BioPreservation Today®

FEATURE ARTICLE:

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BioLife Solutions®
BIOPRESERVATION TOOLS FOR CELLS, TISSUES, AND ORGANS

# WEB-CONNECTED BIOLOGISTICS:

## COLD CHAIN LESSONS LEARNED FROM THE PHARMACEUTICAL INDUSTRY; SMART SHIPPERS COME OF AGE


## PHACILITATE 2015

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## WEB RESOURCES

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**www.aabb.org** | American Association of Blood Banks
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**www.celltherapysociety.org** | International Society for Cellular Therapy
**www.ishrs.org** | International Society of Hair Restoration Surgery
**www.phacilitate.co.uk** | Phacilitate
**www.regenerativemedicinefoundation.org** | Regenerative Medicine Foundation

## UPCOMING EVENTS

**13th Annual Cold Chain GDP & Temperature Management Logistics Summit Canada**
Hilton Montreal Bonaventure, Montreal, Quebec
February 23-26, 2015

**ISBER 2015 Annual Meeting and Exhibits**
Phoenix, AZ
May 5-9, 2015

**ISCT 2015 Annual Meeting**
Las Vegas, NV
May 23-27, 2015

**13th International Cord Blood Symposium**
San Francisco, CA
June 11-15, 2015

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# EDITOR'S CORNER

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

Readers of BioPreservation Today®,

Welcome to Phacilitate in Washington, DC and thank you for your interest in BioLife Solutions.

This Winter 2015 issue of BioPreservation Today (BPT) features an overview of critical considerations in cold chain management of temperature sensitive biologics and the emergence of smart shippers, by Kevin O'Donnell, a pharmaceutical industry cold chain expert and former consultant, now working here at BioLife as Vice President, Cold Chain Standards, Practices & Compliance.

In this issue we also provide an overview of key biopreservation considerations in the development and commercialization of cellular immunotherapies. This article was authored by Aby J. Mathew, Ph.D., Chief Technology Officer, and Senior Application Scientists Brian Hawkins, Ph.D., and Alireza Abarazi, Ph.D., two recent additions to the BioLife team.

A strategic market segment for BioLife's products is the regenerative medicine space, comprised of commercial and clinical organizations developing cellular therapies and tissue-engineered products. In this issue, we provide an update on the adoption of CryoStor® and HypoThermosol® into the storage, shipping, freezing, and clinical deliveries processes of customer clinical trials, now totaling 175.

We recently introduced new aseptic process-friendly packaging options for our biopreservation media products. Michael Weaver, Product Development Manager, authored a summary article outlining key features and benefits.

Lastly, Todd Berard, Sr. Director of Marketing, recaps the formation of our biologistex SM CCM joint venture with SAVSU Technologies. biologistex is also the brand name of a new cloud-hosted, software as a service (SaaS), which receives critical location and payload environmental data from the EVO™ smart shipper. Our customers can now manage and monitor the movement of thermally sensitive biologics to improve clinical delivery and the experience of all stakeholders in the delivery chain.

Please attend our presentation and/or visit our exhibit at the conference. We look forward to seeing you.

Best regards,

Mike

# ASEPTIC PROCESS-FRIENDLY PACKAGING: CRYOSTOR® CS10 AND BLOODSTOR® 55-5 ONE LITER BAGS AND SINGLE-USE SYRINGES

Michael Weaver, Product Development Manager, Marketing

BioLife Solutions serves the biobanking, drug discovery, and regenerative medicine industries with best-in-class cGMP-grade biopreservation tools for cells, tissues, and organs. Proprietary BioLife products CryoStor® and HypoThermosol® are currently embedded into an estimated 175 regenerative medicine clinical trials. As biobanking, drug discovery, and regenerative medicine industries and the surrounding regulatory environment grow and evolve, BioLife is challenged to develop new and innovative tools to support this dynamic environment.


