

Cell Therapy Logistics

The Physics of Failure

or How Mother Nature conspires to ruin your clinical trial before you ship your first dose

Dan O'Donnell
Director, Cell Therapy Logistics
Fisher BioServices



Thermal Capacity

- **Thermal Capacity**

The measurable physical quantity of heat energy required to change the temperature of an object or body by a given amount.

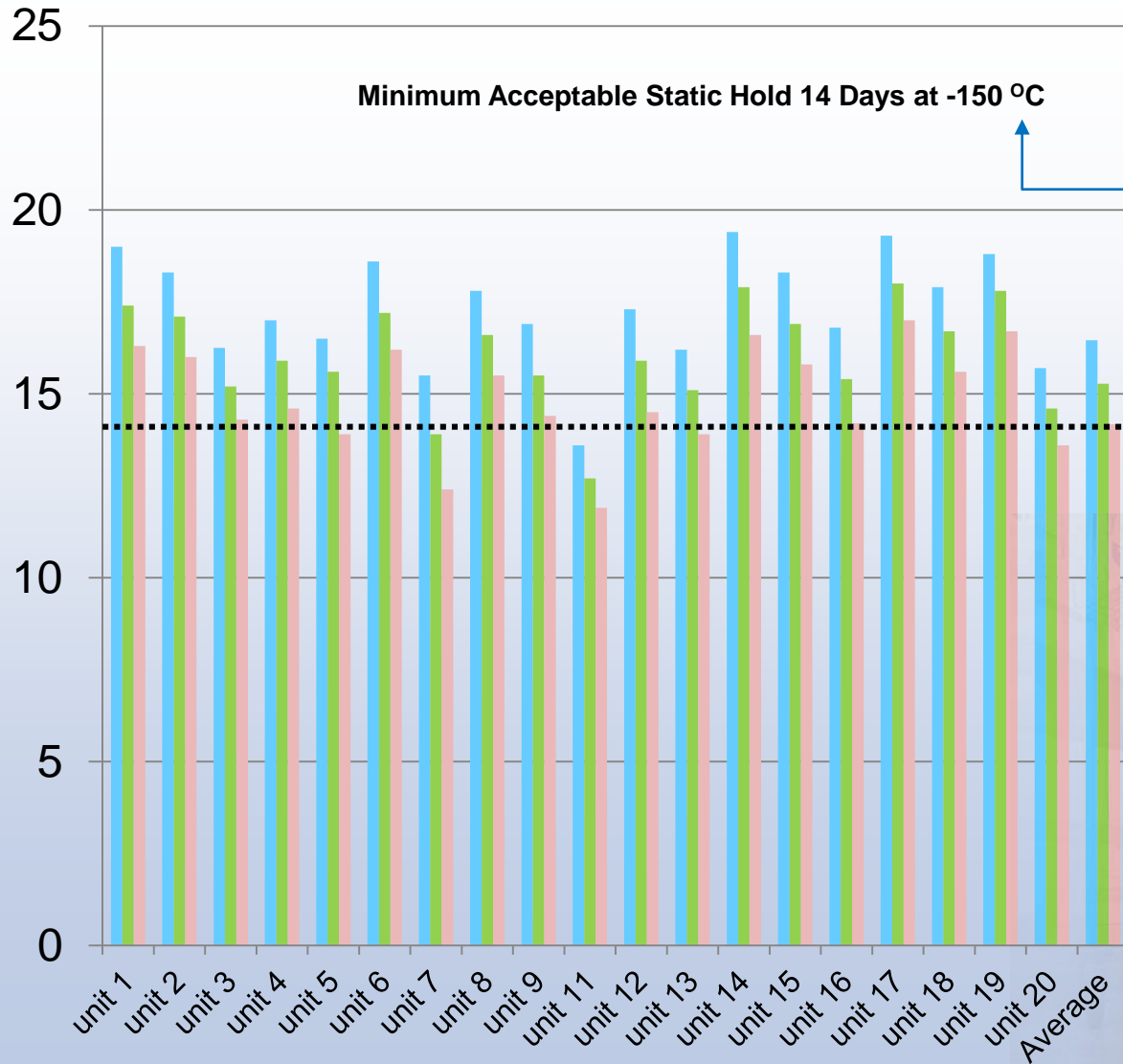
- Given the constituents of a shipping solution; Dry Shipper, Data Logger, Shipping Rack, Payload, Outer Container, Means and Conditions under which it ships. How long can an acceptable temperature maintained.

