

CELL & GENE THERAPY INSIGHTS

INTEGRATION OF MANUFACTURING
& DELIVERY INTO HEALTHCARE

SPOTLIGHT

INNOVATOR INSIGHT

Cell and Gene Therapies in Transit: Caution – Hazards Ahead



Kevin O'Donnell is widely considered one of the principal architects of the modern-day pharmaceutical cold-chain movement. He is internationally respected and uniquely qualified as a tireless advocate, author, blogger, educator, training developer, and champion of good distribution and logistics practices for temperature-sensitive drugs. His pioneering efforts for the advancement of good practices are reflected in his various roles within the industry: as a member of the United States Pharmacopeia (USP) Expert Committee on Packaging, Storage and Distribution; temporary advisor and certified mentor to the World Health Organization (WHO); co-author of PDA Technical Report No. 39; a member of the International Safe Transit Association (ISTA) Thermal Council; and the former chair of the International Air Transport Association (IATA) Time & Temperature Task Force. Prior positions include: Senior Partner at Exelsius Cold Chain Management Consultancy US, an international provider of consultative, research, and training services to manufacturers, airlines, forwarders, and other stakeholders in the life science logistics sector; Director & Chief Technical Advisor at ThermoSafe Brands; and Principle Packaging Engineer at Abbott Laboratories Global Pharmaceutical Division, from where he retired in 2005 after a 26-year career.

Q What are some of the greatest threats to a cell and/or gene therapy once it's in transit?

I would say the greatest threat is the general lack of understanding related to the risk of product exposure to the potential hazards within the transportation environment itself. In the book *Fundamentals of Packaging Technology*, author Walter Soroka states that one cannot protect a product in transport without first having a thorough understanding of the environment through which that product must pass. This requires two things: knowledge of a product's fragility limits and visibility into the transportation environment. Exposure to unwanted environmental events such as temperature, humidity, light, shock, vibration, pressure and package

orientation varies by modes of transport, lanes, duration, location, level of service, even by provider.

The fragility and sensitivity to environmental changes of cell therapies is considerably greater than that of most other biological drugs. This has necessitated the development and introduction of new technology and tools that allow for more precise temperature control and far greater visibility of products in the supply chain with real- or near real-time data streaming of location and condition of a payload through on-board monitoring devices and integrated cloud-based applications – so-called smart shippers. Rather than make assumptions regarding what occurs once a package leaves your care, smart shippers provide documented evidence of lane, mode and time of travel and hazards incurred throughout the shipment. In some cases potential harm to a package can be prevented by intervening beforehand.

By way of a common and frequent example, international shipments of temperature-sensitive goods often get held-up while transiting airlines, ground services, freight forwarding companies or when funneled through customs. The risk that that package is temporarily stored in a refrigerator or freezer during such layovers is significantly high. The risk is increased if the package is stamped or labeled with phrases like “keep refrigerated” or “refrigerate upon arrival” or “contents temperature-sensitive”, to name a few. Inadequate or unqualified insulated packaging often cannot protect the internal product from freezing if improperly stored even for a few hours. Once the package is removed and continues its journey, the product rises to its proper temperature range and is received in at its final destination with no one the wiser that the product went through an uncontrolled freeze–thaw cycle. The use of a drop-in-the-box temperature data logger in such instances can only give an approximation if the product was exposed to potentially harmful temperatures. At best, the product would need to be placed on hold until a determination can be made if the product is still viable. At worst, the product must be destroyed – maybe unnecessarily so.

Q What efforts have been made to try to determine the specific impact of these varying environmental events on a cell therapy product?

BioLife, in conjunction with Brooks Life Sciences Systems recently conducted a series of tests designed to determine if and to what extent, the quality of procedures and products used for preparing, transporting and storing cells at cryogenic temperatures have on the post-thaw viability and functionality of the cells. Sub-standard preparation, handling, storage, and products may subject cells to improper cryoprotectant exposure. Inadequate transport packaging and negligent shipping practices can cause variability in product temperatures and unknown transient warming events throughout the handling, storage and logistics chain. This can negatively impact the viability, recovery and functionality of sensitive cells and therapies.