The challenge for the BioLife Product Development Team was to create single-use, process-friendly packaging to contain and dispense BioLife's protein-free, serum-free, cryopreservation reagents. The Team adopted a phased, quality by design approach to include all the steps needed to take a new product to market. The foundation for development of BloodStor® 55-5 and CryoStor® CS10 in one liter bags and single-use syringes was customer feedback, interviews with industry KOL's, surveys, and market research. The Team also consulted BioLife's Scientific Advisory Board to draw upon its considerable industry experience and expertise, employing the Board's advice and guidance. New products entering design qualification were required to pass strict criteria before advancing through successive developmental phases including research, process development, and manufacturing prior to approval and release to marketing and sales.

## CRYOSTOR® AND HYPOTHERMOSOL® ARE CURRENTLY EMBEDDED INTO AN ESTIMATED 175 REGENERATIVE MEDICINE CLINICAL TRIALS

Based on our surveys and feedback, BioLife Product Development designed the bag to be optimized for bulk/high volume processing with flexible access through multiple ports (weldable tubing, spike port, male luer). The bag material chosen to contain BloodStor® 55-5 and CryoStor® CS10 is a robust, puncture-resistant, multi-laminate film possessing excellent biocompatibility (USP Class VI,

# "PHARMED® BPT AND STERILE CONNECT DEVICE(SCD) COMPATIBLE TUBING CHOSEN FOR STORAGE STABILITY AND CLOSED SYSTEM FUNCTIONALITY"

ISO 10993 compliant), chemical resistance, and extractables profile. The film is composed of a tough outer polyester layer, middle evaporation barrier layer, and biocompatible polyethylene product-contact layer. The system features PharMed® BPT and sterile connect device (SCD) compatible tubing chosen for storage stability and closed system functionality. The PharMed® tubing connected to the bag is DMSO-compatible. The clamp prevents DMSO-containing solution from entering the clear PVC SCD tubing during storage, as PVC tubing is not recommended for long term contact with DMSO-containing solutions. Bag materials are free of animal derived components (ADCF), as are all BioLife Solutions' products. The bags are manufactured according to cGMP so the final product represents a complete cGMP package - from formulation, fill, to finish.

Again, based on surveys and customer feedback, BioLife identified a need to provide CryoStor® and BloodStor® in prefilled, single-use syringes capable of aseptic connection, specifically in cord blood processing. BioLife compared the merits of polymeric syringe packaging versus glass. Cyclic olefin syringes possess class leading breakage resistance (can reduce in-process breakage), glass-like transparency without the flaking and delamination seen with glass, are resistant to a wide range of chemicals (including DMSO), have low extractables, and are naturally "slick" eliminating the need for silicone oil, a potential source of product contamination in glass syringes. FluroTec® film-covered pistons combined with cyclic olefin barrels provide smooth operation and helps confine system extractables to a minimum. Cyclic olefin is quickly becoming the preferred material for pre-filled containers in Pharma due to its class-leading properties.

BioLife products in multi-laminate bags and cyclic olefin polymer (COP) syringes meet the same criteria for release as our products in bottles and vials: visual inspection, pH, endotoxin, sterility, and are performance tested against a metabolic assay. BloodStor 55-5 and CryoStor CS10 in multi-laminate bags and COP syringes joined the BioLife family of products in Q4 2014.

Contributed by Dave Miller, MT(ASCP), Product Development and Technical Marketing Director and Michael Weaver, M.Sc., MBA, Product Development Manager

# WEB-CONNECTED BIOLOGISTICS:

## COLD CHAIN LESSONS LEARNED FROM THE PHARMACEUTICAL INDUSTRY AND HOW SMART SHIPPERS HAVE COME OF AGE

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

There is an unfortunate and deep-seated mind-set pervasive among many in the traditional drug manufacturing industry; that ones' responsibility to the product ends at their dock door. In truth, shipping a drug product – particularly one that is both time-and temperature-sensitive – is only the beginning of a long and circuitous journey where the variety of potential threats and challenges increases and risks to product quality are heightened the further the product travels from its origin. Typically, a package is left to bumble blindly and blithely through a complex supply chain to its ultimate and eventual destination – an awaiting and grateful patient. The probability that the quality of the product could, to an unquantifiable degree, become compromised along the way is real and warrants a risk-mitigation and management best practices approach. Patients deserve better. We can – and should – do all possible to employ evidence-based best practices in the commercialization, distribution, delivery, and administration of cell and tissue-based regenerative medicine products.

