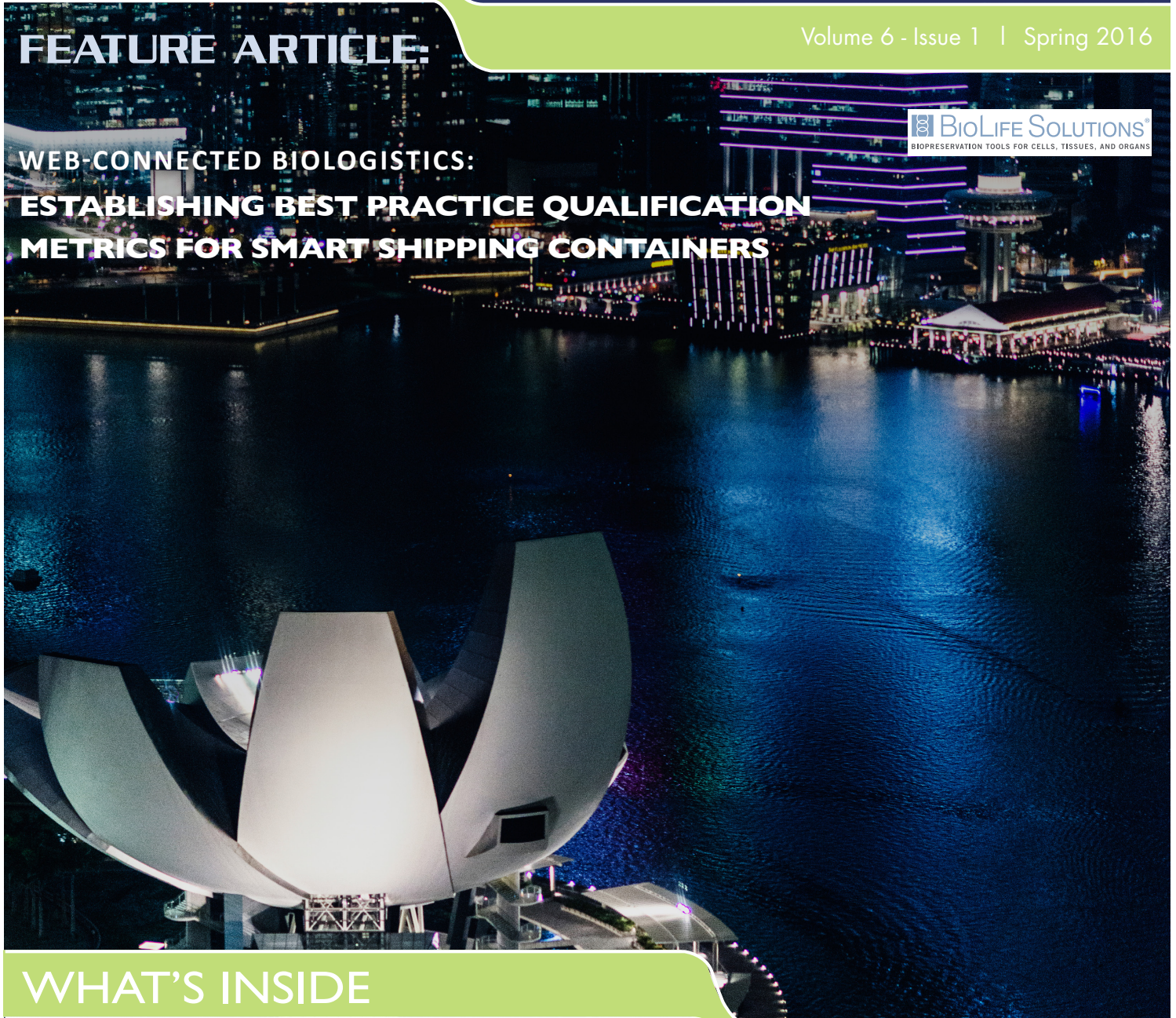


# BioPreservation Today<sup>®</sup>

Volume 6 - Issue 1 | Spring 2016

## FEATURE ARTICLE:

WEB-CONNECTED BIOLOGISTICS:  
ESTABLISHING BEST PRACTICE QUALIFICATION  
METRICS FOR SMART SHIPPING CONTAINERS



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- MNX<sup>®</sup> GLOBAL LOGISTICS PARTNERSHIP





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## WEB RESOURCES

- [www.alliancerm.org](http://www.alliancerm.org) | Alliance for Regenerative Medicine
- [www.aabb.org](http://www.aabb.org) | American Association of Blood Banks
- [www.bestcollaborative.org](http://www.bestcollaborative.org) | BEST Collaborative
- [www.ibclifesciences.com](http://www.ibclifesciences.com) | ibc Life Sciences
- [www.celltherapysociety.org](http://www.celltherapysociety.org) | International Society for Cellular Therapy
- [www.ishrs.org](http://www.ishrs.org) | International Society of Hair Restoration Surgery
- [www.phacilitate.co.uk](http://www.phacilitate.co.uk) | Phacilitate
- [www.regenerativemedicinefoundation.org](http://www.regenerativemedicinefoundation.org) | Regenerative Medicine Foundation

## UPCOMING EVENTS

- Parenteral Drug Association's Advanced Therapy Medicinal Products**  
Berlin, Germany  
June 7-8, 2016
- 14th International Cord Blood Symposium**  
San Francisco, CA  
June 9-11, 2016
- CRYO2016 (The Society for Cryobiology)**  
Ottawa, Canada  
July 24-27, 2016
- CAR-TCR Summit**  
Boston, MA  
September 13-16, 2016
- 14th Annual Cold Chain GDP & Temperature Management Logistics Global Forum**  
Boston, MA  
September 26-30, 2016
- ISCT North America Regional Meeting**  
Memphis, TN  
September 30th – October 2nd, 2016





## EDITOR'S CORNER

Mike Rice, Chairman & CEO, BioLife Solutions, Inc.