The Challenge

- In a world with an average temperature of **14 °C** how do you maintain a temperature of **-140 °C** or less for an extended period of time?



Dry Shipper System Qualification



- Initial Qualification Avg
16.46 Days
- Qualification w/Logger
Avg. 15.27 Days
- Qualification w/Logger
and Payload Avg. 14.17
Days
- Shipper failed 14 days
temperature hold



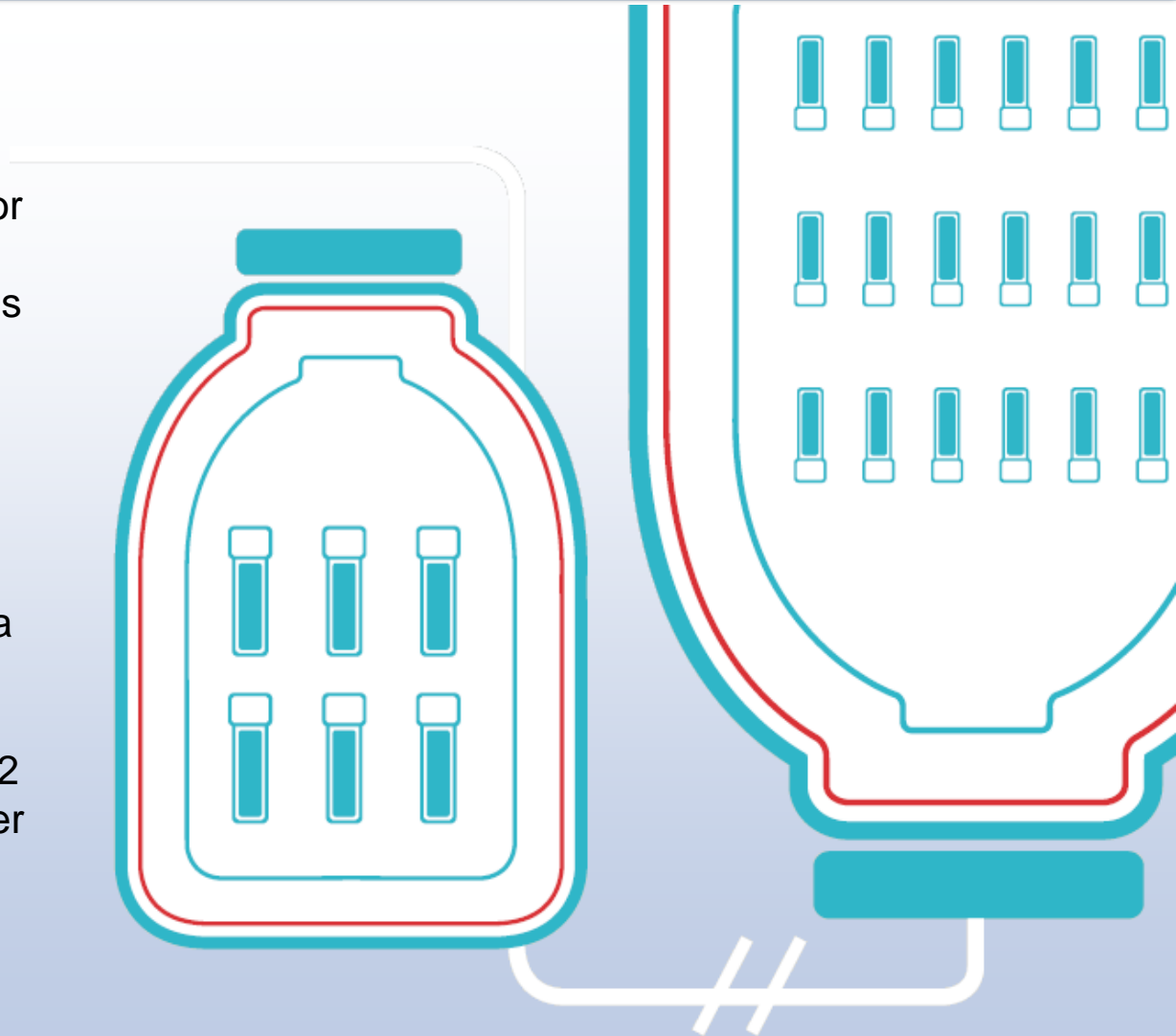
Gravity

- **Newton's Law of Gravity**

The force that attracts a body toward the center of the earth, or toward any other physical body having mass. For most purposes Newton's laws of gravity apply