### Challenging the status quo

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 advanced at what I have often described as "glacial speed." Innovative and ingenious are not adjectives typically used to describe this corner of the universe. In fact, if insulated packaging innovation was a color, it would be beige.

The response to the pharmaceutical industry from its solution and service providers is analogous to a panicky parent of a recalcitrant two year-old, where the triad of packaging providers, data monitoring device manufacturers, and logistics services, too readily acquiesce to the chaotic needs and imploring demands, rather than providing pioneering solutions to unmet needs, in anticipation of where that industry is headed.

Furthermore, the "care and feeding" of these packages through what is often times a hostile and bewildering transportation environment, has not been well understood nor well controlled. There is a fair amount of mutual mystification when it comes to users and providers – those needing to ship these sensitive materials and those actually shipping them. In all, 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. A lack of evolved and enlightened best practices brings risk to brand, market share, and above all, patient safety.

Sadly, the industry is rife with a lack of control – gaping holes and interruptions and blind spots in processes, the unavailability of temperature and other data to justify and augment support for the quality of a drug throughout distribution, and a general lethargy within the industry to embrace change. Consequently, products can be stressed. And when products are stressed, patient outcomes can be impacted.

But what if there was a package and system in place that could close those gaps, determine an assignable cause of failure, or quantify to what extent degradation of a drug product has occurred? What if the package itself could monitor, record

and alert of improper pack-outs, insufficient packaging performance, negligent logistics practices, or abuses in transportation? This is the charter of biologistex CCM, the new joint venture between BioLife Solutions, Inc. the leading manufacturer of clinical grade biopreservation media and SAVSU Technologies, the cutting-edge package design and solution provider. biologistex, which will be operated by BioLife Solutions, is also the brand name of a new cloud-hosted cold chain management service that addresses these issues head-on with the introduction of EVO™, a new generation of smart shippers from SAVSU.

Breaking the mold on passive packaging and logistics, the EVO family of smart, insulated shipping containers provides the ability to document packaging, transportation, logistics and physical condition of time-critical and temperature-sensitive shipments by incorporating multiple technologies into the package itself. EVO seamlessly integrates cellular communications with an on-board multi-parameter environmental, anti-pilfering, theft-deterrent monitoring system, a geo-location / geo-fencing feature, and a secure, web-based app, so that user-appointed designees anywhere in the world can monitor a package in real-time throughout its journey – or in the case of infusion therapy, tissue or organ harvest and re-transplantation – throughout its in-vitro lifetime. The web app includes alert and escalation notifications by email, SMS, or through a customer care representative. The EVO smart shipper is powered by an integrated, rechargeable battery and is not limited to use only with specific carriers, mode of transportation, or logistics service provider. Once received, it is capable of alerting the user to a hassle-free return to its origin.

## Capitalizing On The Benefit of Hindsight

So what was the impetus behind the joint venture that became biologistex? Need. Both BioLife and SAVSU's interests and expertise lie in the regenerative medicine / cell therapy side of the business. They recognized that this underserved and underappreciated corner of the industry is the epicenter of most new drug discoveries. It is the dawn of a new future in cell and tissued-based medicine and biologistex has met it at sunrise.

Knowledge and expertise of cold chain packaging, practices and transport among those in this fledgling field is about where the biopharma industry was 10 years ago. However, the laboriously slow trial-and-error learning curve pharma has charted and the benefit of hindsight can be exploited in this sub-segment of the industry that has largely been ignored. 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

Let's take a look at the highlights of these components and how the EVO smart shipper has been designed 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 due to high value, high volume, and high piece-rate pharma and bio-pharma shipments. 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 improvements 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. The most commonly used insulated container in the healthcare industry, comprising approximately 80% of all insulated packages, are made from polystyrene, which was discovered in 1839. The molding process used to make expanded polystyrene bead (EPS) sheets or tubs, has not changed since WW II. Talk about the lack of innovation.

The customer base for these containers has become somewhat complacent over the years, content with "adequately performing" disposable insulated packaging that, as the industry grows, so do the mountains of land-fillable waste. Concerns about environmental impact grow 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.

