CELL & GENE THERAPY INSIGHTS

PERSPECTIVE

Moving from passive to rescue design packaging: helping cells arrive alive with smart shippers

Kevin O'Donnell

The packaging of time- and temperature-sensitive healthcare products has changed very little over the past quarter century. However, the advent of new, fragile cell therapies demands the need for greater temperature precision, and the ability to collect multiple data of environmental and handling conditions within the distribution environment through continuous real-time monitoring and on-line accessibility. This article explores the lessons learned from the decade-long tortuous path taken by the pharmaceutical and biopharmaceutical industries with regard to shipping environmentally fragile products and how it has led to the development of rescue design packaging capable of precision performance with flexible intervening capabilities during transit - so-called "smart" shipping containers. Embedded electronics provide monitoring and recording a host of data on a per-package basis. The data is managed through a proprietary and secure web-based application where the tracking, management and analytics of each package can be applied in a multitude of ways, from gaining greater understanding of a products' stability in the distribution environment to choosing the best routes and modes of transport.

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IDENTIFYING A NEED FOR CHANGE

Over the past quarter century, the evolution of insulated packaging systems used for the transport of time- and temperature-sensitive drugs, vaccines, biologics and other delicate life-saving materials, has fallen gradually and comfortably into mediocrity. Many drug manufacturers and wholesalers throughout the industry have clung to the notion that insulated transport packaging is little more than a necessary evil, an unavoidable expense with minimal consideration or understanding given to its relationship to performance for maintaining drug quality and efficacy. Until recently, many temperature-sensitive drug products were placed in inexpensive and minimally protective "Styrofoam" boxes with a couple of frozen gel packs, then

blindly sent on their way through a hostile and bewildering transportation environment, that itself is often not well understood nor well controlled, only to arrive at its destination in what always was assumed to be "perfect condition." This paradigm has been slow to change. Innovation has to an extent been stymied too, with packaging and solution providers readily acquiescing to the immediate needs and imploring demands of the pharma and biopharma industry, rather than pioneering solutions to unmet needs in anticipation of the industry's future.

Shortcomings in insulated packaging performance due to the lack of real innovation in insulating materials and refrigerants have increased molly-coddling handling practices of such shipments. Lured by double-digit profit margins in an otherwise single-digit industry, white-glove logistics providers, integrators, specialty carriers and airlines have flourished with a host of expensive and often indistinguishable array of product offerings that cater specifically to high-volume, high-risk biologic medicinal products. Collectively, the state of the industry remains fragmented at best, with storage, packaging, and transport logistics each needing to be individually cossetted, qualified, and managed, placing a considerable burden on both human and financial resources on the various entities throughout the supply chain.

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Growth in global biopharma product availability has generated demand for larger lot sizes and bigger payload capacities. Lengthy and complex international manufacturing and commercialization processes have replaced inter-plant manufacturing putting increased pressure on those offering packaging and transportation solutions. Cold-chain packaging, logistics, transportation and instrumentation spend within this segment of the industry is expected to cross the $10 billion barrier this year, on its way to $13 billion by 2019 while cold chain product sales will rise by around 9% per year [1].

Despite this growth, or perhaps because of it, the industry remains rife with a lack of control. Improvements to date have been incremental. However, gaping holes, interruptions and blind spots in transportation processes still exist. The unavailability of temperature and other critical data to justify and augment support for stability of a drug throughout distribution is common, and a general lethargy within the industry to embrace change endures.

CELL THERAPIES REQUIRE GREATER CONTROL

In many respects cell therapies are carving out a unique position in the healthcare industry, including the cold chain. This nascent technology is at the epicenter of many new drug discoveries and is poised to mainstream personalized medicine. There are many challenges in bringing these therapies from discovery to commercialization, not the least of which is maintaining "needle-to-needle" preservation,

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biologic integrity and functional performance of the living cells. Cells, tissues and organs removed from the body enter an immediate continuum of degradation. Traditional packaging and current biopreservation tools are not optimized to meet these challenges offering limited protection from preservation-induced stress, injury, and death. These stability stresses can occur at multiple levels within the cell and throughout the supply chain and therefore need to be monitored from end-to-end.

