reliability, and safety, from concept to patient.

Fundamental Testing

West's Analytical Services laboratory understands the requirements of compendial analysis for important components in drug product packing, from elastomers to glass and plastics. In addition, the West team can evaluate the effects of sterilization on elastomer moisture content and identify an elastomer for compatibility.

Proven Performance of West Products

West has developed a range of effective packaging solutions for CGTs. Manufacturers can leverage our experience and expertise to develop packaging solutions that meet the unique requirements of their therapies.

Demonstrated Success

West containment solutions are used in six approved gene and viral therapies stored at -80°C. In addition, multiple companies developing new CGTs are also using West containment solutions and are progressing through clinical phases.

Meeting the Challenge of Viral Vector Delivery

Customer: A gene therapy company was bringing a gene therapy treatment for an inherited disease to market.

Challenge: The customer required a containment solution capable of cold storage at -80°C. They had determined that screw cap cryovials were not suitable for commercialization.

Solution: Selected Daikyo Crystal Zenith® vial, West NovaPure® stopper, and Flip-Off® Seal.

Outcome: Customer's gene therapy was approved in 2017, making it the first gene therapy approved to treat an inherited disease in the US.

Overcoming the Challenge of System Reliability and Supply Chain Requiring Low Temperature Storage

Customer: A biotechnology company was developing a gene therapy treatment for a rare neurological genetic disorder.

Challenge: The customer required a leak- and break-proof containment solution capable of cold storage at -80°C. The CGT had orphan drug status with a fast-track designation; therefore, scaleup and speed to market were important for this customer.

Solution: Used West's Ready Pack™ Containment System, including Daikyo Crystal Zenith® vials, West NovaPure® stoppers, and Flip-Off® CCS seals.

Outcome: Customer's gene therapy was approved in 2019, making it the second gene therapy approved in the US, and the first gene therapy treatment for pediatric spinal muscular atrophy.

CONCLUSION

With the number of approved CGTs and sales expected to increase tenfold over a decade, the cell and gene therapy market is clearly growing rapidly. Packaging poses a unique set of challenges for CGT manufacturers. CGTs tend to have cold storage requirements that, combined with leak-resistance, break-resistance, closure integrity, and drug compatibility, can strain available resources. Compounding these challenges, CGTs often focus on diseases that can lead to an accelerated approval pathway. This speed to market can strain an already complicated process.

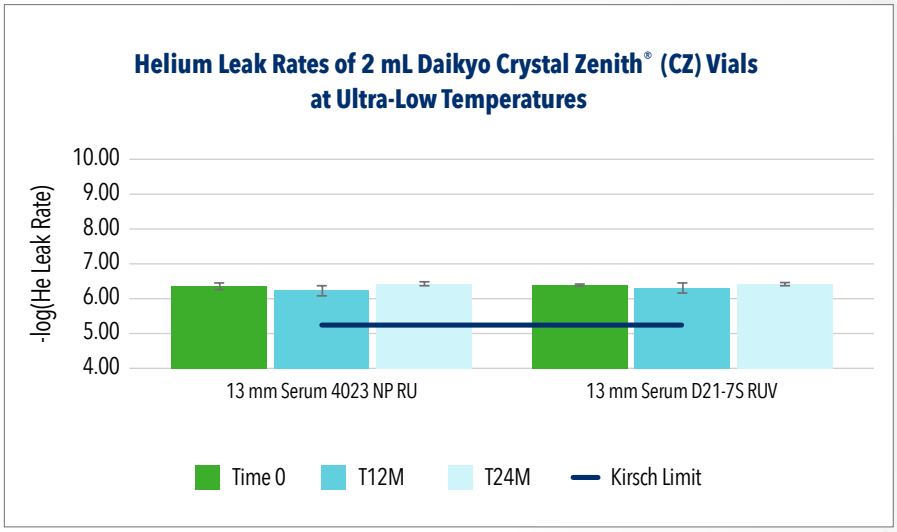
West and Daikyo containment vial-stopper-seal combinations are proven in the market and are already used for packaging six gene and viral therapies in the US and EU. West components can withstand the cryogenic temperatures required for shipping and storing CGT products. West can also support your drug development journey with container selection and analytical services, enabling you to get your drug therapy to market as quickly as possible.