The EVO smart shipper is a reusable, high performance, super-insulated container, designed to easily exceed 72 hour autonomy against a host of challenging ambient profiles. EVO weighs up to 50% less than its comparably sized passive 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 dim weight or actual weight the shipper provides the most bang for the buck when it comes to 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 "consignee and consignor," otherwise known as the shipper and receiver. Their role includes the behind-the-scenes coordination of freight-forwarding activities, chain-of-custody and TSA security procedures, consignments to ground transportation providers and air carriers, customs clearance, temporary storage when needed, and door-to-door delivery. Many well established and well-intentioned logistics providers, large and small, scaled Mt. Pharmaceutical in recent years, seduced by the prospect of huge profit margins. But once they conquered the summit several quickly found themselves way out over the tips of their skis, unable to meet the fickle demands and seemingly outrageous expectations of the pharmaceutical industry, and they simply couldn't adapt. Others underestimated the amount of capital and personnel outlay necessary to meet 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 lured into the snare of FDA or EU/GMP oversight. The strongest and most agile of these companies 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 I find this to be akin to treating the symptom of a disease rather than finding a cure. 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.The nascent sub-segment of emerging regenerative medicine; cell therapy, soft tissue, and organ preservation markets have historically been overlooked by transportation service providers.

"This is the opportunity for the cloud-hosted biologistex service and EVO smart shipper to provide real value 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 transportation system providers and processes completely out their control to do the right thing, 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.

There remains a bit of an "art" to speculating what triggered an event to occur and 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]

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. We can do better!

The EVO SMART shipper has put much of this speculation, interpretation and conjecture to bed. Its imbedded monitoring device has the capability to record and store several payload environmental parameters including 3 separate temperature probes: internal, external and radio/electronics temperature; humidity, light, tilt, shock, vibration, location, pressure, battery consumption, and cell signal strength. The electronics in EVO meet FAA requirements for radio transmission suppression during flight (but still collects and stores the data internally and uploads it upon landing) and is fully programmable on the basis of interval and events. Data are transmitted in real-time, stored internally and in a secure web services hosted environment.

Regulatory Requirements and Maintaining Compliance

Historically, a drug manufacturer's response to thermally protecting temperature-sensitive drugs during shipment was little more than to put the product in a "Styrofoam" box and throw a couple of bags of frozen water on top – you know, to keep it "cold." 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.

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. Current Good Distribution Practices (cGDP) is no longer viewed as the redheaded stepchild it once was. Global regulatory expectations for the storage, handling and transport of these articles has become an extension of Good Manufacturing Practices (cGMP) with citations, levies and fines related to packaging and distribution accounting for a significant number of infractions.

How the Industry Got From There To Here

It wasn't so long ago that the pharmaceutical industry faced the initial challenges of transporting a steadily growing number of time- and temperature-sensitive products in great volumes and on a global scale. The new millennium saw the pharmaceutical tide turn from predominantly benign manufacturing of organic, small-molecule, and temperature-stable solid oral formulas, to large-molecule, protein-based, temperature-sensitive liquid biologics. Manufacturing practices, too, changed along with it going from "interplant" to "international," requiring multiple and complex manufacturing steps in multiple countries or locations. Today, it is not at all uncommon for the manufacturing of a biological drug to pass through 4 or 5 countries over the span of several months on its journey to becoming a final commercialized product, with each step and transport requiring strict temperature control. A growing middle class, coupled with emerging economies, has made biologic therapies available to more people worldwide than ever before. 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 ½ 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)[2] .

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 USD $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 Heath Organization; thus remaining a key driver in the growth of a slowing pharmaceutical industry (WHO)[3].

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 1 ever crosses the finish line. Those are the same odds as someone in the US getting injured as the result of a falling porta-potty (CDC) [4]. It's true; you can look it up. The point is this: 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 wonky 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, more molly-coddled 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 trial arena. This has proven extremely beneficial to minimizing approval delays and curbing costs. Regulatory scrutiny of storage, handling and logistics practices of clinical trials has not generally received the same level of concern or scrutiny as other parts of the process, such as the CMC section of an IND or BLA filing.