### Greetings from the ISCT 2016 Annual Meeting in Singapore,

Customers, suppliers, partners, and friends of BioLife; welcome to Singapore for the 2016 ISCT Annual Meeting. We're pleased and proud to support this key industry event in several ways. We are presenting posters on our CryoStor® clinical grade biopreservation media products, and the evo™ Smart Shipper and biologistex™ cold chain SaaS for time and temperature sensitive biologic materials. On Thursday, May 26th, we are also hosting a thought-provoking corporate tutorial titled, **Addressing the Gaps in Biopreservation and Cold Chain Logistics: Patients Deserve Better than Saline and Beer Coolers!**

In the feature article of this issue of BioPreservation Today® (BPT), Kevin O'Donnell, our Vice President, Cold Chain Standards, Practices and Compliance, presents a comprehensive overview of critical considerations in qualifying thermal packaging with special consideration to reusable smart containers that have embedded electronics.

We're also very pleased to share good news about our new partnership with MNX® Global Logistics. MNX is a specialty, high performance courier serving the life sciences market and of great interest to the cell therapy community, MNX offers same day, next flight out, and door to door couriered and managed shipments of time and temperature sensitive biologic materials and manufactured products. MNX offers peace of mind and eliminates the risk of life saving shipments getting stuck overnight in a hub and in some cases, being rendered unusable due to delayed delivery and/or shelf life expiry. We are working to integrate MNX service options in our biologistex cold chain SaaS.

Lastly, Dave Miller, Business Development and Technical Support Director, authored an introduction to biopreservation and clinical indications for cell and tissue based therapies in the veterinary medicine market.

In follow up to your strong interest in a liquid nitrogen version of the evo™ Smart Shipper, we are very pleased to invite you to our booth to preview our new LN2 evo! This is designed for short term intra/inter campus transport of frozen biologic materials.

Thank you for your continued interest in BioLife Solutions. I hope you enjoy this issue of BioPreservation Today. We look forward to seeing you at our exhibit and during the conference.

Best regards,

*Mike*



## VETERINARY REGENERATIVE MEDICINE

David Miller, Business Development and technical Support Director, BioLife Solutions, Inc.

As evidenced by the growing number of research publications, clinical trials, newly launched companies, and news stories, the Veterinary space is quickly becoming a major player in the application of regenerative medicine technologies. The majority of the current research and available therapies are focused on dogs and horses, but recent articles have highlighted treatments for other companion animals, like the trial at UC Davis for the treatment of a painful inflammatory mouth disease in cats. As in humans, the clinical approaches involve the use of stem cells to restore structure and function to tissues or organs damaged by disease, injury, or age.

Although allogeneic research and treatments are gaining ground, most applications involve autologous therapies primarily segmented into two categories. The first is clinical research and trials being performed by or in collaboration with academic centers, and by individual companies. The second involves services being offered by companies to treat individual animals or “athletes” in the case of high performance horses and dogs, in which the owner pays for out of pocket or possibly with pet/animal health insurance. A few companies are offering stem cell storage services similar to the human model where cells are collected, processed, cryopreserved, and stored for potential future use. (e.g. Veticell ([www.veticell.com](http://www.veticell.com)), Vet-Stem Biopharma, ([www.vet-stem.com](http://www.vet-stem.com)))

According to Sean Owens, DVM, DACVP, an associate professor at UC Davis School of Veterinary Medicine and medical director for the school's Regenerative Medicine Laboratory, the most common and successful veterinary use of stem cells treats osteoarthritis (OA) in dogs, as well as injuries to bones, joints, tendons, ligaments, and the spinal cord.<sup>1</sup> About one in five dogs over one year of age will develop degenerative joint disease, with the number climbing to four out of five for some large breeds.<sup>2</sup>

Companies offering stem cell treatment for dogs with OA include Vet-Stem Biopharma ([www.vet-stem.com](http://www.vet-stem.com)), Vetcell Therapeutics ([www.vet-stem.com](http://www.vet-stem.com)), and MediVet Biologics ([www.vet-stem.com](http://www.vet-stem.com)). There are research and treatments underway for a variety of other conditions in dogs as well.



**Veterinary medicine is quickly becoming a major player in the application of regenerative medicine technologies.**

In several equine applications, cells isolated from adipose tissue (fat), bone marrow, and cord blood are being studied and used to treat bone, cartilage, ligament, and tendon defects and injuries. Other applications and useful cell types, such as induced pluripotent stem cells (iPSC), are emerging as the science progresses.

Stem cells have been injected into a number of animals for a variety of different indications including skeletomuscular disorders, renal failure, neurological disorders, and cardiomyopathy; and a quick online search will yield dozens of anecdotes of successful cellular treatment outcomes in horses, dogs and cats. Although there is a growing body of scientific literature, some in the industry warn that veterinary use of stem cells has preceded significant published scientific evidence, and none of these therapies have been cleared by the FDA. Regardless of the viewpoint, this somewhat

<sup>1</sup>Stem Cell Therapy for Cats and Dogs? This novel treatment is a promising option for some pet conditions. Collins S. WebMD Magazine, April 15, 2014. <http://pets.webmd.com/features/stem-cell-cats-dogs>

<sup>2</sup>Osteoarthritis, joint anatomy, physiology, and pathobiology, Johnston SA. Vet Clin North Am Small Anim Pract. 1997 Jul;27(4):699-723.





## “THE POTENTIAL HUMAN BENEFITS OF VETERINARY STEM CELL THERAPY HAS BROUGHT INCREASED FOCUS TO THE INDUSTRY, AS THESE LARGE ANIMAL MODELS CAN BE MORE REPRESENTATIVE OF CERTAIN HUMAN CONDITIONS.”

nascent industry appears destined for significant growth over the next several years. According to AVMA data (U.S. Pet Ownership & Demographics Sourcebook- 2012), there are approximately 70 million dogs, 74 million cats, and 4.9 million horses in the US. The same report indicated that 63.2% of pet owners considered their pets to be family members, so it is likely that emerging treatments and therapies will be adopted (and paid for) by the animal-loving public.

