High-tech Packaging for High-tech Medicine

As more biologics and biosimilars come on to the global pharmaceutical market, they can and will present unique packaging and containment challenges. For materials that are sensitive to glass or that may require larger-dose volumes or custom configurations, cyclic olefin polymers may offer a solution. These novel materials for drug container closure systems can provide a needed alternative to traditional glass containment systems for advanced therapeutics.

Many biotech drugs are sensitive injectable drug products that can interact with containers and packaging components made from glass, potentially leading to delamination, particulates or protein aggregation. Additionally, some biopharmaceuticals have a high pH; others require storage at extremely cold temperatures.

Daikyo Crystal Zenith®, a cyclic olefin polymer, offers a low-risk, high-performance alternative to glass when faced with these or similar challenges. Available for the full life cycle of a medication, the Daikyo Crystal Zenith® cyclic olefin polymer can be molded to form containers and delivery systems that work from the research and development phase, through clinical testing, to patient delivery.

Researchers at the (U.S.) universities of Indiana and Kansas put Daikyo Crystal Zenith® cyclic olefin polymer to the test to determine how they'd fare in typical real-life storage situations. The results of these peer-reviewed findings are outlined below.

Meeting the Needs of Biologics

Biologics that exhibit such nuances and sensitivities to glass containment put demand on drug manufacturers and their packaging and delivery system providers to deliver innovative, sophisticated solutions for securely containing and delivering advanced therapies while ensuring both drug efficacy and patient safety.

Glass has been used to store or deliver pharmaceuticals for years—in syringes, cartridges and other containers. Glass is readily available, relatively inexpensive and in many cases, works very well. However, it has inherent flaws that may cause issues for drug manufacturers and patients. Drug makers are exploring safe, effective alternatives – especially for sensitive and complex drugs.

Glass has a tendency to break, chip or fragment, which can pose a significant danger to patients from particulate. Its range of viable shapes and configurations is limited. It does not perform well at extreme temperatures. In addition, glass is not inert. When paired with medications that have a high pH, glass can interact with the drug's chemistry, potentially leading to dangerous contamination.

As the next generation of drugs become available, these limitations are becoming more pronounced. Advanced therapies, such as biologics and biopharmaceuticals, commonly have a high pH and require storage at extremely cold temperatures. At the same time, innovations in drugs and delivery systems are enabling manufacturers to push design parameters. Many pharmaceutical manufacturers are seeking to differentiate their product through containment and delivery systems that offer more flexibility in the

types of shapes and configurations used for containers and individual parts. Cyclic olefin polymer delivery systems such as Daikyo Crystal Zenith® can provide drug manufacturers this opportunity for differentiation in an increasingly crowded marketplace.

Testing in Cold-storage Environments

A major obstacle in bringing biologics to market is the need for quality packaging and storage systems that can withstand low temperatures and resist breaking while also maintaining the viability and functionality of a living cell product.[1]

To investigate the ability of Daikyo Crystal Zenith® cyclic olefin polymer vials to meet these requirements, the Indiana University School of Medicine and West conducted drop tests and cell preservation tests under low temperature (-85°C) and cryopreserved (-196°C) conditions.

In drop tests, freezing did not affect the mechanical strength and durability of Daikyo Crystal Zenith® cyclic olefin polymer vials or their closures. No gross external damage was found on the vial surfaces, and there was no noticeable cracking or damage on the caps. Temperature or length of storage did not affect the outcome.[2]

In tests examining cell preservation after long-term storage, cells stored for six months exhibited rapid recovery two hours after thawing and all samples showed greater than 95% viability. Doubling rates for cells were consistent with controls.[3]

How pH Impacts Glass and Polymers Differently

Glass is not an inert material. Its chemistry can and does interact with certain medications in ways that can alter a medication's safety, stability, purity or effectiveness. When a drug's chemistry interacts with the chemistry of a glass vial, a process called delamination may occur, causing the glass to corrode and flake.

Glass vials are particularly susceptible to delamination in areas that have been flamed during manufacturing, such as the vial's base or shoulder. This interaction is especially prevalent with high-pH medications, such as many biologics, biopharmaceuticals, and other new and advanced therapies.

