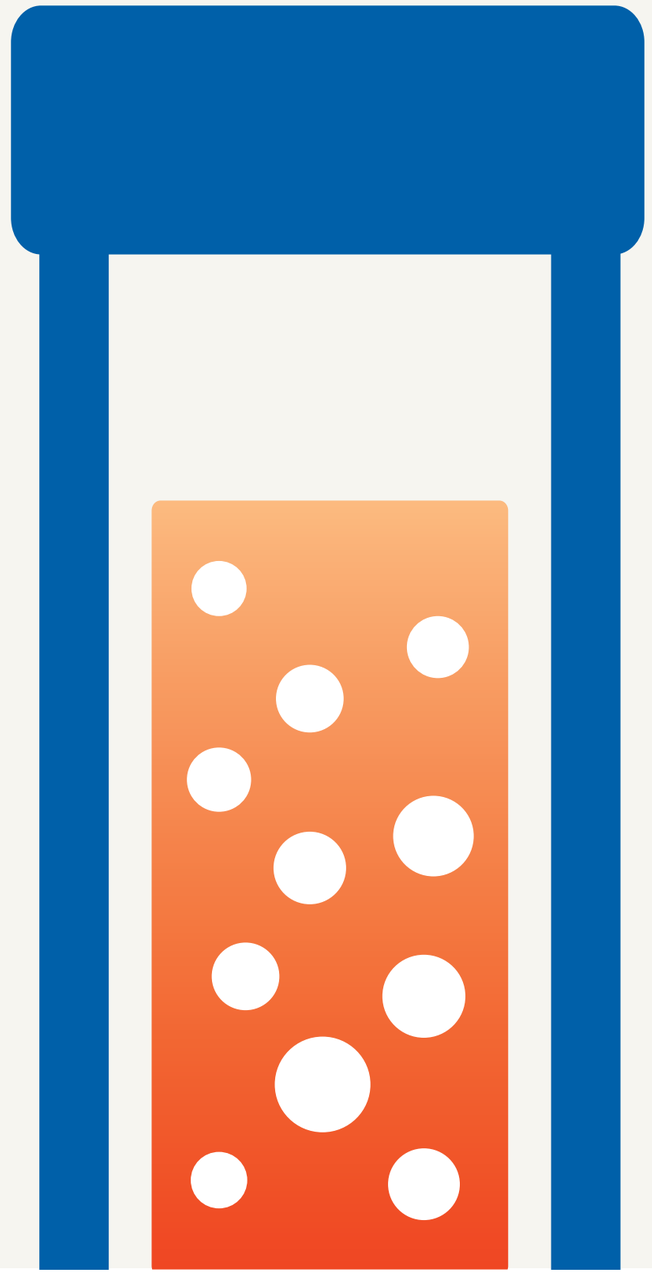
Commercially Successful Cell Therapies:

Navigating the Ultra Cold Chain Distribution Minefield

By Dan H. O'Donnell, Associate Director of Cell Therapy Logistics, Fisher BioServices



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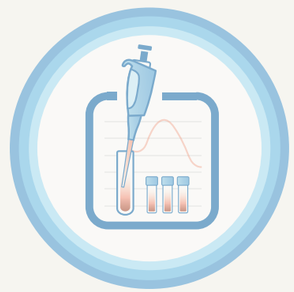
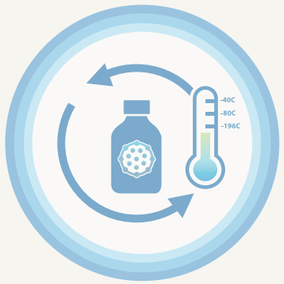


Clinical Trial Sample Management



Biologic-API Management

Qualification / Validation Services

Cold-Chain Logistics

About The Author

Dan O'Donnell has extensive experience in the development and deployment of strategies for the distribution of clinical agents for phase II and III clinical trials, in both international and domestic locations. He specializes in cryogenic and ultra low temperature (ULT) product management and distribution, with an emphasis on developing chain of custody processes and documentation for compliance with 21 CFR part 11 requirements. Dan is also versed in the validation and qualification of storage and shipping solutions for complex biological applications and possesses an in-depth knowledge of biobanking and management of biologically active pharmaceutical ingredient (bio-API).

Previously, Dan served as a Vice President for Disease Management Programs with both Baxter Healthcare and United Healthcare, where he developed population-based health care models and coordination-of-care processes to address high risk patient groups. Dan has also worked extensively in the development of reimbursement models for high cost and high risk disease states and therapies.