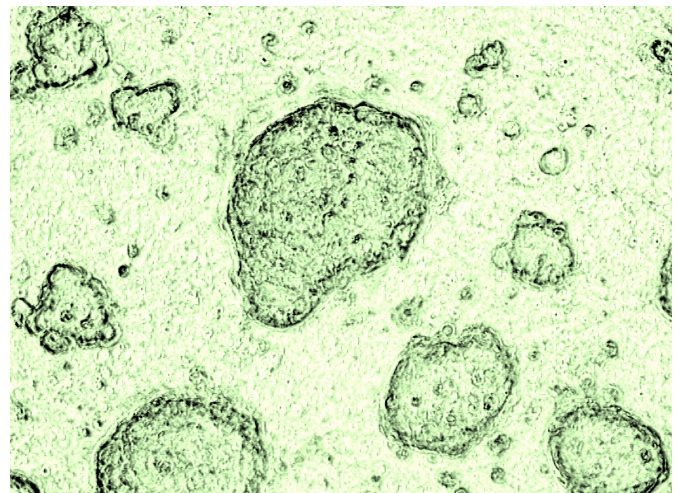
An American Pet Products Association report found that spending on veterinary care by U.S. pet owners continues to increase every year with a total of \$15.42B in 2015, and an estimated \$15.92B for 2016. According to Bob Vetere, APPA president and chief executive officer: “Health and wellness-related themes represent the most powerful trends across all segments of the industry and will continue to do so again this year.” (AVMA.org)

According to David Simpson, PhD (Assistant Director, Veterinary Institute for Regenerative Cures - UC Davis, School of Veterinary Medicine) “The biggest limitations to successful advancement of veterinary regenerative medicine therapeutics to the market are funding and oversight.” Although funding continues to be a major hurdle; considering the growth in research and treatments, industry oversight is certainly not far behind. In June 2015, the FDA published a final Guidance for Industry on the regulation of veterinary cell therapy. The Center for Veterinary Medicine (CVM) used many of the same guidelines developed for human cellular therapy by CBER. As such, the terms and definitions “autologous,” “minimally manipulated,” “homologous use,” and “GMP” could be similarly applied to both humans and animals. The main points of this guidance define what constitutes an animal drug - requiring an Investigational New Animal Drug (INAD) filing and other items outside of this requirement, namely autologous treatments that are minimally manipulated and for homologous use in nonfood-producing animals.

The potential human benefits of veterinary stem cell therapy has brought increased focus to the industry, as these large animal models can be more representative of certain human conditions. Probably the most significant recent development in veterinary regenerative medicine is the ‘One Health Initiative’. One Health is the integrative effort of multiple disciplines

working locally, nationally, and globally to attain optimal health for people, animals, and the environment. Because of their expertise, veterinarians play critical roles in the health of animals, humans, and even the environment...veterinary medicine is the only profession that routinely operates at the interface of these three components of One Health (AVMA.org). “The biggest opportunity for the industry is through advocating for a “one health” approach to regenerative medicine. I think that when people realize and can actually see data that supports the use of naturally occurring disease models (companion animals) to further both veterinary and human patients, more people including industry and government funding agencies will buy into the importance of veterinary regenerative medicine and its potential impact on human regenerative medicine.” (Dr. Simpson). At several universities, veterinary scientists are involved in stem cell research projects that may someday help humans with conditions like Crohn’s disease, diabetes, chronic hepatitis and kidney disease, lupus, etc. At UC Davis, there are plans for human stem cell therapy trials to treat inflammatory mouth disease as early as next year.

As the industry matures, along with the need for funding and oversight, there is an onus to bring the quality of human cellular therapies into the veterinary arena. According to Tom Ramos (Director of Marketing and Product Development – Vetcell Therapeutics), “At Vetcell Therapeutics, we are focused on bringing the quality of animal cellular therapy up to



Stem Cells

the level of human cell therapy. This is accomplished by being consistent, controlling our processes, understanding time and temperature effects, creating robust SOP's, and ensuring compliance with GMP's; this has been our group's main investment." (ReGen OA from VetCell Therapeutics is an autologous stem cell therapy for dogs that is uniquely processed for each patient's OA condition)

Some of the companies involved with animal stem cell regenerative medicine:

- Animal Cell Therapies, Inc.
- Aratana Therapeutics
- Cell Therapy Sciences, Ltd.
- Celavet
- Cook Regentec/Renovocyte, LLC
- EquiCord
- Equi-Stem, LLC
- eQcell therapies
- Invitrx Therapeutics
- MediVet Biologics
- Regeneus
- Scistem Therapeutics
- StemLutions
- Vet Biologics
- Vet BioStem International
- Vetcell Therapeutics
- Veticell
- Vet-Stem Biopharma

At BioLife Solutions, we have had the unique opportunity to collaborate and share our expertise with several of these groups. Our biopreservation solutions, CryoStor® and HypoThermosol®, are embedded into many of the ongoing veterinary trials and treatments. Additionally, we are excited to expand our support of this growing industry with our evo™ Smart Shipper and cloud-based biologistex™ cold chain logistics app to ensure that time and temperature-sensitive veterinary cell and tissue products are properly maintained, monitored, tracked, and protected during shipment from procurement, to processing centers, to clinical delivery.



CryoStor® and HypoThermosol® are embedded into many ongoing veterinary trials and treatments.