Over the past several years, delamination has emerged as a source of FDA concern and product recall for injectables.[4] These recalls can cost in excess of $50 million per incident. Unlike glass, the unique Daikyo Crystal Zenith® cyclic olefin polymer will not delaminate. A comparison of a glass vial with a Daikyo Crystal Zenith® cyclic olefin polymer vial after 57 days at pH 10 found signs of delamination in the glass vial, but not in the Daikyo Crystal Zenith® cyclic olefin polymer vial, even at microscopic levels.[5]

Barrier Films Help Solve Silicone Oil Issues

Many peptides and proteins have a higher tendency to interact with glass, resulting in protein aggregation and adsorption. One such substance is silicone oil, a common primary packaging lubricant in prefillable drug delivery systems.

Silicone oil is also a major contributor to particulate load. The interaction of silicone and proteins can decrease the physical or chemical stability of drug formulations, causing failure during accelerated or long-term storage.

The Daikyo Crystal Zenith® cyclic olefin polymer replaces silicone oil with a FluroTec® barrier film. The film, applied to the plunger and tip cap of drug delivery systems, helps minimize extractables and leachables while providing superior functional performance.

In a 2008 study,[6] the University of Kansas and West studied protein aggregation using Daikyo Crystal Zenith® cyclic olefin polymer silicone oil-free and siliconized glass prefillable syringe systems. The study found a reduced extent of aggregation in the syringes incorporating Daikyo Crystal Zenith® cyclic olefin polymer compared with the glass: at high protein concentrations, the silicone oil-containing glass syringes did affect protein aggregation, especially under agitation and air shipment.

Partnering for Quality

To ensure the safety and efficacy of a drug product, pharmaceutical manufacturers should partner with drug packaging and delivery experts to properly evaluate material compatibility and select the highest-quality container closure system for a particular drug product.

Collaborating with a single partner with diverse and longstanding expertise in primary packaging, delivery systems and custom design can help ensure the optimal packaging and containment solution throughout a drug product's lifecycle. Packaging manufacturers who also provide analytical laboratory services can offer product recommendations on the latest alternative technologies and provide prescreen stability work early in the process to limit risks for interaction between containment materials and the drug product.

One of the most important services a packaging company can provide is material and stability testing. While it may not be possible to tell which drug product and delivery system interactions may result in delamination, several tests can help predict the possibility. Delamination can occur at any point in the drug manufacturing process, including vial manufacture and heat treatment or sterilization processes.

Cutting-edge quality control is a major part of West's manufacturing processes: Container closure systems can be examined microscopically for visible indications of defects, particles, pitting or delamination before filling. For example, the neck and base of a vial represent areas of high stress in the glass; microscopic evaluation of these areas after exposure to a stressed environment can detect the potential for delamination. Validating packaging and containment choices through materials testing processes can help eliminate problems that could potentially lead to costly recalls and safety issues with patients.

As the next generations of drugs and biologics become available, the potential limitations of glass container closure systems in some cases are becoming more pronounced. As a full product lifecycle solution, drug delivery systems incorporating cyclic olefin polymers are quickly becoming an ideal solution for their ability to provide a high-performance, low-risk alternative. Working together,

pharmaceutical and packaging and delivery systems companies can develop innovative cyclic olefin polymer containment solutions that can safely contain today's advanced biopharmaceuticals.

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FluroTec® is a registered trademark of West Pharmaceutical Services, Inc., in the United States and other jurisdictions.

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[1] Woods E, Bagchi A, Nase R, Vilivalam V. A Novel Container System for Cell Therapy Products. General BioTechnology, LLC; Department of Microbiology and Immunology, Indiana University School of Medicine; and West Pharmaceutical Services, Inc. http://www.westpharma.com/en/support/Scientific%20Posters/A%20Novel%20Container%20System%20for%20Cell%20Therapy%20Products.pdf. Accessed January 28, 2016.

[2] Ibid.

[3] Woods EJ, Bagchi A, Goebel WS, Vilivalam VD. Container system for enabling commercial production of cryopreserved cell therapy products. *Regen Med.* 2010;5(4):659-667.

[4] US Food and Drug Administration. Advisory to Drug Manufacturers: Formation of Glass Lamellae in Certain Injectable Drugs. http://www.fda.gov/Drugs/DrugSafety/ucm248490.htm. Published March 25, 2011. Accessed January 28, 2016.

[5] CZ sale brochure #8427.

[6] Esfandiary R, Joshi SB, Vilivalam V, Middaugh CR. Characterization of Protein Aggregation and Adsorption on Prefillable Syringe Surfaces. University of Kansas and West Pharmaceutical Services, Inc. 2008. http://www.westpharma.com/en/support/Scientific%20Posters/Characterization%20of%20Protein%20Aggreagation%20and%20Adsorption%20on%20Prefillable%20Syringe%20Systems.pdf. Accessed January 28, 2016.