This is the sweet-spot for the EVO smart shipper. 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. 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

BioLife and SAVSU have taken a page from the pharmaceutical industry's playbook to incorporate the best-of-the-best practices and technology for the transport and management of time-critical and temperature-sensitive products; packaging, monitoring, logistics practices, and data collection and data management, and rolled them into a unique, innovative and completely self-contained system - the EVO smart shipper and biologistex web app.

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# CELLULAR IMMUNOTHERAPIES: CRITICAL BIOPRESERVATION CONSIDERATIONS

by Brian J. Hawkins, PhD and Alireza Abazari, MSc/PhD, BioLife Solutions, Inc.

Improvements in the diagnosis and treatment of cancer have led to significant reductions in mortality. This is especially evident by the fact that childhood cancers once fatal in the 1950's now achieve a survival rate approaching 90%[1]. Despite this tremendous success, overall cancer mortality remains high, and more aggressive treatment regimens are often ineffective and toxic to patients[2]. There is also the ever-present risk that even effective treatment is only temporary, and that the cancer may relapse. Novel technologies and therapies are needed in order to realize future declines in cancer mortality.

## Employing the immune system to treat cancer

Recent advances in molecular and genetic analysis identified key molecules specific to cancerous tissue. These cancer-specific molecules form the basis for antibodies that 'mark' cancerous cells for clearance by the body's immune system. Indeed, the introduction of anti-CD20 Rituxin® (co-marketed by Biogen IDEC and Genentech) in 1997 transformed cancer treatment and facilitated a dramatic reduction in mortality associated with B-cell cancers such as non-Hodgkin's lymphoma[3]. Immunotherapies such as Rituxin® are generally considered safer than chemotherapy, but antibody-based therapies carry the risk for adverse immune reactions, infection, and autoimmune disease[4].

Using harvested immune cells as 'living drugs', cellular immunotherapies have the potential to actively seek out and eradicate cancerous cells without many of the drawbacks of antibody-based passive immunotherapies. Cellular immunotherapies also can be used to treat cancers in which the immune system is compromised and can persist in the body to prevent cancer relapse[5]. The FDA approved the first cellular immunotherapy in 2010, which is marketed by Dendreon under the trade name Provenge®. Provenge is an autologous therapy (i.e. originating from the patient's own body) in which circulating mononuclear leukocytes are harvested from an individual patient with terminal metastatic prostate cancer. These cells are then re-engineered in the laboratory and infused into the same patient to target and kill cancerous prostate tissue[6].

On the heels of Provenge, next generation strategies utilize tumor-infiltrating lymphocytes (TILs), engineered T-cells such as T-cells expressing artificial chimeric antigen receptors (CARs) and T-cell receptor (TCR)-modified cells, and cellular therapies that are not restricted to an individual patient (autologous) but rather can be used 'off-the-shelf' to treat multiple patients (allogeneic). Early data demonstrated that CAR T-cells targeting cancerous B-cells resulted in the complete remission of 27 out of 30 patients with relapsed or refractory acute lymphoblastic leukemia (ALL)[7]. Although ALL is one of the most common and treatable forms of childhood cancer, those patients that experience relapse normally have an extremely poor prognosis[8]. The high remission rate of patients infused with the CAR T-cell therapy represents a fundamental leap in our ability to treat cancer. Cellular Immunotherapies represent the future of oncology and personalized medicine.

**CELLULAR ATTACK**

Adoptive cell transfer (ACT) attacks cancer using either tumor-infiltrating lymphocytes (TILs) or genetically engineered T-cells. Engineered cells are given either a new T-cell receptor (TCR) or an antibody-like molecule called a chimeric antigen receptor (CAR); both activate the T-cell when they encounter a particular cancer antigen.