## BIOLOGISTEX LLC AND MNX GLOBAL LOGISTICS PARTNER TO OFFER ENHANCED COLD CHAIN LOGISTICS SERVICES FOR TIME AND TEMPERATURE SENSITIVE BIOLOGICS, VACCINES & CELL THERAPIES

**MNX**® MNX Same Day/Next Flight Out Door to Door Logistics Services to be Available in biologistex™ Cloud-Based Cold Chain App

GLOBAL LOGISTICS

**BOTHELL, WA and IRVINE, CA** — April 26, 2016 — Biologistex CCM, LLC, a joint venture of BioLife Solutions, Inc. (NASDAQ: BLFS), a leading developer, manufacturer and marketer of proprietary clinical grade cell and tissue hypothermic storage and cryopreservation freeze media and a related cloud hosted biologistics cold chain management app for smart shippers, and SAVSU Technologies, LLC, a leading designer and manufacturer of innovative high performance passive storage and transport containers for temperature sensitive biologics and pharmaceuticals, today announced a partnership with MNX Global Logistics, a premier global provider of specialized, expedited transportation and logistics services, to offer enhanced cold chain logistics services to the biopharma, biobanking, and regenerative medicine markets via the biologistex SaaS app.

MNX serves hundreds of customers that ship life saving, time and temperature sensitive biologic materials around the world every day. MNX offers specialized, expedited transportation and logistics services to ensure mission critical APIs, cord blood, manufactured cell products, and other biologics are securely transported and delivered on time to the intended destination.

BioLife Solutions has built a franchise in the regenerative medicine market by gaining a critical mass of cell therapy customers including most of the private and public immuno-oncology companies developing various T cell immunotherapies to treat blood cancers and solid tumors. To date, BioLife's CryoStor® and HypoThermosol® biopreservation media products have been embedded into more than 200 pre-clinical validations and clinical trials of novel cell based products and therapies targeting the leading causes of death and disability.

SAVSU Technologies is the designer and supplier of the award winning evo™ Smart Shipper to the biologistex joint venture.

MNX and biologistex have agreed to integrate their respective IT systems to enable users of the biologistex cloud based cold chain logistics app to directly order and purchase MNX support and logistic services, including next flight out, same day delivery and door to door professional courier pickup and delivery of time and temperature sensitive biologic shipments.

"We continually add products and services to our offering that enhance the value that we bring to our customers," said Paul J. Martins, Chief Executive Officer at MNX. "The evo Smart Shipper and biologistex cloud SaaS complement our drive to leverage cutting-edge technologies that help simplify cold-chain shipments for customers in the cell therapy and regenerative medicine markets."



Mike Rice, BioLife's President & CEO, remarked, "We are very pleased about our partnership with MNX, a global, best in class cold chain support services provider, and are excited to promote their logistics and support services to our customers via the biologistex app. A key goal of our biologistex joint venture with SAVSU Technologies is to provide organic and partner solutions to help our life sciences customers optimize cold chain logistics for scalable, secure distribution of time and temperature sensitive source material and manufactured biologic products including CART-cell therapies. MNX logistics services, specifically door to door same day delivery, offer our customers the peace of mind of secure delivery of life saving cell-based therapies, with enhanced shipment monitoring and alerts at a fraction of the cost of traditional specialty couriers, while eliminating the risk of delayed shipment delivery from multi-leg air cargo flights and the potential for packages to get stuck in a connecting hub."

### ABOUT MNX GLOBAL LOGISTICS

MNX is a premier global provider of specialized, expedited transportation and logistics services. Clients include multinational leaders in the aviation, life science, medical device, secure custody and control and entertainment industries. These organizations rely on MNX's exceptional record of transporting time-critical items around the world.

Headquartered in Irvine, CA, MNX maintains regional headquarters in Singapore, Amsterdam and Miami. MNX serves over 190 countries, including key Asia Pacific, South American and EMEA markets. [www.mnx.com](http://www.mnx.com)



## ESTABLISHING BEST PRACTICE QUALIFICATION METRICS FOR SMART SHIPPING CONTAINERS

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

Wernher von Braun, the father of modern rocketry famously stated, “one test is worth a thousand expert opinions.” The FDA has put their own regulatory spin on this axiom: “if you didn’t document it; it didn’t happen.” This extends beyond the drug therapies themselves to the packaging and logistics practices that are used to distribute them; what the FDA refers to as the “holding” of a drug.<sup>1</sup>

The fragile nature of cell therapies requires special consideration with regard to temperature variation and other hazards known to exist in the distribution environment. Well-designed tests and documenting the robustness of transport packaging are essential for ensuring cell viability and function, especially during the clinical trial phases before commercialization.

Not all specialty-packaging companies go through the time and expense of qualifying their packaging products to meet the rigors of transportation. Some do, but only to the extent that they meet basic minimum standards. Others perform to a self-designed standard. All of these practices can lead to inadequate performance and detrimental risk to the products they are intended to protect.

### REGULATORY IMPERATIVES

Most global regulatory authorities have followed Health Canada’s lead: “it is incumbent upon the license holder of a drug to ensure that all persons and companies including fabricators, packagers/labelers, testers, distributors, importers, and wholesalers have the responsibility for ensuring appropriate storage and transportation conditions from the point of manufacturing up to the delivery of the drug products to the final distribution point.”<sup>2</sup> The FDA is a little more succinct: “A drug or device shall be deemed to be adulterated if the methods used in, or the facilities or controls used for, its manufacture, processing, packaging or holding do not conform to or are not operated or administered in conformity with current good manufacturing practices...”<sup>3</sup> The European Union goes even further. The most recent, (October 2015), and to date most stringent of regulations comes from the European Commission EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use<sup>4</sup> which requires verification of transportation. There are three areas of focus related to transportation requirements.

- “It is recognized that verification of transportation may be challenging due to the variable factors involved however; transportation



routes should be clearly defined. Seasonal and other variations should also be considered during verification of transport.”

- “A risk assessment should be performed to consider the impact of variables in the transportation process other than those conditions which are continuously controlled or monitored, e.g. delays during transportation, failure of monitoring devices, topping up liquid nitrogen, product susceptibility and any other relevant factors.”