- **Dry Shippers & Gravity**

For our purposes it is the process that takes place when a carrier lays the dry shipper on it's side or upside down during transit forcing the remaining LN2 to the side and out of the shipper reducing hold time dramatically



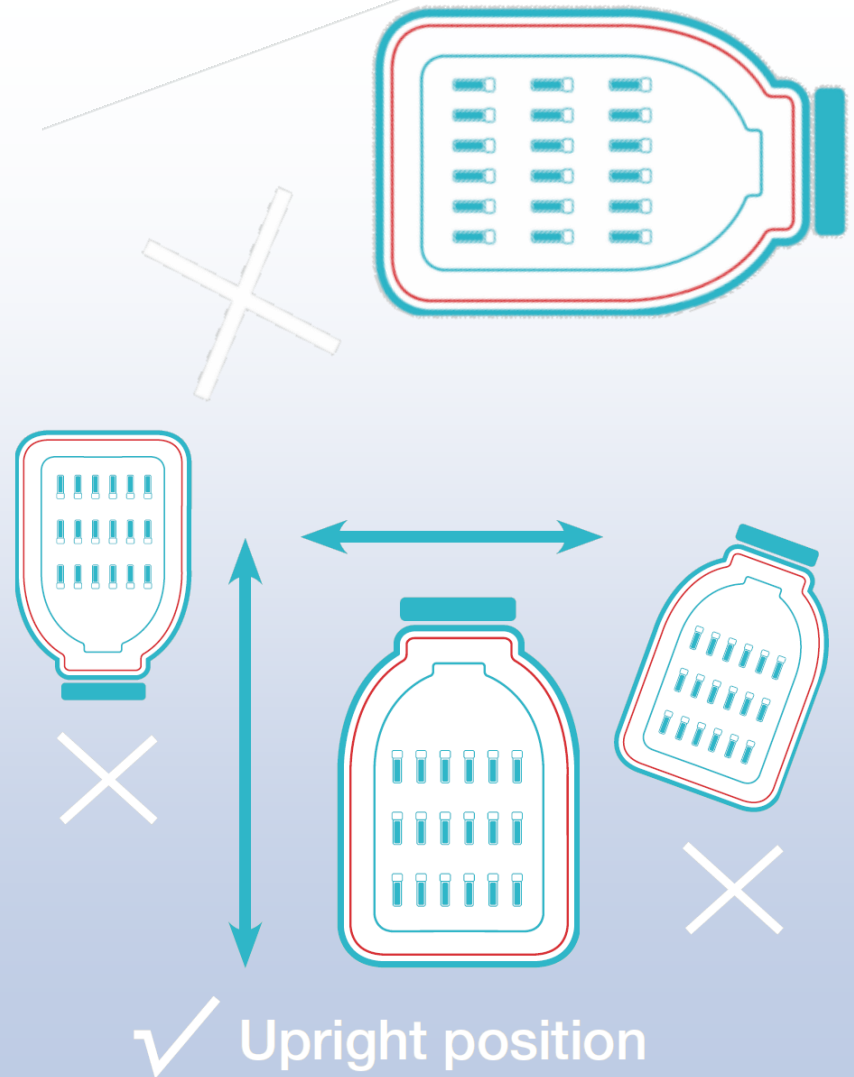
Orientation Risk

- **Why Orientation Matters**

- A shipper on its side for as little as 6 hours can lose 40% to 70% of its hold time
- An inverted shipper can lose 60% to 90% of its hold time
- The bigger the shipper the more rapid the loss of hold time

- **Orientation Risk Escalating Scenarios**

- This can be a serious concern if your product:
 - If the shipper experiences extended customs clearance times
 - Is in the dry shipper and is used for short term storage at the receiving site