The objective of the study was to compare two methods of preparing, transporting and storing living cells to achieve the highest post-thaw viability. One method was intended to show an optimized cold chain and improved best practice, the other was considered current common practice. The outcome of this study revealed some interesting results.

With respect to media preservation, Jurkat T-cells frozen in CryoStor CS5 were similar to, but exhibited less baseline variability, than reference 'homebrew' cryomedia. Jurkat T-cells frozen in traditional 95/5% cryomedia and shipped in a customary EPS container on dry ice experienced a significant decline in viability immediately post thaw and a delayed return to function 48 hr post-thaw. The combination of CryoStor CS5 and the CRYO evo smart shipper afforded superior protection from cryopreservation and transportation stress with no measurable decline in structural and functional viability as a result of freezing, thawing over two cross-country transit events. The CRYO evo smart shipper and its biologistex™ integrated cloud-based shipment application allowed real-time status, tracking and event alarms throughout the entire shipping process, permitting enhanced tracking and knowledge of any environmental excursions as they happen. The design of the CRYO evo smart shipper prevented warming from dry ice sublimation and maintained the Jurkat T-cells within the desired temperature range throughout transit.

Q From your experience, how much awareness is there within the sector as to these threats?

There is generally a lack of awareness, as the nascent industry has not yet had to deal with these logistical issues on a large scale. But it is encouraging to see that as these promising cell therapies advance through the clinical trials process toward commercialization, companies recognize the importance and criticality of potential hazards within the transportation environment that may adversely affect their product.

The level of risk to those hazards, which may negatively impact the quality or viability of cell therapies, varies and is often dependent upon the levels of service provided by the transport or logistics provider. Shipping via general cargo through a freight forwarder places the product at the greatest risk of unwanted exposures. Specialty courier services that offer hand-carried deliveries are the least riskiest. Somewhere in between are the integrated services (UPS, FedEx, DHL, etc.) and where the bulk of transportation of cell therapies occur.

Q At what stage do cell and gene therapy companies typically start to consider cold chain logistics for their products?

Typically, companies that are not already using BioLife preservation solutions or cryoprotectant solutions in their cell therapy processes turn to us during the scale-up process in Stage II to Stage III clinical trials. Early on in the Stage III process is an ideal time to engage. The amount of data that can be collected from multi-parameter

on-board monitoring can enhance a documented data package, ensure greater control, and reduce variability of results. Those that do use BioLife products in their manufacturing of cells are already familiar with the quality of products and service. Adding the biologistex Smart Shippers, its integrated cloud application for transport in partnership with MNX specialty logistics service provides a comprehensive solution to our customer base.

Q As we see an increasing number of diverse cell and gene therapies heading towards the clinic from multiple manufacturers, what efforts are being made to standardize the handling of these products to ensure consistency in end product?

One major industry organization in the United States that is attempting to address these issues is the Georgia Research Alliance, in conjunction with Georgia Institute of Technology and the National Institute of Standards and Technology (NIST). Together they have formed the Cell Manufacturing Consortium (CMC) and its member participants are leading the development of a cell manufacturing industry roadmap whose aim is to provide a pathway to overcome cell manufacturing, storage and transportation challenges and capitalize on opportunities that will maintain the US's position at the head of the rapidly expanding global cell manufacturing industry.

The CMC have identified and prioritized a variety of research and development activities that the cell manufacturing industry must pursue to help maintain and advance the US's lead in the global cell manufacturing industry. These activities aim to increase cell manufacturing scale and speed while also improving cell quality and functionality, reducing cost, and ultimately improving the safety and efficacy of cell therapies.

The group has identified 6 areas of focus:

- ▶ Automation and Closed- System Processing;
- ▶ Critical Product Quality and Process Controls;
- ▶ Production Scalability at Good Manufacturing Practice (GMP) Facilities;
- ▶ Culture Platforms and Downstream Processing;
- ▶ Cell Preservation, Distribution, and Handling;
- ▶ Supply Chain Robustness and Management.

Q Are there any regulatory guidelines in place to ensure the efficacy of cell and gene therapies once they leave the manufacturing site?