<sup>1</sup>Federal Food, Drug and Cosmetic Act, Section 501 (a)(2)(B)

<sup>2</sup>Guidelines for Temperature Control of Drug Products during Storage and Transportation (GUI-0069), Health Canada, April 28, 2011

<sup>3</sup>Federal Food, Drug and Cosmetic Act, Section 501 (a)(2)(B)

<sup>4</sup>European Commission EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use. Section 6 (October 1, 2015) in Annex 15: Qualification and Validation



## “ONE TEST IS WORTH A THOUSAND EXPERT OPINIONS.”



### PICK A STANDARD

The test protocols, materials, processes, test equipment, calibration, and facilities used in the execution of a packaging qualification process should meet or exceed the minimum requirements established by known industry standards. Three of the most rigorous and thorough standards include:

- The International Safe Transit Association (ISTA) *Standard 20: Design and Qualification of Insulated Shipping Containers (2011)*. This is a design and qualification process that provides the structure and path to design, test, verify and independently certify a specific Insulated Shipping Container (ISC) for use.
- The Parenteral Drug Association 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*. This guidance document provides a design approach to develop and implement specialized packages and systems that protect temperature-sensitive products during transport, especially between climactic zones and by various modes of transportation.
- The World Health Organization *Technical Supplement to Annex 9: Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products, Qualification of Shipping Containers*. This procedure covers the qualification of all single-use and reusable active, passive, hybrid, and cryogenic dry/vapor shipping containers or systems used for the transport of time- and temperature-sensitive pharmaceutical products in external distribution.

It should be noted that each of these documents have their own areas of strong focus. The evo™ Smart Shipper has been qualified to meet or exceed the minimum requirements for all of three standards, not just one. But as thorough as these documents are, none address the operational capabilities of on-board electronic monitoring, data collection, radio transmission and Software as a Service (SaaS) integrated into the insulated shipping container. This is a technology powered by the evo™ Smart Shipper; the first of its kind. No standards for performance exist. Likewise, the industry has yet to adequately address the demanding requirements for shipping sensitive cell therapies. Given no available precedents, very stringent standards needs to be written, resulting in a new level of performance acceptability.

- Due to the variable conditions expected during transportation, continuous monitoring and recording of any critical environmental conditions to which the product may be subjected should be performed, unless otherwise justified.

This is just a sampling of the global expectations that have evolved regarding understanding, controlling, monitoring and documenting the packaging and logistics practices used to ship medicinal products. Meeting these requirements is challenging. There are only a few current standards that can help comply with these requirements.

## “RELYING ON THE PRACTICE OF WHOLE NUMBER ROUNDING AS IT RELATES TO TEMPERATURE IS FRAUGHT WITH RISK.”



### WHAT WAS OUR PROCESS?

The qualification of all evo™ Smart Shippers (2° C to 8° C, Controlled Room Temperature – CRT – and the CRYO -80° C), follows FDA CDER IQ/OQ/PQ Principles of Process Validation, wherein;

- IQ/DQ –Design Qualification: the process of establishing confidence that designed components are capable of consistently operating within established limits and tolerances.
- OQ – Operational Qualification: Documented verification that under simulated test conditions, the packaging system, performs as intended throughout anticipated operating ranges.
- PQ –Performance Qualification: Documented verification that transport tests of product or representative product contained

within the packaging system and subjected to actual transportation and distribution routes, can perform effectively and reproducibly.

### INDEPENDENTLY VERIFIED

While the design qualifications were initially performed by the container manufacturer, they were repeated and verified by an independent, 3rd Party ISTA Certified Thermal Test Lab to remove bias. The same independent lab performed all subsequent Operational Qualifications.

All of the best practice documents cited above call for the use of a preapproved protocol with established acceptance criteria. The qualification must be performed on new, randomly selected production components and run in triplicate to ensure repeatability. It is recommended that thermal performance is measured against rigorous but representative heat and cold ambient temperature profiles to account for seasonal variation, crossing of hemispheres, changes in geography and differences in modes of transport. It is crucial that the qualification is bracketed to perform with any combination of payload - maximum and minimum. Since payloads can be of an undetermined form factor (powder, liquid, solid, semi-solid), a minimum payload consisting of no payload ensures thermal mass of the product will not unduly influence performance.

Data collection should be at a resolution sufficient to capture subtle changes to product payload. Ideally every 5 to 15 minutes.

### NO MATHEMATICAL ROUNDING

Maintaining a specific temperature range of a product, particularly in transportation can be incredibly challenging given the complexity of supply chains, exposure to potential hazards, logistical unknowns and the distances packages travel within a distribution environment. Relying on the practice of whole number rounding as it relates to temperature is fraught with risk. Stretching the boundaries of 2-8 ° C for example, can literally mean to 1.5° C to 8.4° C. However, that additional 9/10ths of a degree translates into a 15% increase in overall temperature range – a range likely outside of a product's stability profile. When a packaging will not or cannot meet the standard, some packaging providers take it upon themselves to change the standard by conveniently implementing whole number rounding. This falls far short of best practices.

### MULTIPLE DATA POINT COLLECTION

Temperature stratification is common in all insulated shipping



## FRAGILE CELL THERAPIES AND REGENERATIVE MEDICINE PRODUCTS CALL FOR AN INCREASED LEVEL OF CARE TYPICALLY NOT FOUND IN THE TRANSPORT OF MOST OTHER PHARMACEUTICALS AND BIOLOGICAL DRUGS.