APPENDIX: PERFORMANCE OF WEST CONTAINER CLOSURE SOLUTIONS

Container Closure Integrity (CCI) of Daikyo Crystal Zenith® Vial Solutions at Ultra-Low and Cryogenic Temperatures

Helium Leak Rates

The container closure integrity (CCI) of CZ vials at low and cryogenic temperature storage was investigated. All tests utilized 2 mL CZ RU (Ready to Use) vials, together with 13 mm laminated serum stoppers from both West and Daikyo.

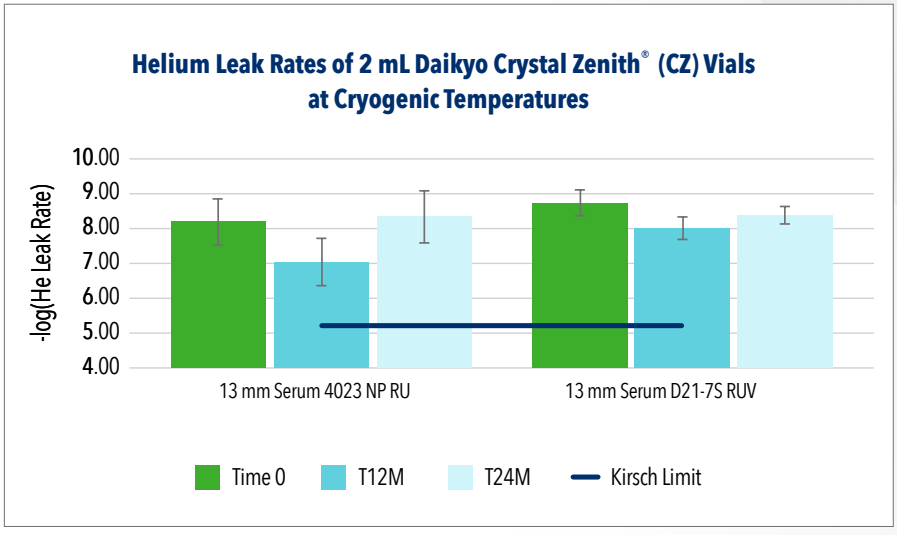


Shown is the helium leak rate measured for storage at -80°C for a period of 24 months. The blue line is the Kirsch Limit. The y-axis represents the Helium Leak Rate as a negative log. Results above the Kirsch Limit represent no CCI leakage.

All four systems using CZ vials were able to maintain CCI over a period of 24months at low -80°C temperatures.

NP RU: NovaPure® Ready-to-Use

D21-7S RUV: Formula D21-7S Ready-to-Use-Validated



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All four systems using CZ vials were able to maintain CCI over a period of 24 months at cryogenic -130°C temperatures.

NP RU: NovaPure® Ready-to-Use

D21-7S RUV: Formula D21-7S Ready-to-Use-Validated

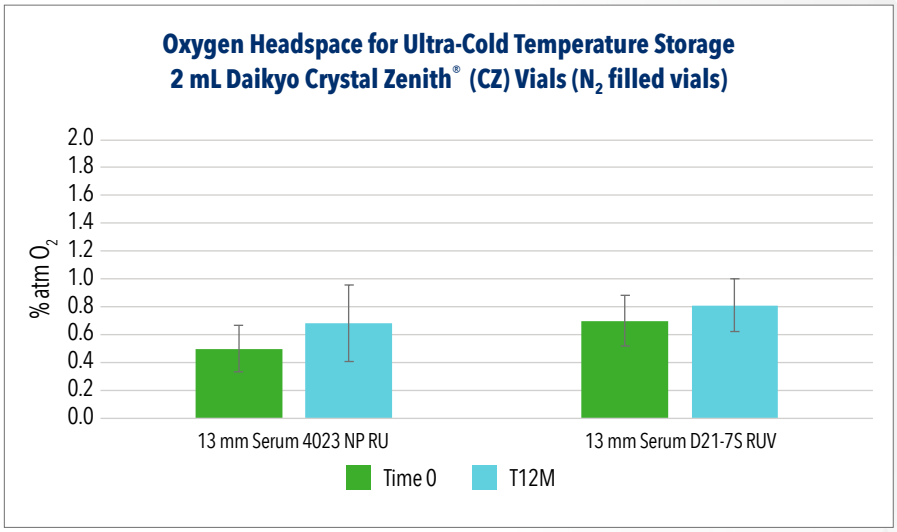
APPENDIX: PERFORMANCE OF WEST CONTAINER CLOSURE SOLUTIONS *(Continued)*