At this time there are no specific regulatory guidelines focused on packaging and transportation of cell therapies. Any investigative or commercial cell therapy fall under the regulatory auspices of the FDA in the US and their regulatory counterparts in respective countries. There

has been a growing trend among regulatory authorities worldwide that focuses on packaging and transportation practices as an extension of manufacturing. This is an outgrowth of the evolution in how biologic drugs are manufactured, which, over the past decade has evolved from inter-plant to international. It is not uncommon for a biologic drug to pass through multiple manufacturing steps in multiple countries before becoming a finished product. As a result, regulators have given much greater scrutiny to the practice of inter-plant transport of unfinished product, making transportation part of the cGMP process and requiring drug makers to demonstrate performance of their transport packaging and control over their transportation practices. The same hold true for clinical trials. Greater regulatory emphasis on documented processes for transport and control has been trending in the US, Canada, the UK, the EU and other regions throughout the world.

Q So much of the discussion around optimizing cell & gene therapy manufacturing focuses on automation of processes – to what extent can cold chain processes be automated to improve standardization?

A **by Mathew:** The discussion around automation has focused thus far primarily on the closed system manufacturing and scale-up of the cell product itself. The formulation of cell and gene therapies with biopreservation media and automated filling/packaging machines is a current focus for several industry manufacturers nearing commercialization. In fact, as scaled up manufacturing has encountered bottlenecks related to integrating biopreservation media addition into closed systems, our group has been able to provide modified biopreservation method optimization to evolving manufacturing processes that allow for closed systems integration and multi-solution transition into final formulation and fill.

Just as an automobile coming off an automated assembly line would still require some manual steps for transport, the final cell dose would likely still require some manual intervention steps regarding cold chain delivery for the foreseeable future. Risk mitigation and tracking would likely be the first points of focus within cold chain management. The use of electronic bar codes that can be scanned and integrated into healthcare software management has already been implemented. Bar code tracking can also be integrated with courier logistics. Although RFID tracking has been utilized for large scale shipments of consumables, and even pallet-sized tracking of pharmaceuticals, the smaller shipments associated with cell and gene therapies is more aligned with the emerging tracking systems designed to be integrated with the cellular network systems. This can allow for more real-time collection and analysis of the data parameters. It would not be unrealistic to imagine integrated delivery of these personalized medicines via driverless vehicles and/or unmanned drones via software programs and cloud-based services. It may also not be far off from realization for integrated cloud-based biologistics software to automatically re-route a shipment that might encounter delivery delays – either via transfer to alternate

transportation routes or transfer to white glove couriers in real time. At the end of the cold chain, there are also initiatives to develop automation for thawing of cryopreserved doses without the use of a manual waterbath. Several groups have brought first generation cell thawing devices to market, or for internal use with their cell products, however there is still room for further optimization of these devices and reduction of manual steps.

Kevin O'Donnell: In terms of downstream processes, packaging, storage and distribution, there is a lot the cell therapy industry can learn by standing on the shoulders of the pharmaceutical and bio-pharmaceutical industry. The regulatory perspective is all about providing sound, documented evidence and scientific justification demonstrating the minimization of risk.

High-performance Smart Shippers provide unparalleled thermal performance against uncontrolled and unwanted temperature exposures in distribution. They also provide monitoring ability to a host of other

environmental hazards to which a package is exposed in transit that can have a negative impact on fragile cell therapies.

There needs to be less reliance on periodic drop-in-the-box temperature monitoring and reporting after a shipment is concluded – the validate and assume approach – and greater reliance on real-time environmental

reporting, intervention and quality improvement through the use of intelligent, informed, and precise biologistics that Smart Shippers provide.

The promise of cell therapies ushers with it many new and exciting prospects for getting these miraculous cures to the patients in need. Improved preservation *in-vitro* allows for increased cell viability and higher cell recovery. New concepts in ultra-high performance packaging, Smart Shippers with multi-parameter monitoring and logistics performance, provide for greater continuity of the process allowing for data-driven decisions and factual reliability with regard to product condition prior to and up to the point of infusion. This was unimaginable just a few years ago. There is also an opportunity for less reliance on costly integrator services and white glove handling, as packages can be “visible” and self-managed in transit. It’s reasonable to assume that same-day delivery across country or next day delivery around the world will become increasingly common for these delicate products.

The promise of cell therapies ushers with it many new and exciting prospects for getting these miraculous cures to the patients in need.

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