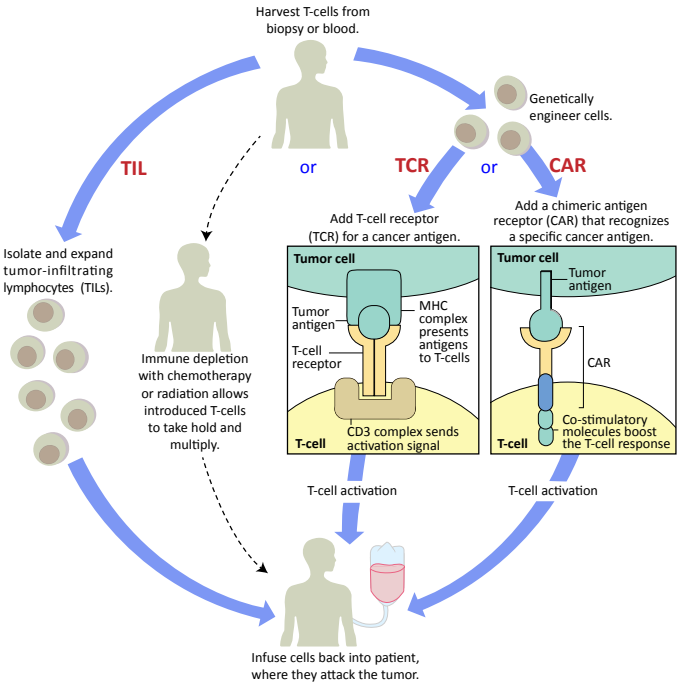


Figure 1; Adoptive cell therapy: Honing that killer instinct • Courtney Humphries
Nature 504, S13–S15 (19 December 2013) doi:10.1038/504S13a
Published online 18 December 2013

## Biopreservation of Cellular Immunotherapies

Although cellular immunotherapies hold significant promise, they present unique clinical challenges. For example, as a 'living drug,' Dendreon's Provenge must be transported from the manufacturing facility and administered to the patient within 18 hours. To complicate matters further, cellular therapies must not only be alive, but also need to exert their targeted biological function. This important point was tragically emphasized recently when four children at London's Great Ormond Street Hospital died after receiving stem cell transplants that were alive but did not function normally[9]. While no consensus on the root cause of this incident could be reached, a leading hypothesis is that the cells were damaged when removed from cryopreservation storage. It is therefore of utmost importance that cell viability and health are not only considered during manufacturing, but also during storage and transport. Biopreservation describes the processes needed to support cell recovery, viability, and post-preservation functional return in addition to structural integrity[10]. It is recommended that biopreservation best practices be considered early in the development process to enable optimization and efficiencies, however biopreservation optimization may still be implemented at later stages (including Phase III clinical trials or afterwards) with understandably greater investment of resources required to validate.

Critical issues related to the biopreservation of cellular immunotherapies include the preservation temperature, media, and transportation conditions. Regarding temperature, metabolic activity of human tissues decreases 50% for every 10°C reduction in temperature[11]. Hypothermic storage (2-8°C) has therefore been the preferred short-term method of preserving cells and tissues for decades[12]. For longer-term storage of cellular immunotherapies, metabolic activity may need to be arrested in suspended animation by freezing in liquid nitrogen (i.e. cryopreserved). Furthermore, effective cryopreservation is an invaluable tool to bank and reconstitute large numbers of cells at commercial scale. Unfortunately, improper hypothermic and cryogenic storage can result in elevated cell death and altered biological function (as was likely the case at Great Ormond Street Hospital).

With reduced metabolic activity at low temperatures, there is less energy available to maintain appropriate ion concentrations inside and around the cell. As a result, abnormal ionic balance and subsequent water flux triggers membrane swelling, rupture, cell stresses, and eventually death[13]. It is therefore imperative that the ionic composition of the storage media most closely match the intracellular composition of the cells used for cancer treatment. The choice of intracellular-like media buffers cell stresses while maximizing functional return[14]. For clinical applications, it is also critical to consider whether or not the biopreservation media is manufactured per Good Manufacturing Practices (GMP) and has a Quality/Regulatory footprint that supports qualification as a clinical grade ancillary material or excipient. Finally, careful management of biopreservation temperature and media are meaningless if cell therapies are dysfunctional upon arrival at the clinic. Steps must be taken to ensure that transport options have safeguards in place to deliver cell/tissue payloads within acceptable environmental parameters and appropriate risk management beyond the current 'validate then assume' (VTA) paradigm. An integrated biologistics platform is pivotal to maximize the viable recovery and health of cellular immunotherapies for the treatment of cancer patients.