Container Closure Integrity (CCI) of Daikyo Crystal Zenith® Vial Solutions at Ultra-Low and Cryogenic Temperatures

(Continued)

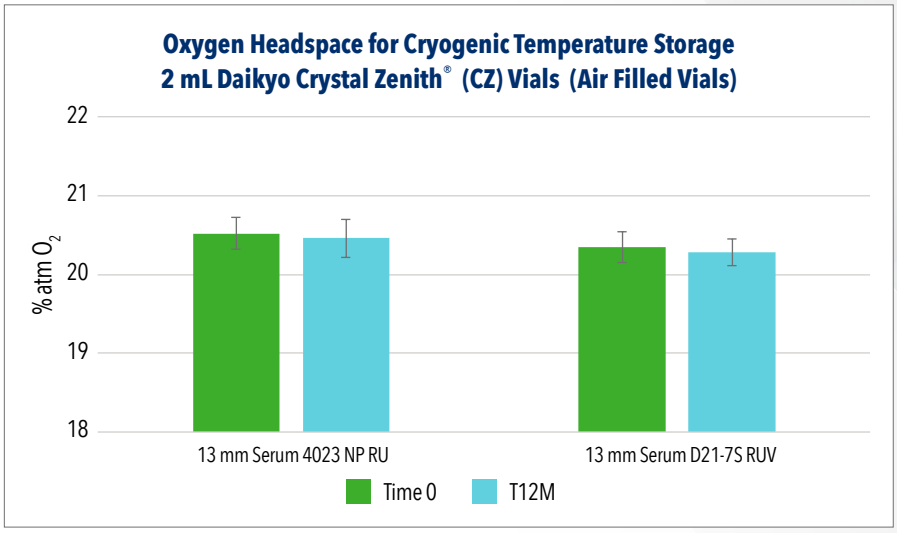
Oxygen Headspace

The container closure integrity (CCI) of CZ vials at low and cryogenic temperature storage was investigated using an oxygen headspace analysis method. All tests utilized 2 mL CZ RU vials, together with 13 mm laminated serum stoppers from both West and Daikyo, filled with nitrogen gas and air.



Shown is the oxygen headspace measured for storage at -80°C. Samples were measured at time zero and at the 12-month timepoint. The oxygen headspace test was performed on the assembled vial samples at the 24-month timepoint. The y-axis represents the % atm O_2.

Both systems using CZ vials exhibit minimal oxygen ingress into the vial and are thus able to maintain CCI over a period of 12 months at storage -80°C temperatures.



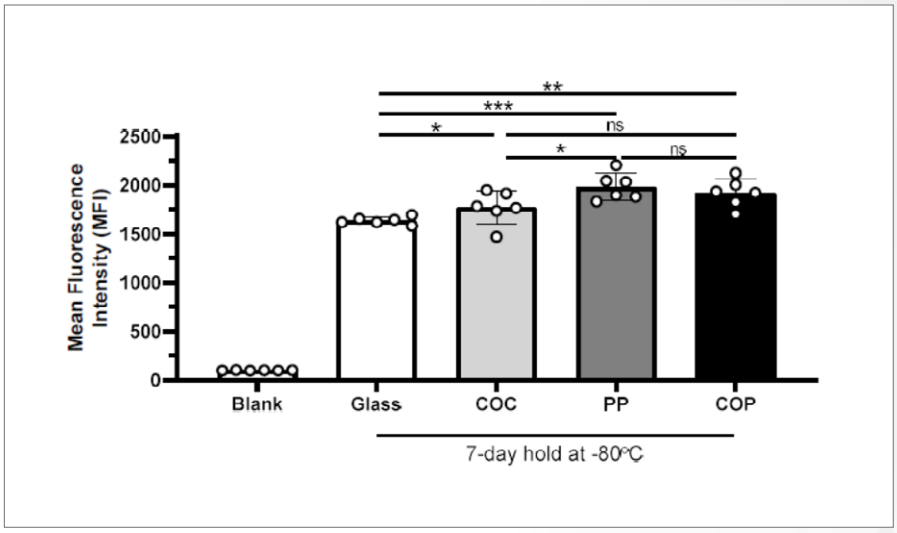
Shown is the oxygen headspace measured for cryogenic storage at -130°C. Samples were measured at time zero and at the 12-month timepoint. The oxygen headspace test was performed on the assembled vial samples at the 24-month timepoint. The y-axis represents the % atm O_2.