Introduction

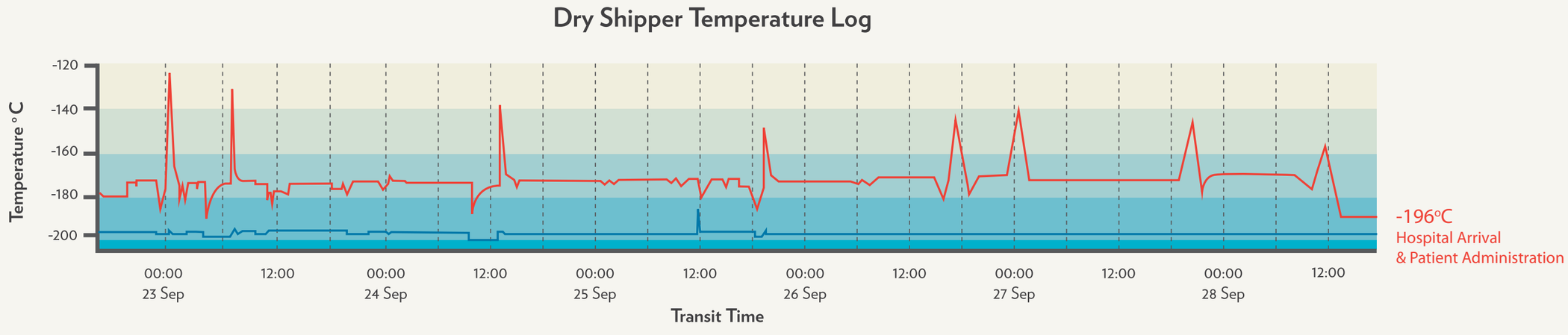
If you have a cell-based therapy in development, then you need to consider such variables as packaging, storage, inventory management, monitoring systems, distribution, and even clinical site capabilities well before you begin to prepare the Investigational New Drug (IND) submission to the Food and Drug Administration (FDA). By sidestepping these issues until clinical trials begin, you may discover late in the game that you have inadvertently limited your product's scalability and commercial viability, incurred unnecessary costs and complications downstream, and failed to meet FDA criteria for documentation of cold chain and chain of custody requirements.

5 Hidden Landmines Overview

1. **Landmine A:** Adverse Temperature Events
2. **Landmine B:** Packaging and Distribution
3. **Landmine C:** Clinical Site Limitations
4. **Landmine D:** Patient Administration
5. **Landmine E:** Establishing a Chain of Custody

Landmine A:
Adverse Temperature Events

Landmine A: Adverse Temperature Events



To be commercially successful, cell therapies must retain their viability and potency, and this requires protection from exposure to adverse temperatures. **Keep in mind that any given individual dosage of a cell-based therapy is potentially exposed to up to eight adverse temperature events between manufacture and patient administration.** These events occur when:

Landmine A: Adverse Temperature Events

1.

The dose is removed from storage at the distribution center and placed in a container for **transfer** to a clinical site;

2.

The dose is **transferred** from the controlled rate freezing unit to the manufacturer's temporary storage unit;

3.

The dose **leaves** the manufacturing facility (removed from temporary storage and placed in a container then loaded on a truck);

4.

The dose is removed from the container it was **transferred** in and placed in a storage container at a distribution center;

5.

The dose is removed from the **transfer** container and either placed in a controlled thawing unit or a storage unit at the clinical site pharmacy;

6.

The dose is removed from storage in the pharmacy and placed in a cryocart for **transfer** to the patient bedside;

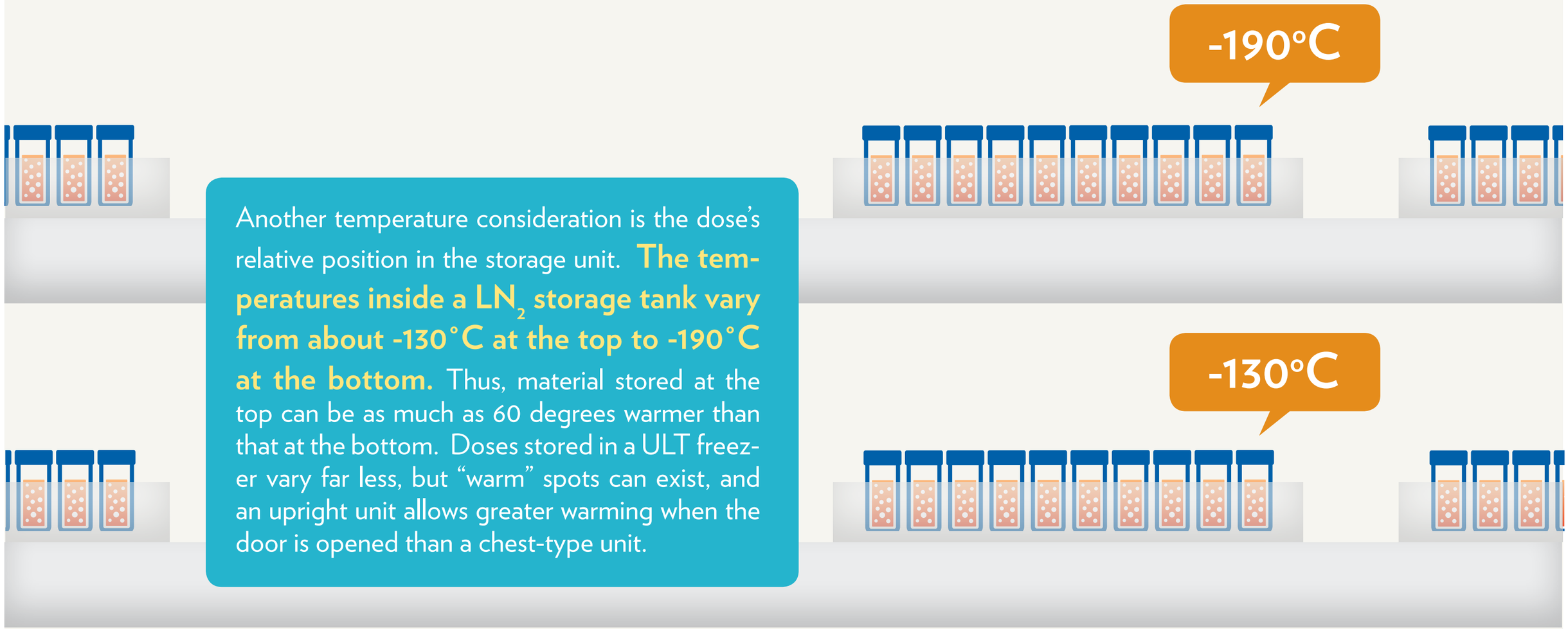
7.