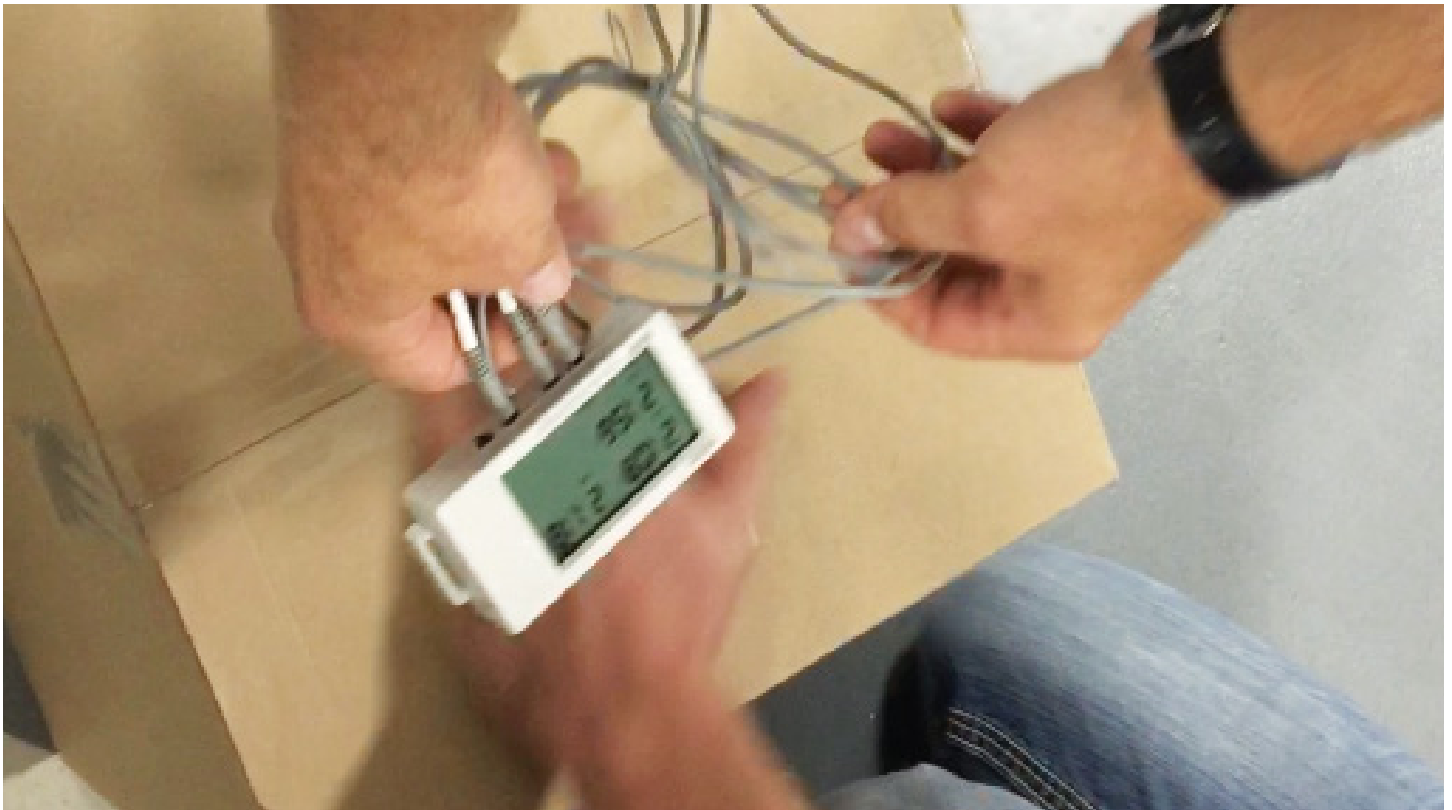
systems. Dynamics of conduction and convection cause temperature variability within the payload. Therefore, it is essential to place multiple probes in various locations throughout the container, not just in a single location.

### MECHANICAL TESTS:

In addition to thermal reliability, protective performance of a packaged-product related to vibrations, shock, pressure, light and other stresses normally encountered during handling and transportation must be evaluated. Since no standards for reusable insulated containers with on-board electronic monitoring exists, it is recommended that each reusable container is subjected to multiple general simulations of actual transport hazards, i.e. drop and vibration sequences such as those outlined in ISTA 3A *Packaged-products for parcel delivery system shipments 70 kg (150 lbs) or less*. Additionally, between each series of 3A Transportation Tests, a 24 -hour Temperature Verification test should be performed on each package to ensure thermal integrity and repeatability and verification of electronic data monitoring, collection and radio transmission.

### CONCLUSIONS

- Fragile cell therapies and regenerative medicine products call for an increased level of care typically not found in the transport of most other pharmaceuticals and biological drugs.
- The transport of cell therapies does not typically follow the transportation routes, lanes, modes and logistics paths of commercial drug products.
- Not all specialty-packaging containers are qualified. There is no single qualification process embraced by industry.
- Self-qualification of insulated packaging products presents a conflict of interest. Qualification should be performed by an independent, 3rd party testing facility with critical expertise.
- The advent of smart shippers with on-board electronic monitoring, data collection and a web-based user interface enables



## THE QUALIFICATION PROCESS FOR THE LINE OF EVO™ SMART SHIPPERS INVOLVES EXTRAORDINARY THERMAL AND MECHANICAL TESTING TO ENSURE BEST-IN-CLASS PERFORMANCE FOR TEMPERATURE STABILITY, DURABILITY AND CLOUD-BASED MONITORING AND REPORTING CAPABILITIES.

- increased visibility, security, and protection from environmental hazards at the individual package level.
- No current standards exist for the qualification of smart shippers but rigorous testing to multiple standards can ensure that well designed smart shippers can meet or exceed global regulatory requirements.
  - The increase of global regulations requiring a higher degree of accountability of other stakeholders in the supply chain has placed an additional burden on drug license holders ultimately responsible for the drug product.
  - Smart shippers can help mitigate gaps in the supply chain and are considered best practice for their ability to maintain thermal integrity while providing visibility in the supply chain and protection from various environmental hazards associated with handling and transportation through the use of on-board sensor-based data collection.
  - Inadequate and insufficient package qualification can lead to unexpected or unknown failures in the field related to hazards in transportation.
  - Repeated mechanical tests of insulated packaging systems in conjunction with thermal verification tests are necessary for a reusable packaging system and are directly related to maintaining thermal integrity and performance over time.

### PERFORMANCE OF THE EVO™ SMART SHIPPER

The qualification process for the line of evo™ Smart Shippers involves extraordinary thermal and mechanical testing to ensure best-in-class performance for temperature stability, durability and cloud-based monitoring and reporting capabilities.