## Final Thoughts

According to the Centers for Disease Control (CDC), Cancer remains the second most common cause of death in the United States. However, promising advances in cellular immunotherapies may significantly reduce that grim statistic. The clinical adoption of 'living drugs' for the treatment of cancer will require a comprehensive program that ensures maximum viable cell recovery and function from the time of harvest to the time of infusion (i.e. needle-to-needle). Biopreservation is a critical, and often underappreciated, component of this process that is best optimized early in the development process to ensure that cellular immunotherapies effectively translate from the bench to the bedside, and realize their much-heralded clinical and commercial potential.

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# BIOLIFE NEWS UPDATE: BIOLOGISTEX CCM JOINT VENTURE FORMED

by Todd Berard, Senior Director of Marketting, BioLife Solutions

*BioLife Solutions announces joint venture partnership with SAVSU Technologies to bring smart shippers to life.*

At the end of the third quarter of 2014 we announced an expansion of our relationship with SAVSU Technologies via the formation of biologistex CCM, a joint venture created to bring the first generation of integrated smart shipper technology to the cold chain management market. biologistex is also the brand name of a cloud-hosted web app for customers to monitor and manage the movement of temperature and time sensitive biologic materials throughout the delivery chain.


BioLife will staff and manage all key operational functions needed to provide an exceptional customer experience, including customer service, sales, technical support, software support, training, and account management. SAVSU will continue to develop, test, and supply current and future versions of the EVO™ smart container, complete with embedded electronics that transmit real-time payload and location information to the cloud-hosted app. Initial product operating ranges include 2-8°C, controlled room temperature (CRT) between 15°C - 25°C and near -80°C using dry ice.

Todd Berard, BioLife's Director of Marketing, commented on the formation of biologistex CCM by stating, "We are very pleased to announce the creation of biologistex with SAVSU. This is a great opportunity for our sales and marketing team to introduce SAVSU's next generation EVO smart container platform to our strategic markets, where we have built and maintain very strong relationships with hundreds of customers that can benefit from using improved biologistics tools.

Bruce McCormick, President of SAVSU Technologies, remarked on the creation of biologistex CCM with BioLife by stating, "We are keen to partner with BioLife to launch biologistex CCM and commence deployment and market adoption of our next generation smart shippers for temperature sensitive biologics. BioLife has established a significant base of customers, who along with clinicians and patients, can benefit from improved biologistics throughout the manufacturing and delivery chain. We highly value BioLife's reputation, scientific marketing approach and proven, high quality operations in their Bothell facilities."

biologistex aims to fill a much-needed gap by providing a series of benefits that the current generation of shipper simply cannot provide. Today, clinicians are handicapped with data that is either inaccurate, old, or becomes available far too late for it to matter. With biologistex and EVO, temperature, location, security, and several other critical payload and shipment data elements are available in real time or near real time; empowering cell therapy manufacturers, clinicians, quality professionals, and cold chain logistics professionals with actionable data to ensure thermally sensitive biologics are delivered and administered within validated stability profiles.

**biologistex**

Intelligent • Informed • Precise

Biologic Materials Management

# BIOLIFE PRODUCTS IN CLINICAL TRIALS

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

Proprietary, Clinical Grade HypoThermosol® and CryoStor® Extending Shelf Life and Improving Survival & Function of CAR-T Cells, Dendritic Cells, Etc.

The adoption of HypoThermosol and CryoStor biopreservation media products has greatly increased in customer clinical trials of novel cellular immunotherapies and other cell-based approaches for treating and possibly curing the leading causes of death and disorders throughout the world.

In January 2014, we estimated that BioLife products were incorporated into the storage, shipping, freezing, and/or clinical administration processes and protocols of 100 regenerative medicine clinical trials. For the calendar year 2014, we believe that an additional 75 regenerative medicine clinical trials using BioLife products were confirmed, bringing the total to 175. Confirming and supporting information is sourced from customer requests to cross reference our US FDA Master Files for CryoStor and HypoThermosol in clinical trial applications, other customer and distributor communications, and the www.clinicaltrials.gov website.