The dose is **transferred** from the cryocart to a thawing or processing unit;

8.

The dose is removed from the thawing unit and sits on a tray, awaiting **administration** to the patient.

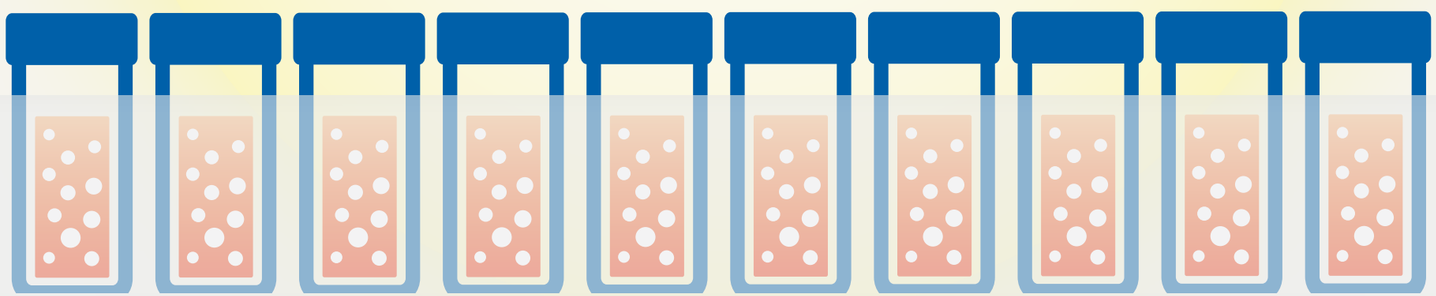
Landmine A: Adverse Temperature



Another temperature consideration is the dose's relative position in the storage unit. **The temperatures inside a LN_2 storage tank vary from about -130°C at the top to -190°C at the bottom.** Thus, material stored at the top can be as much as 60 degrees warmer than that at the bottom. Doses stored in a ULT freezer vary far less, but "warm" spots can exist, and an upright unit allows greater warming when the door is opened than a chest-type unit.

Landmine A: Adverse Temperature

Repeated exposure while in storage can also be a problem: individual units of a cryogenically frozen cell-based therapy are typically placed in slots in a rack that is lowered as a unit into the LN_2 tank. If the rack holds 10 doses, then the dose which is removed first is exposed only once—when it is removed from the storage tank.