RESCUE DESIGN PACKAGING

Rescue design transport packaging is a unique and an entirely new concept in packaging enabling the user flexibility to intervene or "rescue" a shipment from potential risks while in transit. This is especially important in the transport of autologous cell therapies where viability is typically measured in hours, not months, and can often mean the difference between life and death of a patient. Rescue design provides the ability to document the packing, transportation, logistics and physical condition of time-critical and temperature-sensitive payloads by incorporating multiple technologies into the package itself. The packaging seamlessly integrates on-board multi-parameter environmental, anti-pilfering, theft-deterrent, and geo-location/geo-fencing capabilities, with cellular communications and a secure, web-based app, so that user-appointed designees anywhere in the world can monitor a package in real-time, virtually anywhere throughout its journey; in the case of infusion therapy, tissue or organ harvest and re-transplantation – throughout its *ex-vivo* lifetime. The web app includes alert and escalation notifications by email, SMS, or through a customer care representative. Smart packaging is self-powered and blind to carriers, modes of transportation, or logistics service providers. A complex algorithm built into the unit allows for automatic termination of signal transmission aboard aircraft, while data during flight is continuously collected and uploaded once the aircraft has landed. Once received, a smart package is capable of alerting the user to a hassle-free return to its origin for redeployment.

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Unlike other systems that collect data at the truckload level or pallet level, rescue design enables unprecedented visibility and identification of process gaps, and allows for unparalleled analytics for the determination of an assignable cause of failure, or to quantify to what extent degradation of a drug product has occurred within an individual package prior to administration to a patient. The packaging itself is able to monitor, record and alert of improper pack-outs, insufficient packaging performance, negligent logistics practices, or abuses in transportation that can negatively affect product quality.

CAPITALIZING ON THE BENEFIT OF HINDSIGHT

Advanced treatments such as cell therapy and regenerative medicine have precipitated the need for rescue design and smart packaging. Five main components ubiquitous to all time-critical and temperature-sensitive drug shipments include:

- A temperature-controlled shipping container;
- The logistics/transportation;
- Temperature monitoring devices;
- Temperature data management software;
- An understanding of the regulatory requirements for maintaining compliance.

Taking a closer a look at these components one can see how rescue design and smart shippers rise to meet the needs of the overall industry – not just those in the regenerative medicine space.

PACKAGING

Temperature-controlled packaging providers have been around for a long time, focusing their opportunities in the pharmaceutical industry's high-value, high-volume, and high-piece-rate pharma and bio-pharma shipments, with no indication of slowing down. The *Sixth Edition of the Biopharma Cold Chain Sourcebook* projects 44% growth in the temperature-controlled supply chain over the 2013–2019 span [1]. Here, the prospects for packaging providers are plentiful, and margins high, although recent trends have leaned toward an increasing commoditization of the industry. Today there exists many dozen insulated packaging providers whose solutions for maintaining temperature range extend from the ridiculous to the sublime. The industry has made fractional advances with regard to materials and design over the years and constructed ever-larger shippers to accommodate more product, but the cost for doing this usually results in an increase in components and packout complexity – not to mention additional storage space requirements.

The vendor exhibition area at any industry cold-chain conference attracts a cavalcade of solutions providers – active and passive – each with their own take on the same basic package design: an insulated box with ice packs, or some other temperature stabilizer wedged inside, that is intended to keep the product at a predetermined temperature, for a predetermined time, when subjected to a pre-determined (and usually narrow) set of ambient conditions. In this respect, the industry is stuck in second gear. Capable of providing reasonable protection from external temperature extremes, current passive packaging systems do not have the ability to monitor, store and retrieve shipment data without the addition of a secondary component, a drop-in-the-box monitoring device. Access to that data is often not attainable until the package transport is completed, and the package is opened. This can prove to be too little too late and the gap in data visibility can be costly. In a 2012 global survey conducted by Pharma IQ, 30% of the more than 100 respondents indicated that they experienced excursions beyond the allowable temperature ranges in excess of 6% of their total temperature-sensitive product shipments. This lack of information frequently forces those

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in charge of product quality to remove their product from the supply chain, replace the shipment and destroy the questionable inventory.

Content with marginal or adequately performing disposable insulated packaging has become a mainstay of the biopharma industry. However, as the industry grows, so do the mountains of land-fillable waste. Concerns about landfill volume and environmental impact of petroleum-based packaging grows daily. The across-the-board one-and-done approach to packaging for the transport and distribution of temperature-sensitive drug products is reaching critical mass and the situation will soon become untenable.

Smart shippers are reusable, high performance, super-insulated and designed to easily exceed 3-day autonomy against a host of challenging ambient temperature profiles. They weigh up to 50% less than comparably sized passive shipper counter-parts. Efficiency in design provides for the maximum cubic volume and weight specifically designated by the parcel environments through integrator services such as FedEx and UPS (referred to as dimensional weight), so that either way – dimensional weight or actual weight – the shipper optimizes shipping costs.