Within the cellular immunotherapy segment of the regenerative medicine market, our products are embedded in the manufacturing, storage, and delivery processes of at least 75 clinical trials of chimeric antigen receptor T cells (CAR-T), T cell receptor (TCR), dendritic cell (DC), tumor infiltrating lymphocytes (TIL), and other T cell-based cellular therapeutics targeting solid tumors, hematologic malignancies, and other diseases and disorders. A large majority of the currently active private and publicly traded cellular immunotherapy companies are BioLife customers.

The Roots Analysis market research report titled Dendritic Cell and CAR-T Therapies, 2014 – 2024, published in November 2014, estimates that the cellular immunotherapies market could grow to $4 billion by 2024. BioLife's addressable share of this market is attributed to the demand for biopreservation media and controlled temperature shipping containers. The combined market caps for the leading pure play publicly traded regenerative medicine companies, including developers of cellular immunotherapies, recently exceeded $11 billion, with several successful IPOs, follow on offerings, and strategic corporate investments.

The distribution of regenerative medicine clinical trials where BioLife's biopreservation media are embedded, by phase of development, is provided in the table below.

| Indication | Pre-Clinical | Phase I | Phase II | Phase III |
|---|---|---|---|---|
| Solid Tumors | 4 | 17 | 36 | 5 |
| Hematologic Malignancies | 8 | 8 | 11 | 2 |
| Heart Disease | 1 | 2 | 8 | 2 |
| Stroke | 0 | 0 | 4 | 0 |
| Joint Disease | 4 | 1 | 1 | 2 |
| Vision Loss | 1 | 1 | 0 | 0 |
| Immune Disorders | 8 | 9 | 9 | 2 |
| All Others | 7 | 9 | 8 | 8 |
| Totals | 33 | 47 | 77 | 21 |

*Note: some customers incorporated BioLife products in a later phase of development: after pre-clinical work and earlier clinical trial phases were completed.*

Mike Rice, BioLife President & CEO, remarked on the increased adoption of CryoStor and HypoThermosol in the cellular immunotherapy and broader regenerative medicine markets by stating, "2014 was a pivotal year for BioLife, with expanded product adoption by several very promising high profile and well-funded regenerative medicine companies. Nearly half of the clinical trials sponsored by our customers using our biopreservation media products to store, freeze, ship, and administer cells to patients involve some type of T-cell based immunotherapy."

Biopreservation, the science of ensuring survival and function of cells, tissues, and organs once removed from the body, includes reducing the temperature of these biologics to reduce

# BioLife Solutions Biopreservation Media Products: Embedded in 175 Cellular Immunotherapy & Other Regenerative Medicine Clinical Trials

metabolic activity and the demand for oxygen and nutrients. Hypothermic storage and frozen storage enable delivery of temperature sensitive biologics to patients throughout the world, with varying degrees of success, based on the preservation efficacy of the storage or freeze media, and functional performance of the shipping container employed. BioLife's clinical grade biopreservation media products are engineered for low temperature preservation of cells and tissues, and have been broadly adopted in numerous clinical applications based on a large body of performance evidence generated by customers, which supports extended stability (shelf life) and improved yield (survival and functional recovery) of a broad array of cells and tissues, as compared to the use of home brew and other non-optimized formulations.


Rice continued, "We are very well positioned to participate in the growth of the regenerative medicine market and the truly remarkable cellular immunotherapy segment of oncology care. BioLife is a classic embedded technology story, with our biopreservation media products part of our customer processes, and also with our new biologistex cold chain management service, which can improve logistics and monitoring shipments of high-value manufactured cell products. We've worked very hard to build this marquee customer base in what could emerge as one of the largest growth opportunities in the history of medical innovation and market development."

BioLife Solutions develops and markets patented hypothermic storage/transport and cryopreservation media products for cells, tissues, and organs. BioLife's proprietary HypoThermosol®, CryoStor®, and BloodStor® platform of biopreservation media products are marketed to academic research institutions, hospitals, and commercial companies involved in cell therapy, tissue engineering, cord blood banking, drug discovery, and toxicology testing. BioLife products are serum-free and protein-free, fully defined, and formulated to reduce preservation-induced, delayed-onset cell damage and death. BioLife's enabling technology provides research and clinical organizations significant improvement in post-preservation cell and tissue and viability and function.