Landmine A: Adverse Temperature

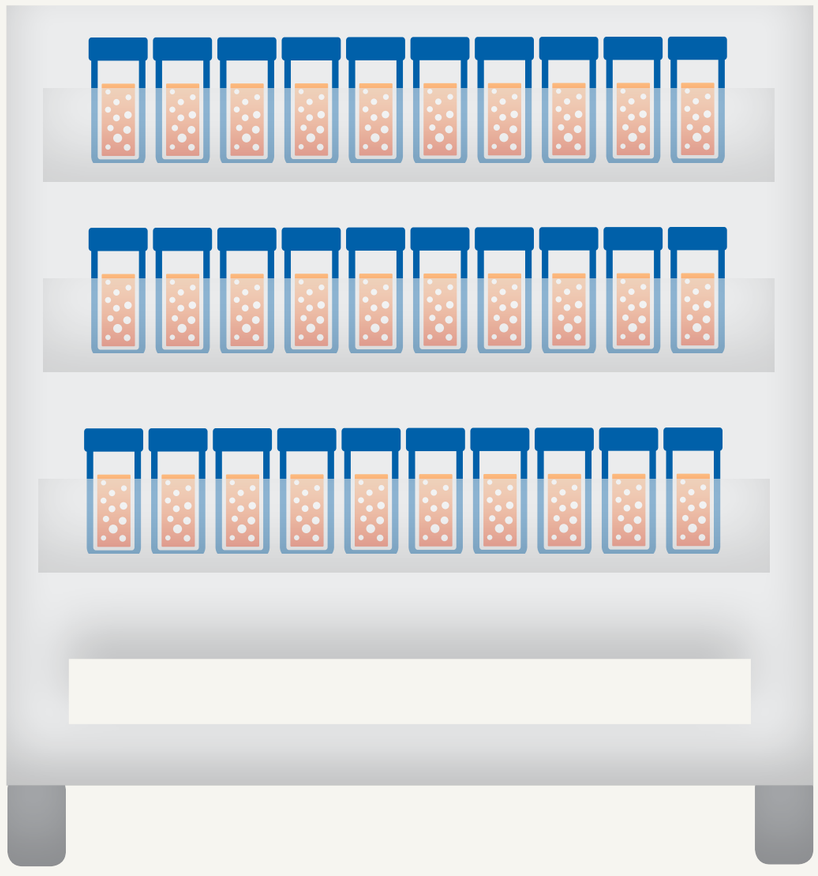
However, the unit on the bottom in the 10th slot may have been exposed to ambient or near-ambient temperatures nine additional times before it is removed from the tank. If each slot in the rack holds a box containing 10 vials, than each vial has been exposed to abrupt warming every time the box was opened as well.

Landmine A: Adverse Temperature

Stepping Carefully:

Risk Mitigation

Stepping Carefully: Risk Mitigation



Minimizing temperature shock: design your product handling processes to reduce exposure to the lowest level possible. For instance, use a cryocart to transfer material from one container to another.

Consider the dosage volume: a product with a volume of only 1ml is at greater risk of temperature shock than a product with an administration volume of 200ml. Each out-of-temperature event puts the material at risk, regardless of volume.

Stepping Carefully: Risk Mitigation

However, a larger administration volume combined with effective packaging can make achieving the minimum threshold in temperature compliance and preservation of therapeutic potency easier (and less costly) to manage.

Landmine B:
Packaging & Distribution

Landmine B: Packaging & Distribution

The packaging of the product should be considered during the very early stages of product development. If not, the result may be that the package necessitates additional handling for storage and distribution, resulting in a higher potential risk of temperature excursion as well as higher costs. Bulky storage configurations can require extensive customization and add cost and risk to the logistics process. **Effective packaging takes into consideration the storage requirements, transit requirements, processing requirements and the administration requirements of the material.**

Requirements:

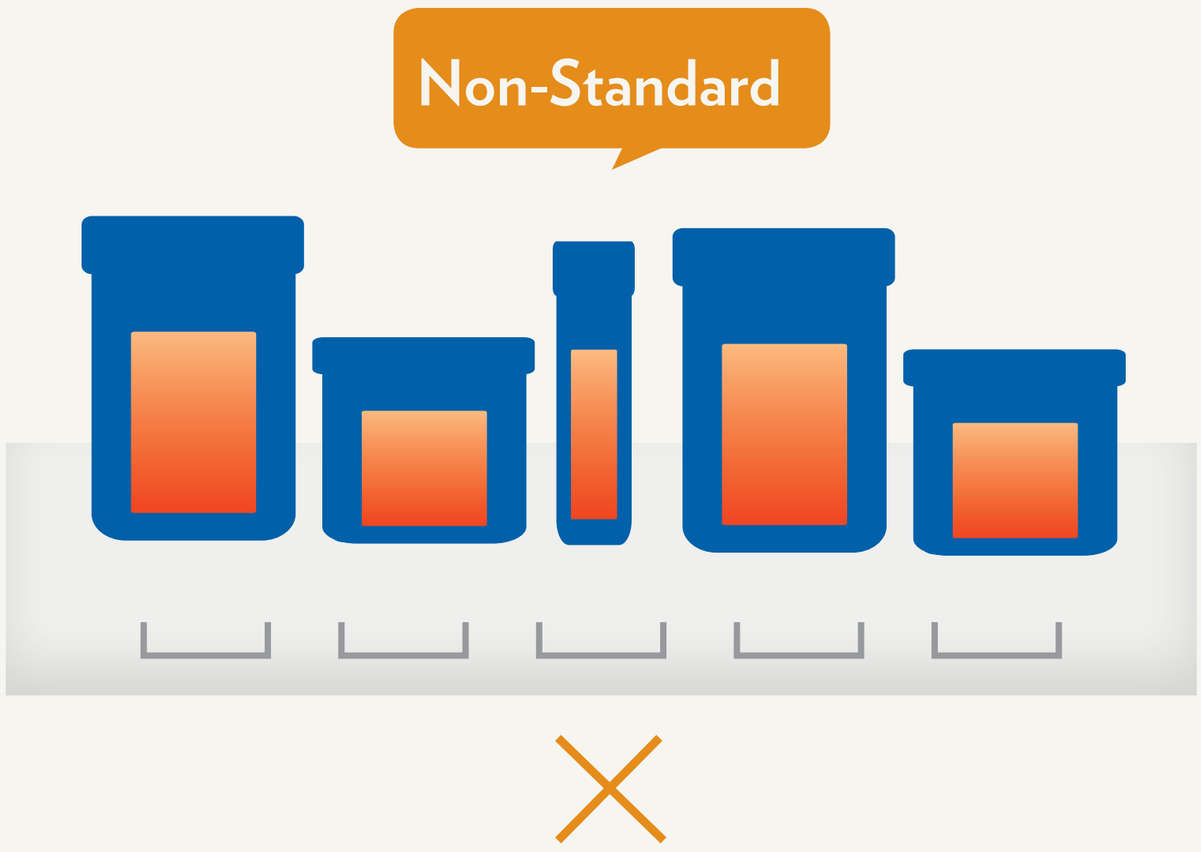
- Storage
- Transit
- Processing
- Administration