Representative examples of the performance of the evo™ 2°C to 8° C Smart Shipper are shown on the next page.

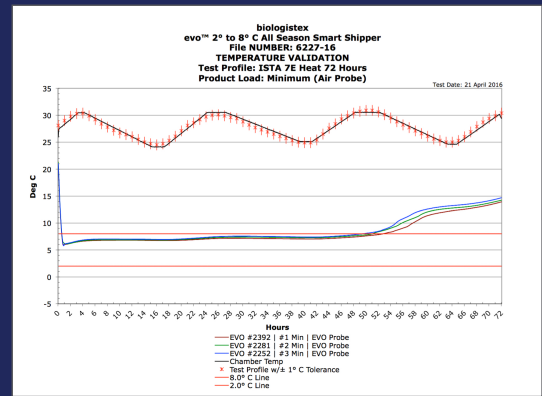




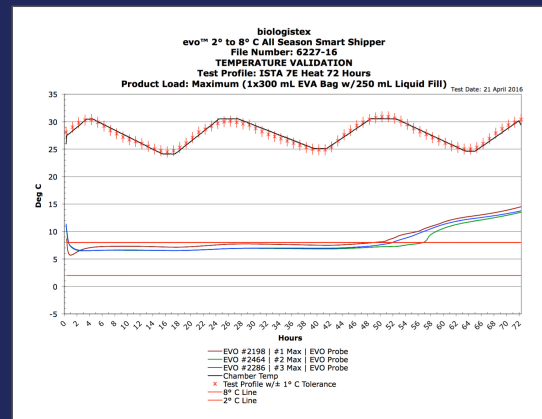
## OQ TEST PROTOCOL SUMMARY

1. The Operational Qualification for all evo™ Smart Shippers is performed in triplicate.
2. No mathematical rounding is employed. Acceptance is to one decimal place, (0.1° C).
3. All thermocouples and thermistors used in the qualifications are pre-calibrated to a NIST traceable standard and post-verified after each run. Accuracy is to within 0.25° C.
4. All evo designs are designed to meet a bracketed temperature range of operation against very challenging external temperature profiles.
5. There are no seasonal packing configurations. The profiles were selected for their statistical accuracy and fair representation of global air/road transportation, handling and logistics practices.
6. The heat profile (ISTA 7E) was developed by the International Safe Transit Association in conjunction with the biopharmaceutical industry and Parenteral Drug Association. The cold profile (ISC Silver) was developed by ISC Labs, a division of Sonoco/ThermoSafe Brands.
7. Maximum and minimum payload configurations were run in triplicate. Given that payload form factors, volume, density, specific gravity, specific and sensible heat can vary, minimum payloads consisted of no payload, requiring the inside air temperature of the payload box to remain within a predetermined temperature range.

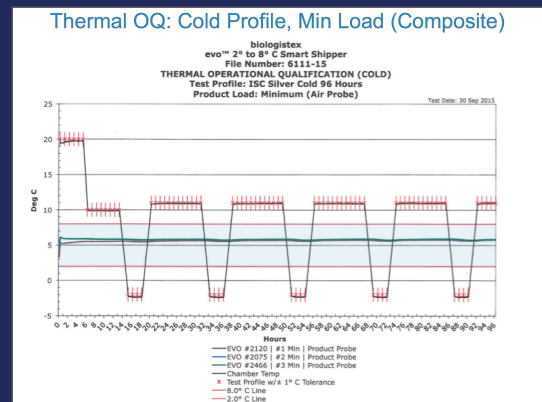
**Fig. 1.** Composite chart of  $n=3$  Thermal Operational Qualification of the evo™ All Season configuration with no payload against the ISTA 7E Heat Profile. Acceptance criteria: maintain internal payload box temperature between 2.0° C and 8.0° C for a minimum of 48 consecutive hours. **Result: PASSED**



**Fig. 2.** Composite chart of  $n=3$  Thermal Operational Qualification of the evo™ All Season configuration with maximum payload against the ISTA 7E Heat Profile. Acceptance criteria: maintain internal payload temperature between 2.0° C and 8.0° C for a minimum of 48 consecutive hours. **Result: PASSED**



**Fig. 3.** Composite chart of  $n=3$  Thermal Operational Qualification of the evo™ All Season configuration with no payload against the ISC Silver Winter (Cold) Profile. Acceptance criteria: maintain internal payload box temperature between 2.0° C and 8.0° C for a minimum of 48 consecutive hours. **Result: PASSED**



**Fig. 4.** Composite chart of  $n=3$  Thermal Operational Qualification of the evo™ All Season configuration with maximum payload against the ISC Silver Winter (Cold) Profile. Acceptance criteria: maintain internal payload temperature between 2.0° C and 8.0° C for a minimum of 48 consecutive hours. **Result: PASSED**

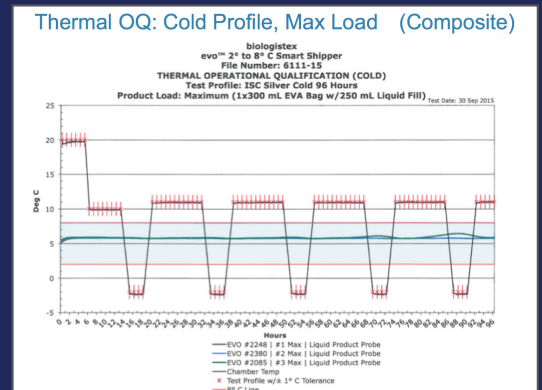
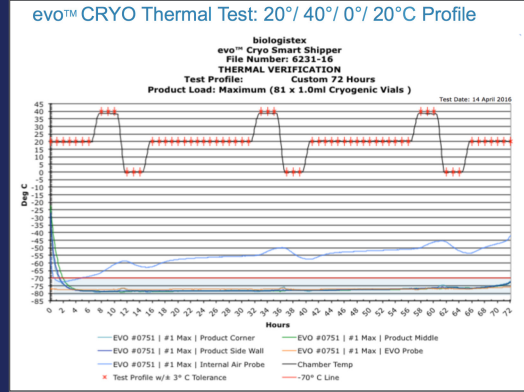