Both systems using CZ vials exhibit minimal nitrogen ingress into the vial and are thus able to maintain CCI over a period of 12 months at cryogenic -130°C temperatures.

APPENDIX: PERFORMANCE OF WEST CONTAINER CLOSURE SOLUTIONS *(Continued)*

Daikyo Crystal Zenith® Vials For Ultra-Cold Preservation of Viral Vectors: From Research to IND

West investigated an existing container system commonly used for commercial drug products as an alternative to the current polypropylene (PP) screwcap cryovials used for cryopreservation of advanced therapies. The Daikyo Crystal Zenith® (CZ) vial solution was composed of a commercially available CZ vial, a rubber stopper, and an aluminum seal. For comparison, AAV2-eGFP was stored at ultra-low temperature (-80°C)in various volumes and titers in CZ COP vials, glass vials, PP screwcap cryovials. Test effects were measured by mean fluorescence intensities (MFI) from cells transduced functional assay as an indication of AAV2 function.

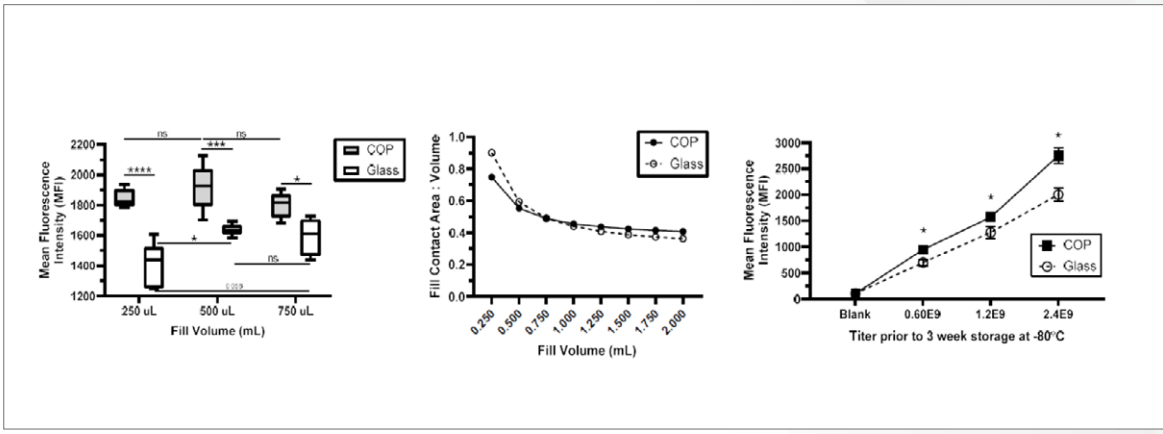


Shown is the containment of AAV therapy-material in four container systems. The y-axis represents the mean fluorescence intensity (MFI) as measured from cells transduced by AAV2 after a 7-day hold at -80°C.

Abbreviations: COC–cyclic olefin copolymer, CZ COP–cyclic olefin polymer, ns–not significant, PP–polypropylene screwcap cryovials.

The main findings of the study are that post-thaw AAV2 stored in 2 mL CZ vials systems maintains equivalency to and can outperform AAV2 stored in glass vials in terms of recoverability. This outperformance is increased at higher titers and lower storage volumes, likely due to the inherent differences in the material properties and vial design. CZ vials have been shown to functionally outperform glass for storing and recovering AAV2 viral vector material.

In summary, this study shows that 2 mL CZ container system is compatible with storage of AAV viral vectors and can serve as a storage solution for gene therapies.



Shown is the containment of AAV fill volume and titer.

Abbreviations: COP–cyclic olefin polymer, ns–not significant, PP–polypropylene screwcap cryovials.