LOGISTICS/ TRANSPORTATION

Logistics services – including the "all-inclusive" offerings provided by integrators, white glove couriers, and freight carriers, have always been the fulcrum between the shipper and receiver. Their role includes the behind-the-scenes coordination of freight-forwarding activities, chain-of-custody and Transportation Security Administration security procedures, consignments to ground transportation providers and air carriers, customs clearance, temporary storage when needed, and door-to-door delivery. In recent years, many well established and well-intentioned logistics providers, large and small, seduced by the promise of high profit margins found themselves unable to meet the fickle demands and seemingly outrageous expectations of the pharmaceutical industry, and simply couldn't adapt. Others underestimated the amount of capital and personnel outlay necessary to meet Good Distribution Practice (GDP) standards and were not prepared to stand by the "if you build it they will come" philosophy of business investment. Still others were dissuaded by the notoriously protracted sell cycle, or did not want to be ensnared in FDA, EU/Good Manufacturing Practice (GMP), or other regulatory oversight. The strongest and most agile of these companies have survived. In the end, that's a good thing. The overall service approach of the logistics segment has curiously been to modify the processes to accommodate the growing global proliferation and complexities of the products. But this is akin to treating the symptom of a disease rather than finding a cure.

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Smaller, more specialized sectors of the healthcare industry – such as those conducting and coordinating clinical trials, have the attention of a spate of specialty service providers. Growth in this end of the industry is enticing. Clinical trial logistics ticked upward in 2014, following several years of relatively flat growth, and this trend is likely to continue for a few years at least. Overall, clinical trial logistics spending is estimated at $3.0 billion in 2015, rising to $3.29 billion in 2019, a compound annual growth rate of 2.5% [1].

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Rescue design packaging provides real value in this arena by enabling intelligent, informed and precise biologic materials management.

DATA MONITORING/DATA MANAGEMENT

An anxious pharmaceutical industry's habitual over-reliance on, and underwhelming confidence in the abilities of the transportation service providers to meet their critical demands, coupled with the industry's own past ignorance and misunderstanding of the distribution environment, has invariably led them down the path of monitoring their shipments. Not to say this is a bad thing. Temperature monitoring – defined as the ability to reliably collect, store and retrieve accurate temperature information; at a minimum after delivery and at best, upon regular intervals during the course of a temperature-sensitive shipment, has become commonplace. Serendipitously, "drop-in-the-box" type electronic temperature monitoring and data logging devices provide a "snapshot" of circumstantial (and sometimes interpretive) evidence of otherwise unknown hazards and hiccups within a particular mode of transport, along a lane segment, or across an entire distribution process, merely by aligning temperature along a timeline. Without location visibility, there remains a bit of an "art" to speculating what triggered an event to occur, and where. There is no shortage of device manufacturers or anecdotal evidence floating round the industry to confirm this. But the bigger questions are: what to monitor? And when to monitor? Regulations and best practice guidance generally leave this open to the user with interpretative statements like "periodic and appropriate monitoring is recommended" [1].

Smart shippers, in addition to providing outstanding insulating performance and prolonged thermal stability are capable of monitoring several environmental and transportation conditions at once. In addition to product payload temperature, imbedded electronics within the insulated container can record and store external (ambient) temperature, humidity, light, tilt, shock, vibration, location with geo-fencing capabilities, pressure, battery consumption, and cell signal strength, with more parameters on the way. The electronics meet

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Federal Aviation Administration requirements for radio transmission suppression during flight (but still collect and store data internally uploading it upon landing), and they are fully programmable on the basis of interval, events, and notification to key stakeholders. Data are transmitted in real-time, stored internally and within a secure and proprietary web-services hosted environment. The Lithium-ion battery used to power the data collection and transmission is not regulated in air transport as the lithium content falls well below the declarable limit.

Another key benefit of smart shippers used for transport of cell therapies with critically short stability, allows the user to enable a stability countdown timer with actionable alerts. Arrival notification via e-mail or text can be sent directly to the doctor or facility performing the infusion therapy and the condition of the treatment can be assessed up to the time of administration to the patient.

Then there is the problem of record keeping – managing all that data and investigating deviations and excursions that occur during shipment – none of which is generally known until after the fact when the process is completed and possible damage has already been done. It is necessary to download and analyze the data before making a determination on the disposition of the shipment. This involves the time and effort of several people in multiple departments scattered throughout an organization. Valuable time is lost as the product is held or quarantined until such a determination can be made. In the clinical trial environment, not all biologic drugs are analyzed for exposure to temperature excursions before the patient is dosed. This commonly accepted practice is based on a basic n = 3 "validate then assume" approach to stability protocols and delivery assumptions.

With infusion therapy, this can be very risky. Smart shippers, with the breadth of critical information they provide significantly reduces and can even eliminate speculation, interpretation and conjecture surrounding the integrity of a product.