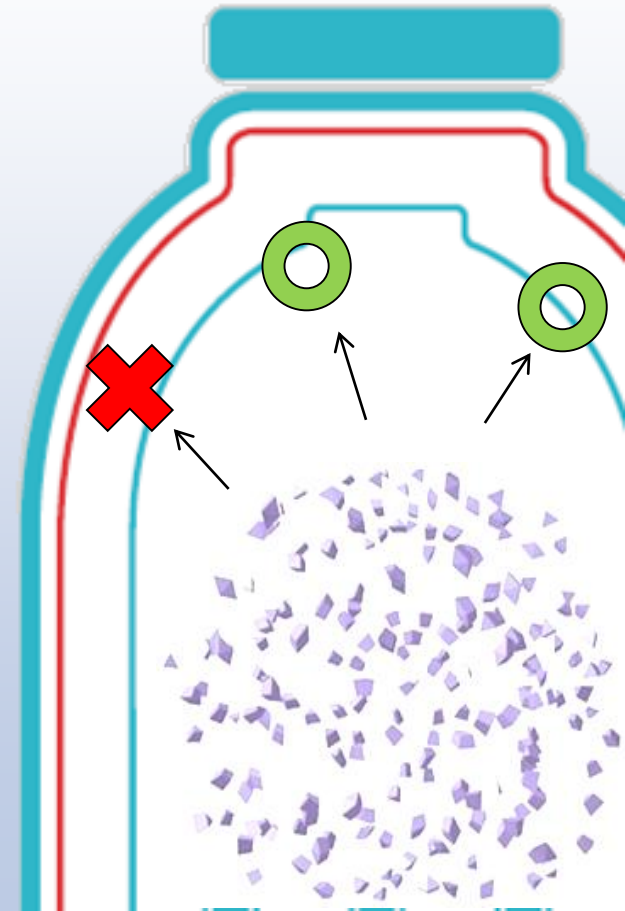
Orientation Risk Mitigation

- **Labeling**
 - Makes sense in theory does little in practice
- **Tilt Indicators**
 - Always return actuated
- **Packaging Solutions**
 - Secured to a pallet
 - Upright configurations
- **Orientation monitoring Devices**
 - Cannot intervene but do let you know with some confidence level of the hold time remaining



Entropy

- **Lack of order or predictability; gradual decline into disorder**
- **It Is The Gradual Deterioration of the Primary Constituents Of The Dry Shipper**
 - Vacuum
 - Hydrophobic absorbent material which holds the LN₂
- **Deterioration Can Be Caused Age And Damage**



You Can't Stop Entropy but...

- **You Can Test For It**

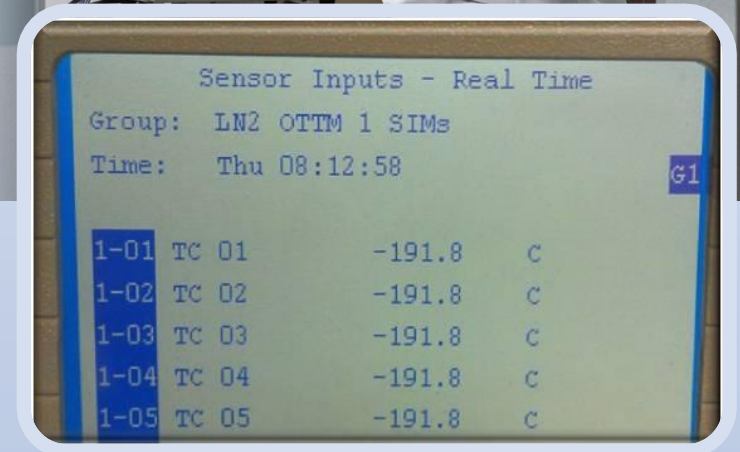
- Testing should be done on a regular basis
- Highly recommended after each use
- Monthly or Quarterly if used infrequently