Landmine B: Packaging & Distribution

Stepping Carefully:

Standardize

Stepping Carefully: Standardize



Vials, bags, and other containers are each associated with varying shipping containers and requirements, and their costs vary considerably as well. **Freezing individual doses in a container that does not fit into a standard cryogenic racking system or box will add cost and possibly time-out-of-temperature.** Using custom racks will also add to the timeline between development and clinical trials, distribution costs (custom racking may require customized dry shippers), and may also further limit clinical sites to those that can accommodate your racking system.

Stepping Carefully: Standardize

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Landmine C:
Clinical Site Limitations

Landmine C: Clinical Site Limitations

Ideally, your cell-based therapy will be stocked at the clinical site, ready for use. Of course, the medical staff must be prepared to administer doses to patients, but managing these therapies goes well beyond medical staff. **The operations and pharmacy staff must also be equipped to handle these materials. ULT freezers require extra HVAC capacity, while cryogenic storage tanks require a supply of liquid nitrogen.** Both storage systems require temperature monitoring and other infrastructure, on-call staff to respond to mechanical and other issues, and staff trained in the safe management of liquid nitrogen-containing shippers and/or containers of dry ice, which is classified as a hazardous substance. At this point in time, only a minority of clinical sites can manage these therapies in a FDA-compliant manner.

Landmine C: Clinical Site Limitations

Stepping Carefully:

Ensure Consistency

Stepping Carefully: Ensure Consistency

Ensuring consistency among all investigative sites is critical in meeting **FDA criteria**. If an unique process for patient administration is unavoidable, then in addition to training site personnel, consider providing each clinical site with **identical equipment**. If the consumables required are critical to the processing and administration, consider including an **administration kit** with each dose.

Landmine D:
Patient Administration

Landmine D: Patient Administration

Will your therapy in development require complex preparation for administration? Non-standard administration will necessitate committing resources to training site personnel in preparation and administration procedures, and possibly additional equipment.

Is this an autologous therapy? An additional layer of diligence is required for regimens created for a specific patient: great care must be taken to create a robust system that securely pairs the patient to the dose. In addition, the pharmacy staff may require training in any storage or handling variables that are unique to the regimen.

Landmine D: Patient Administration

Stepping Carefully:

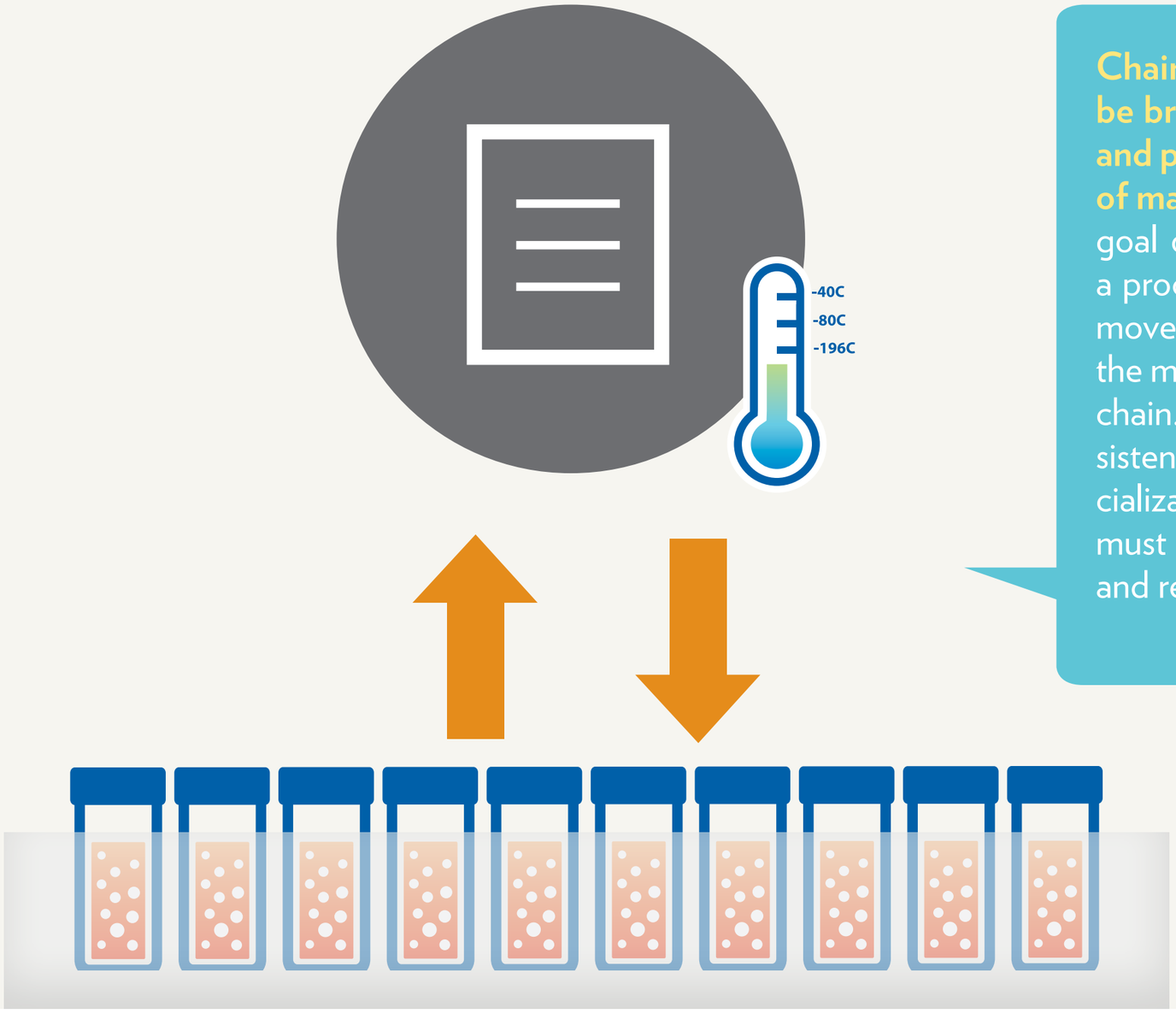
Pairing the Therapy with the Patient

Stepping Carefully: Pairing the Therapy with the Patient

Give thought early on to creating labeling, packaging, equipment, and an information management system that consistently ensures that the correct dose is given to the correct patient.

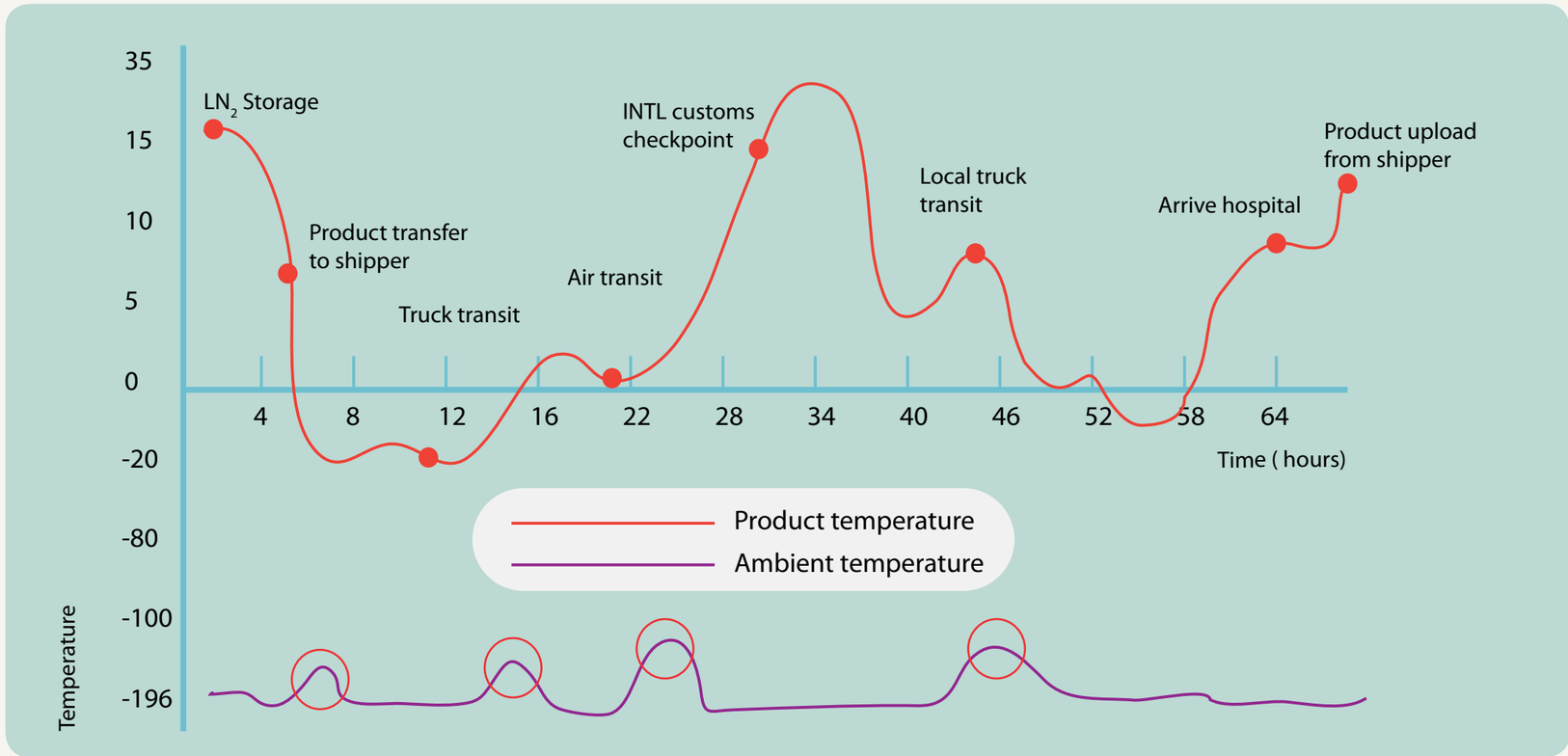
Landmine E:
Establishing a Chain of Custody