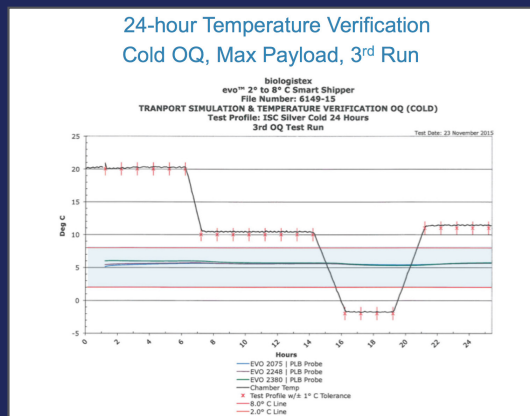
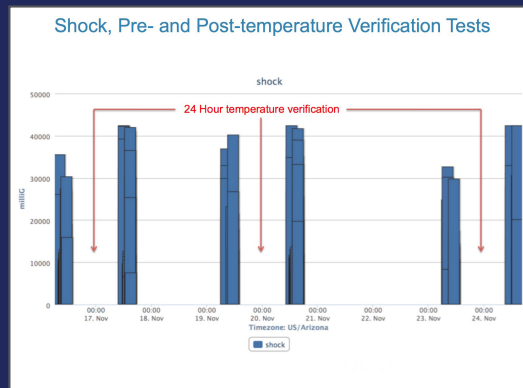
Fig. 5. The CRYO evo™ is designed to maintain temperatures below -70° C for a minimum of 72 hours on just 5 kg of dry ice, regardless of ambient temperature. The graph illustrates how warm the internal air temperature above the level of dry ice can be. The patented design of the CRYO evo™ secures and confines the product payload and eliminates exposure to internal air regardless of package orientation or amount of dry ice remaining after 72 hours of sublimation. Temperature stratification is also eliminated and temperature uniformity throughout the payload is constantly maintained.  
**Result: PASSED**



## TRANSPORTATION SIMULATION TESTS

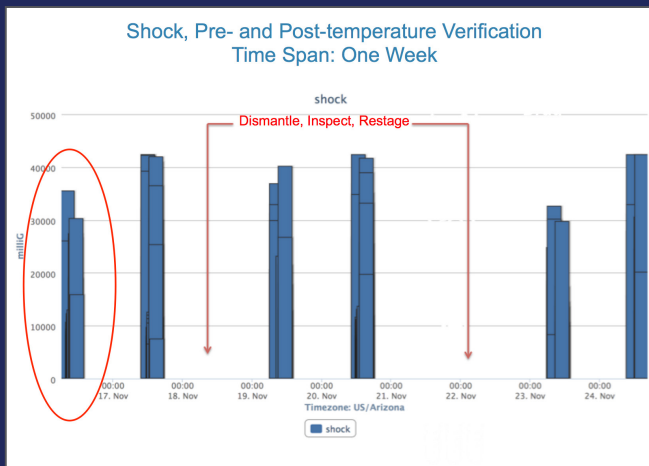
A total of 102 free-fall drop tests and 15 hours of random vibration tests – with and without top loads in various orientations were performed on the evo™. This represents 6X the minimum amount of subject hazards than the ISTA Standard requires per package. In addition, between each series of 3A Transportation Tests, a 24-hour Temperature Verification test was performed on each package to ensure thermal integrity and repeatability and verification of continuous electronic data monitoring, collection and radio transmission.

Each grouping represents series of shock (drop) tests and random vibration tests of one evo™ container. 24 hour thermal verification tests were run between each cycle before dismantling, restaging and re-running another transportation series. Shock from impact (drops) frequently resulted in forces in excess of 40 G's. It is notable that the G forces were less prior to the thermal verification test than after. This is attributed to the removal of the outer corrugate box on the return shipment. An outbound evo™ shipment typically has two corrugate boxes, one nested inside the other. The return shipment has only one corrugate. This speaks well of the protective value of corrugated shipping boxes.  
**Result: PASSED**

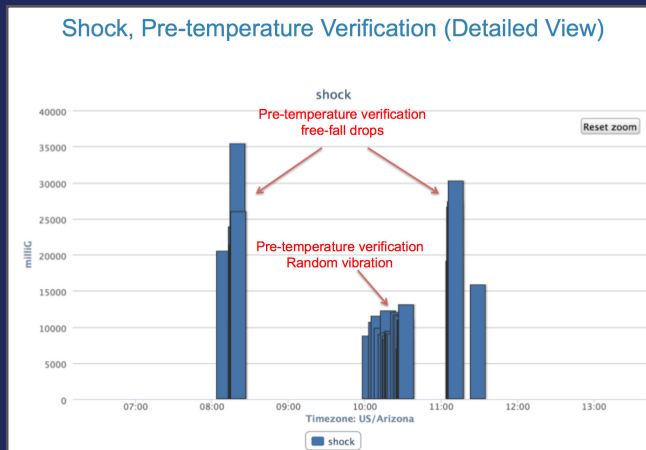




Results of the first series of shock (drop) and vibration tests (in red oval) are typified in the detailed zoomed view on the next chart.



While extreme G forces are the result of impact (drop), it is imperative that each sample receive a series of mechanical random vertical vibrations over a period of time and in multiple orientations other than “upright.” Vibration spectrums differ from unitized long-haul road transport and short-haul delivery van/truck vibrations. Both can cause subtle but increasing fatigue damage. For this reason the evo™ was subjected to both spectrums of vibration repeatedly to simulate multiple uses. Extremes in over-the-road and aircraft frequencies in loose-load and unitized load configurations with repeated forces in the range of 8 to 10 G’s, showed no deleterious affect on thermal or protective performance. **Result: PASSED**



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