- **Test when you suspect the unit has been damaged**

- Reduction in hold time
- Visible damage

- **Handle with Care**

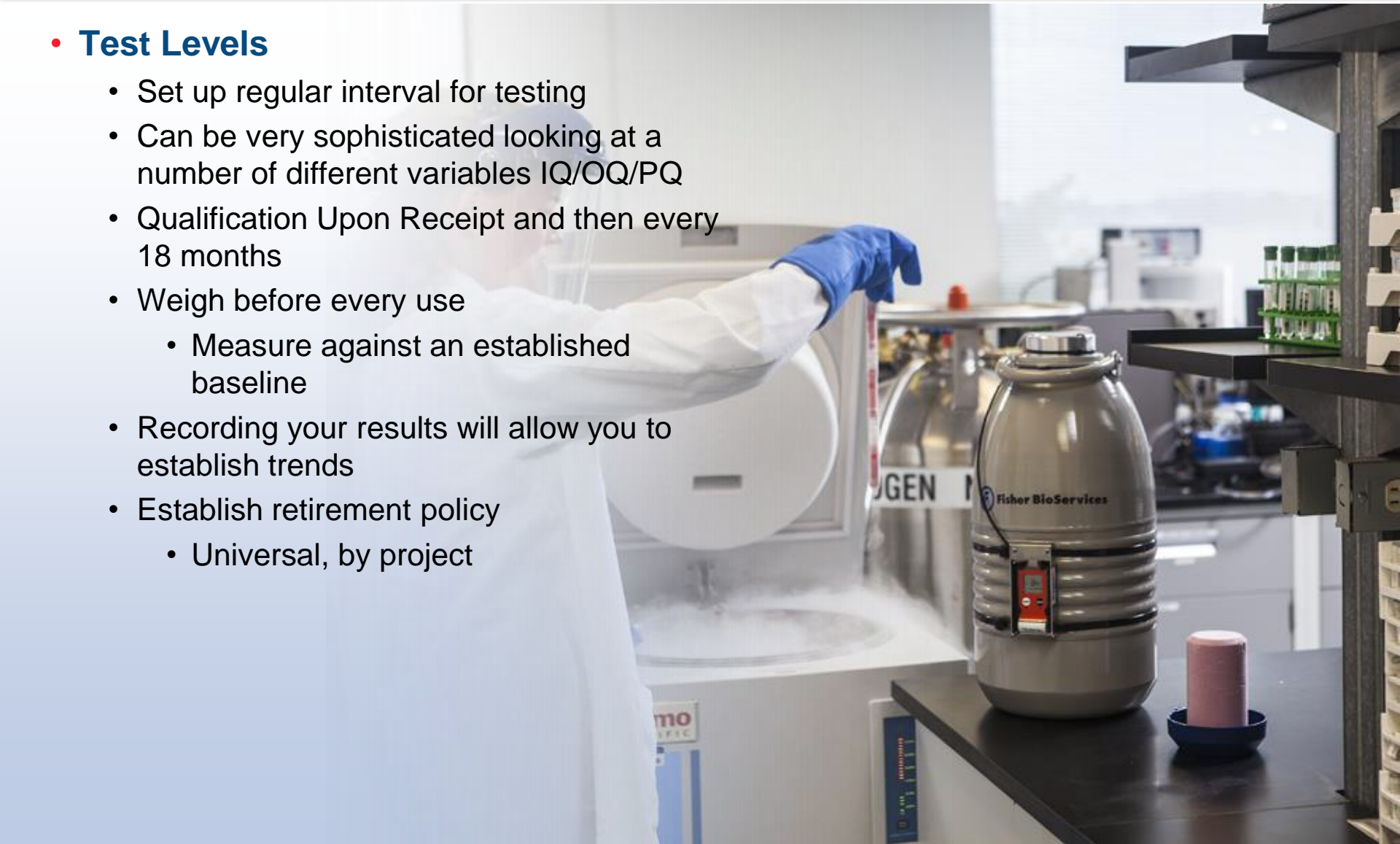
- Don't drop or bang them around
- Keep them cold
- Don't attempt to disinfect the interior chamber



You Can't Stop Entropy but...

- **Test Levels**

- Set up regular interval for testing
- Can be very sophisticated looking at a number of different variables IQ/OQ/PQ
- Qualification Upon Receipt and then every 18 months
- Weigh before every use
 - Measure against an established baseline
- Recording your results will allow you to establish trends
- Establish retirement policy
 - Universal, by project



The Gas Laws

Laws that Govern the Movement and Temperature of Gases

- **Dalton's Law of Partial Pressures**

- The total pressure of a mixture of gases is equal to the sum of the partial pressures of the various components

- **Charles' Law**

- The Volume of a gas is directly proportional to the Temperature (Kelvin) at constant P and n .