Landmine E: Establishing a Chain of Custody



Chain of custody for a cell-based product can be broadly defined as the movement, storage and processing of the materials from the point of manufacture to patient administration. The goal of a chain of custody solution is to create a process that both controls and documents the movement, the temperature, and the handling of the material at all times and points in the logistics chain. This process must be scalable and be consistently applied from Phase I through commercialization. The documentation of this process must comply with 21 CFR part 11 requirements, and requires data regarding:

Landmine E: Establishing a Chain of Custody



- All temperature deviations or excursions to which a dose of cell-based medicine is exposed.
- The number of times it was exposed.
- The duration of each exposure event.
- The person that was handling the material.

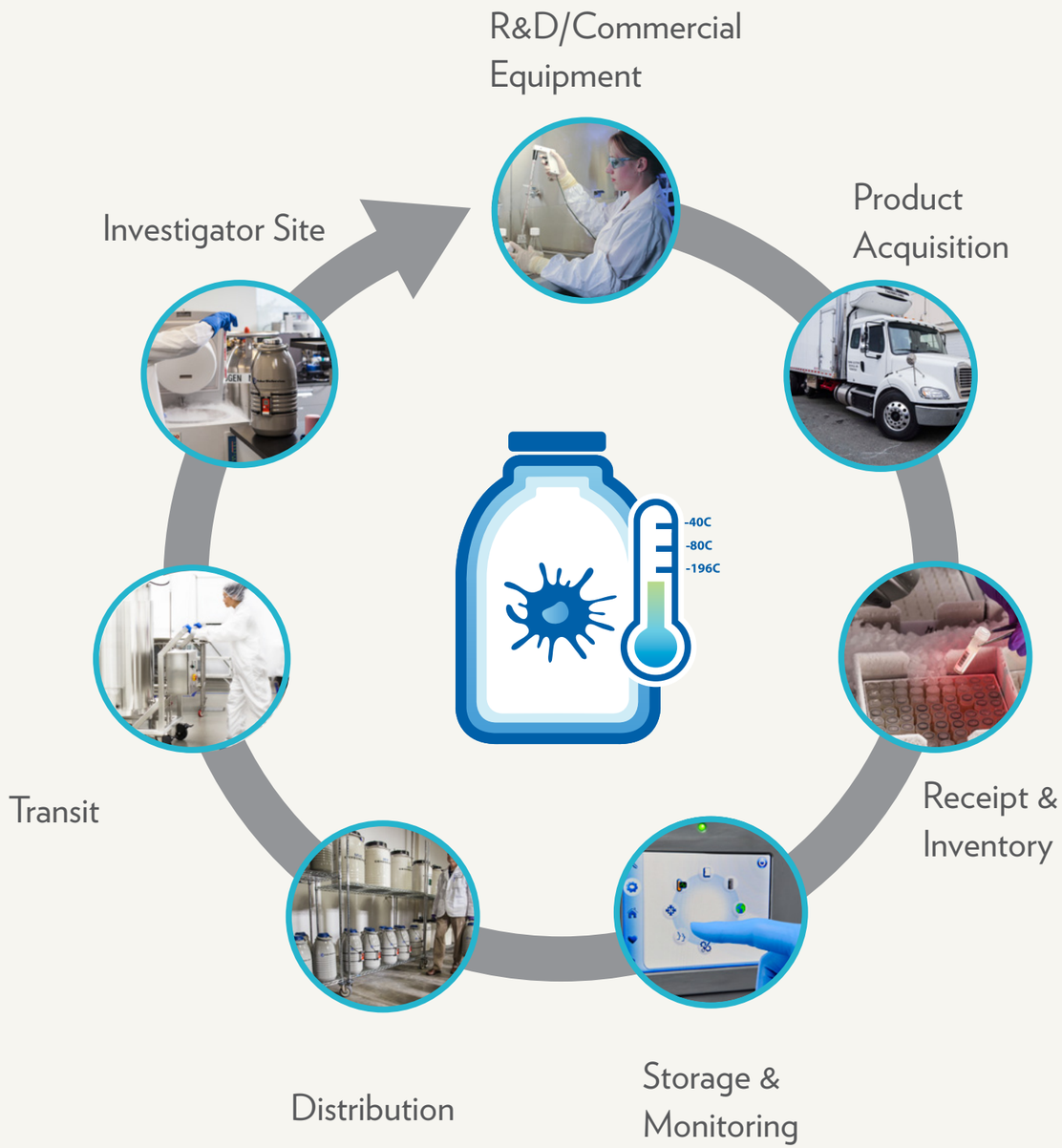
Landmine E: Cold Chain Distribution Expertise