REGULATORY REQUIREMENTS & MAINTAINING COMPLIANCE

As late as 2007 there was no guidance to industry whatsoever stating the essential principles or practices of transporting temperature-sensitive medicinal products through the transportation environment; nor was there a standardized process for qualifying temperature-controlled shippers that users could adopt or regulators reference. The publication of the PDA *Journal of Pharmaceutical Science and Technology* Technical Report No. 39: Guidance for Temperature-Controlled Medicinal Products: Maintaining the Quality of Temperature-Sensitive Medicinal Products through the Transportation Environment, changed all that. TR 39, as it is commonly called, has become globally embraced by users and regulators alike, as a standardized framework for qualifying temperature controlled shippers.

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The evolutionary process of biological drug manufacturing has seen an explosion of best practices, guidance and regulations for both investigative medicines and commercial products. In 2000 there were only a few such documents available. Today, there are more than 60; specifically addressing storage, handling and transport of time- and temperature-sensitive drugs for both human and veterinary use. Regulatory scrutiny has, invariably, followed suit. In many instances where the manufacture of a drug product occurs in multiple steps in multiple countries, current GDP apply. Global regulatory expectations for the storage, handling and transport of these articles has become an outgrowth of current GMP with citations, levies and fines related to packaging and distribution accounting for a significant number of infractions. Increased control and visibility provide a significant reduction in the risks associated under such conditions.

The total value of bioengineered drug products is now more than $150 billion worldwide; three times what it was 10 years ago. This represents a small but growing fraction of the overall $1.2 trillion pharmaceutical market and analysts predict that by 2018 more than half of the top-selling 50 drugs will require 2–8°C cold-chain storage, handling and distribution, 10 of which will be newly approved drugs (IMS Health) [3].

Then there is the vaccine market. The number of new vaccines – both prophylactic and interventional – continues to grow at a double-digit clip with more than 160 additional vaccines currently in the development pipeline. Sales of vaccine more than tripled between 2000 to 2013, from US $5 billion to $24 billion and they are expected to rise 10–15% annually to a projected $100 billion industry by 2025 according to the World Health Organization; thus remaining a key driver in the growth within the pharmaceutical industry (WHO) [4].

Basic and applied research followed by clinical trials, the obligatory and astronomically expensive approval pathway for new drug therapies, treatments and devices, accounts for billions of dollars of the worldwide healthcare industry total spend. Drug patents are finite; typically 17 years from the date of filing. The protracted process from discovery of a biologic drug to full FDA approval for example, can easily eat up 10 to 12 years with an investment of more than $1.2 billion. For every 10,000 drug discoveries made, only one ever crosses the finish line. Therefore, speed to market is key. By way of example, a new drug projected to earn a modest $1 billion a year in sales will suffer an unrecoverable loss of $2.7 million a day for each day the approval process is delayed – for whatever reason. Often, regulators impose these delays as the result of variable, inconsistent or incomplete clinical data. Until very recently, strict temperature control and temperature data collection and management of clinical trial materials has been, well – a bit spotty. But tighter and better-documented processes have led to a more complete understanding on the impact of temperature control and logistics on product stability in the clinical

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This is the sweet-spot for rescue design smart shippers. Clinical trial managers now have the capability for better control of processes affecting stability and drug performance variability. Comprehensive environmental and other shipment data is monitored, recorded and stored continuously so drug development companies can be more confident in their stability data. Patient outcomes can be improved. Documentation, support and defense of precious stability data is greatly increased and better understood and can add significant value to a developing drug to potential investors. Time-to-market can be significantly reduced as errors that may cause regulatory delay or review and approval can be significantly avoided or at least prevented in some cases.

CONCLUSIONS

Rescue design and smart shippers have taken a page from the pharmaceutical industry's playbook, taking advantage of the best-of-the-best practices and technology for the transport and management of time-critical and temperature-sensitive products; packaging, monitoring, logistics practices, data collection and data management, and incorporated them into a unique, innovative and completely self-contained system.

FINANCIAL & COMPETING INTERESTS DISCLOSURE

K O'Donnell is an employee of BioLife Solutions. The author has no other relevant affiliation with a financial interest in or financial conflict with the subject matter mentioned in this manuscript apart from those disclosed. No writing assistance was utilized in the production of this manuscript.

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AFFILIATION

Kevin O'Donnell, *Vice President, Cold Chain Standards, Practices & Compliance at BioLife Solutions, Inc., USA*

Kevin O'Donnell is Vice President, Cold Chain Standards, Practices & Compliance for BioLife Solutions, Inc. He remains a tireless advocate, author, blogger, educator, training developer, and champion of good distribution and logistics practices for temperature-sensitive drug products, having served in the industry in several capacities for over 35 years.