- **Amonton's Law**

- The Pressure of a gas is directly proportional to the Temperature (Kelvin) at constant V and n .

- **Boyle's Law**

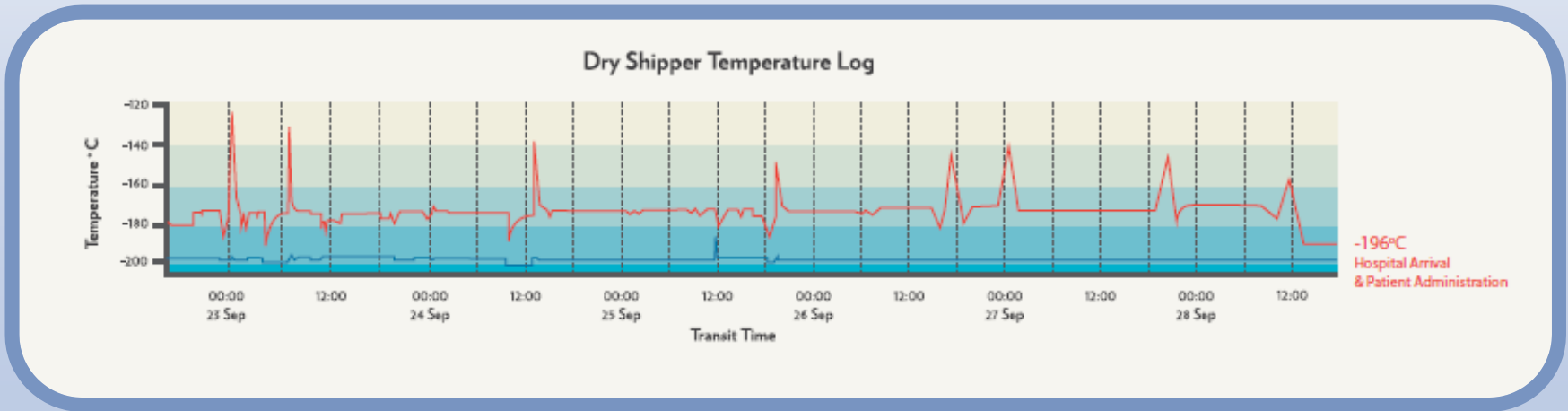
- The Pressure (P) of a gas is inversely proportional to Volume (V) at constant Temperature (T) and moles of gas (n).

The Gas Laws – Impact



Highest Area of Impact

Lowest Area of Impact

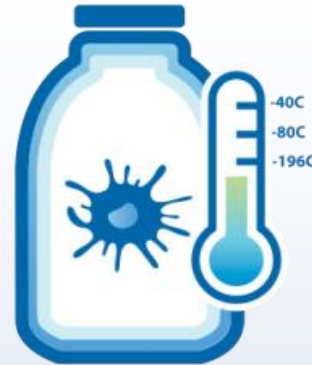
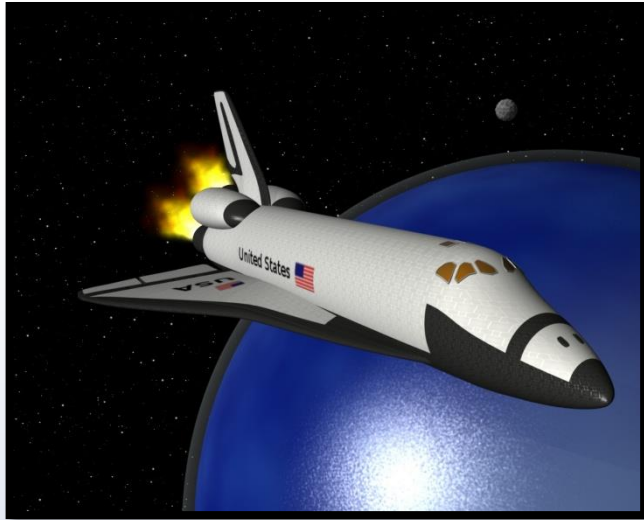


The Gas Laws Overcoming Adversity

Rules to Minimize Impact

- **Position payload at the lowest possible level**
- **Baffle to direct aspirated air away from the payload and probe**
 - If the payload is low baffle to keep aspirated air high
 - If the payload is distributed through out the vessel force the aspirated air low
- **Package to protect the payload**
 - Additional insulation is a plus
- **Map probe to payload**
 - While protecting the payload is paramount but remember the data logger is reading the probe.