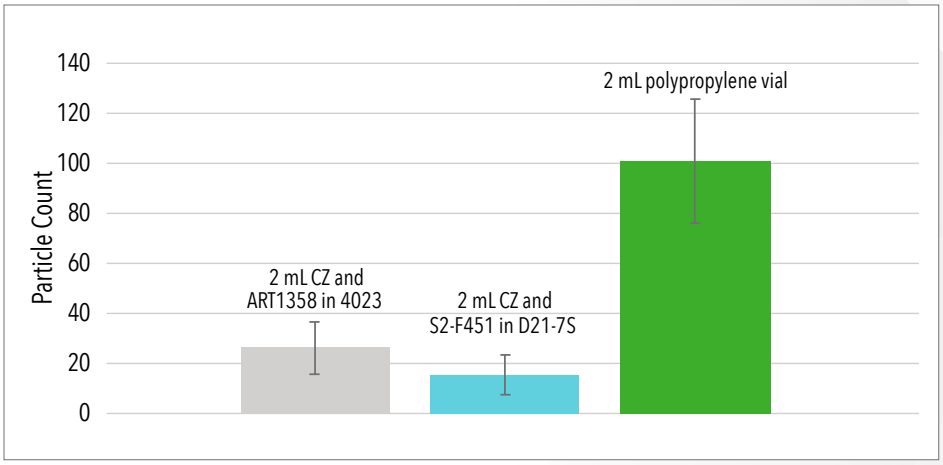
APPENDIX: PERFORMANCE OF WEST CONTAINER CLOSURE SOLUTIONS *(Continued)*

Daikyo Crystal Zenith® Vials For Ultra-Cold Preservation of Viral Vectors: From Research to IND

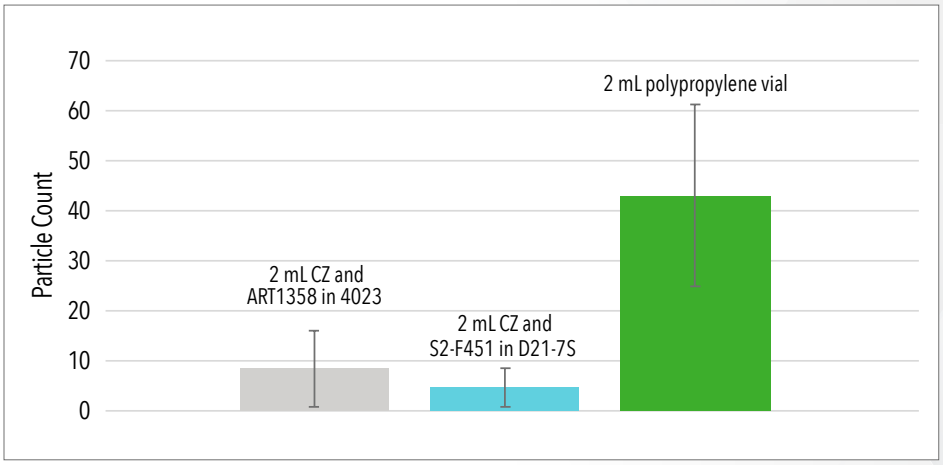
(Continued)

West conducted a study to evaluate particle counts after -80°C storage for both 2 mL CZ RU vials and 2mL polypropylene vials. Vials were filled with 1 mL of a PBS buffer with Pluronic F-68 solution. CZ vials were then stoppered with either 4023 or D21-7S stoppers and stored at -80°C for seven days. They were then evaluated for particles using USP <788> Method 2 (membrane microscopy) and quantified by greater than or equal to 10 µm (first graph), as well as greater than or equal to 25 µm (second graph).

The results demonstrate that the particle counts of CZ vials are lower than the polypropylene vials. The particle counts between 4023 and D21-7S were comparable to each other. Overall, the number of particles found in CZ stoppered vials are less than 10% of the threshold set forth by USP.



Shown is the particle count of particles ≥ 10 µm in 2 mL CZ vial + 4023 stopper, 2 mL CZ vial + D21-7S stopper, and a 2 mL polypropylene vials. The y-axis represents the number of particles counted using USP <788> Method 2 after seven days.



Shown is the particle count of particles ≥ 25 µm in 2 mL CZ vial + 4023 stopper, 2 mL CZ vial + D21-7S stopper, and a 2 mL polypropylene vials. The y-axis represents the number of particles counted using USP <788> Method 2 after seven days.

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