Stepping Carefully:

Cold Chain Distribution Expertise

Stepping Carefully: Cold Chain Distribution Expertise

Working with experts in cryogenic distribution, cold chain/chain of custody, and 21 CFR part 11 compliance, will save you multiple headaches and misdirected resources in your journey to a commercially successful product. Fisher BioServices is on the forefront of cryogenic distribution systems. We are partnering with clinical sites, to equip them for the new era of regenerative and personalized medicine, as well as with companies who are developing call-based therapies. We are the experts in getting your product from the manufacturing facility to the patient bedside in the most cost-effective manner while fully preserving therapeutic potency and viability.



Additional Resources

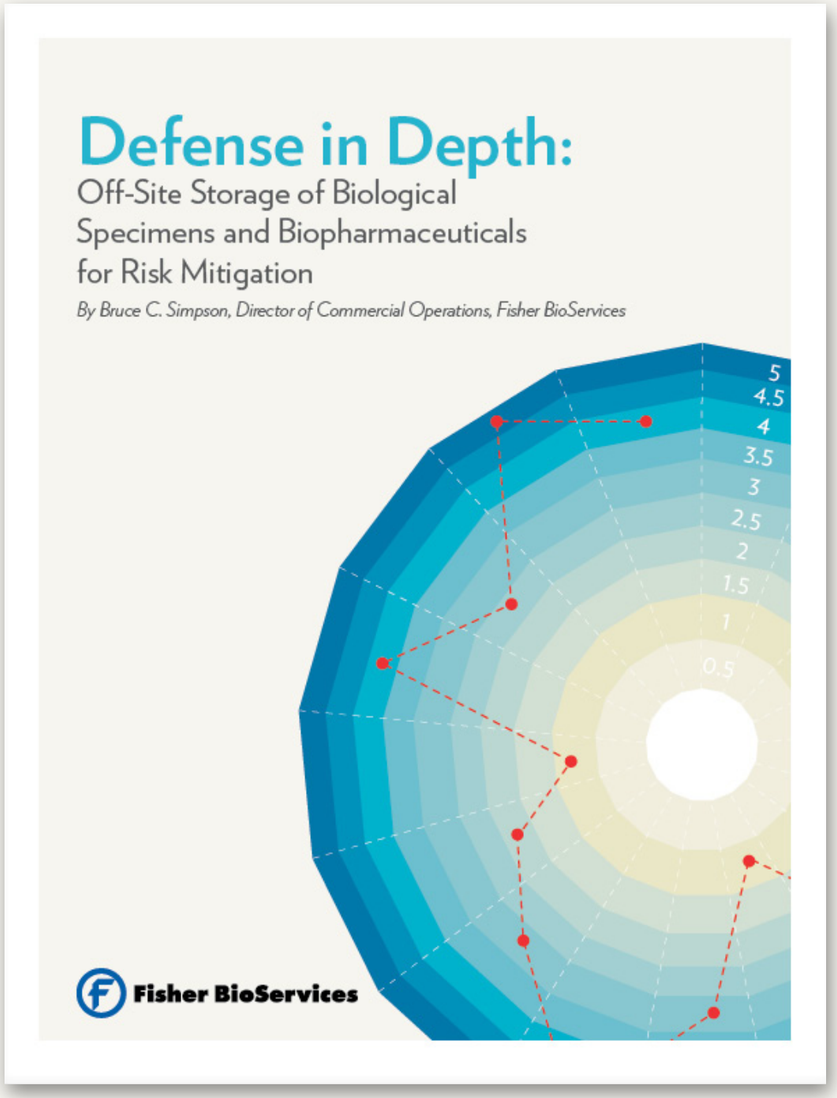
You can also consider setting up a cell therapy meeting or web-demo with Fisher BioServices cell therapy logistics experts about your cell therapy clinical trial.

▶ Request Cell Therapy Solutions

Additional Resources

You may also like our ebook

Defense in Depth:
Off-SiteStorage of Biological Specimens and Biopharmaceuticals for Risk Mitigation



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