It is not Rocket Science but ---



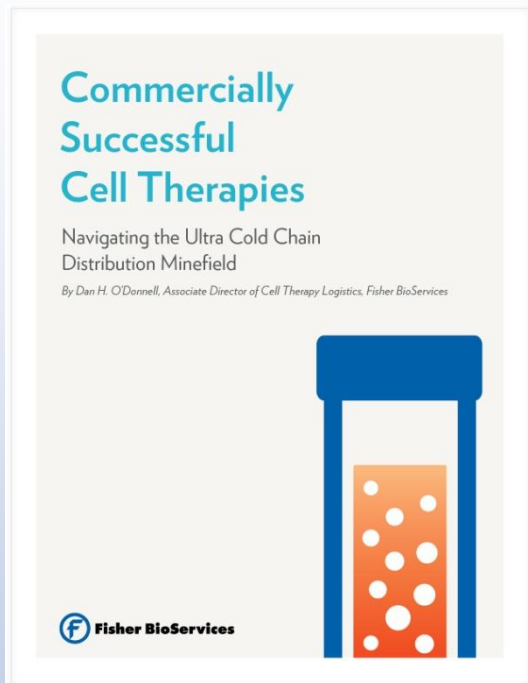
Source: Khooll.com by Jorge Lopez

- **Both involve living material traveling in a vessel with a controlled artificial environment surrounded by a hostile one**
- **In both cases if you get the mission right 99% of the journey you still fail catastrophically**

Reproducible Success is Possible

- **Precise Planning**
- **Meticulous Preparation**
- **Flawless Execution**

Cell Therapy eBook



[InfoPoster] 10 Things You Should Know About Dry Shippers Before Shipping High Value Biologics

1 Not all dry shippers are created equal

There are wide variations in dry shippers with regard to size and temperature (static) hold times and you should select the shipper that best fits your application. Sizes can range from space for a dozen vials or cassettes to shippers that can hold 25,000 vials. Temperature hold times can vary from a few days to more than two weeks. Variations also exist in how well they hold temperature under different environmental and handling conditions.

2 Significant variations can occur among dry shippers of the same make and model

The manufacturer's spec is no guarantee of a specific hold time. While some units are better than others, even among the best, variations of up to 40% are not uncommon. This is particularly important if you plan to use the dewar for temporary storage. In addition, in shipping a dewar internationally, you should anticipate a complicated customs process or an unusually long transit time. Imagine a scenario in which you accounted for eight days maximum!

3 Data loggers will reduce static hold over time

Data loggers allow us to create a record of the internal temperature of the dry shipper while in transit. In addition, they set acceptable temperature windows that will alert the recipient if a temperature excursion occurred during the shipping process. While data loggers are an invaluable tool in tracking and documenting temperature, attaching one to a dry-shipper will invariably reduce static hold times. The logger and probe set create a "heat wick" that draws heat into the interior of the dry shipper, reducing the static hold time. The extent of this wicking effect depends on the logger and probe configuration.

4 Get usable results by evaluating the location of the data logger on a dry-shipper and how it is secured and protected

Data loggers are an aftermarket addition and the quality of their performance is contingent on how they are installed and protected during transit. Not all models work well in the same locations so pick the dry shipper and data logger combination that is best for your particular situation.

5 The ability of dry shippers to hold temperature decreases over time

While dry-shippers have no moving parts, they do have two components that deteriorate over time. The first is the vacuum between the inner and outer vessel. This vacuum is critical and diminishes with use. The other element is the absorbent material that traps the liquid nitrogen. A simple 24-hour evaporation test will allow you to determine if there has been significant deterioration in either or both.

Download at blog.fisherbioservices.com

Questions?

Contact Us

USA | UK | CH

1.301.315.8460

www.fisherbioservices.com

Info.FisherBioServices@Thermofisher.com

 /Company/Fisher-BioServices



Cell Therapy Solutions

Learn more at www.fisherbioservices.com