

Cell Therapy Logistics

Beyond the Basics

Dan O'Donnell, Area Director of Cell Therapy Logistics



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Biobanking & Biorepository



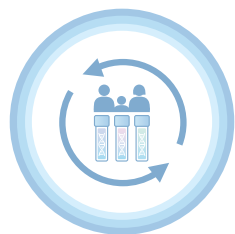
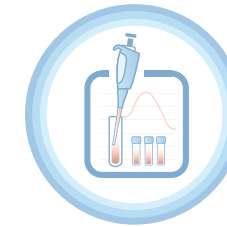
Cell Therapy Solutions



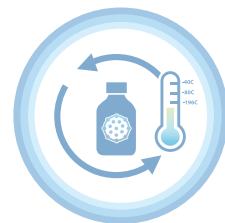
Clinical Trial Kit Production



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About the Author



Dan O'Donnell, Area Director of Cell Therapy Logistics

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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 healthcare 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.



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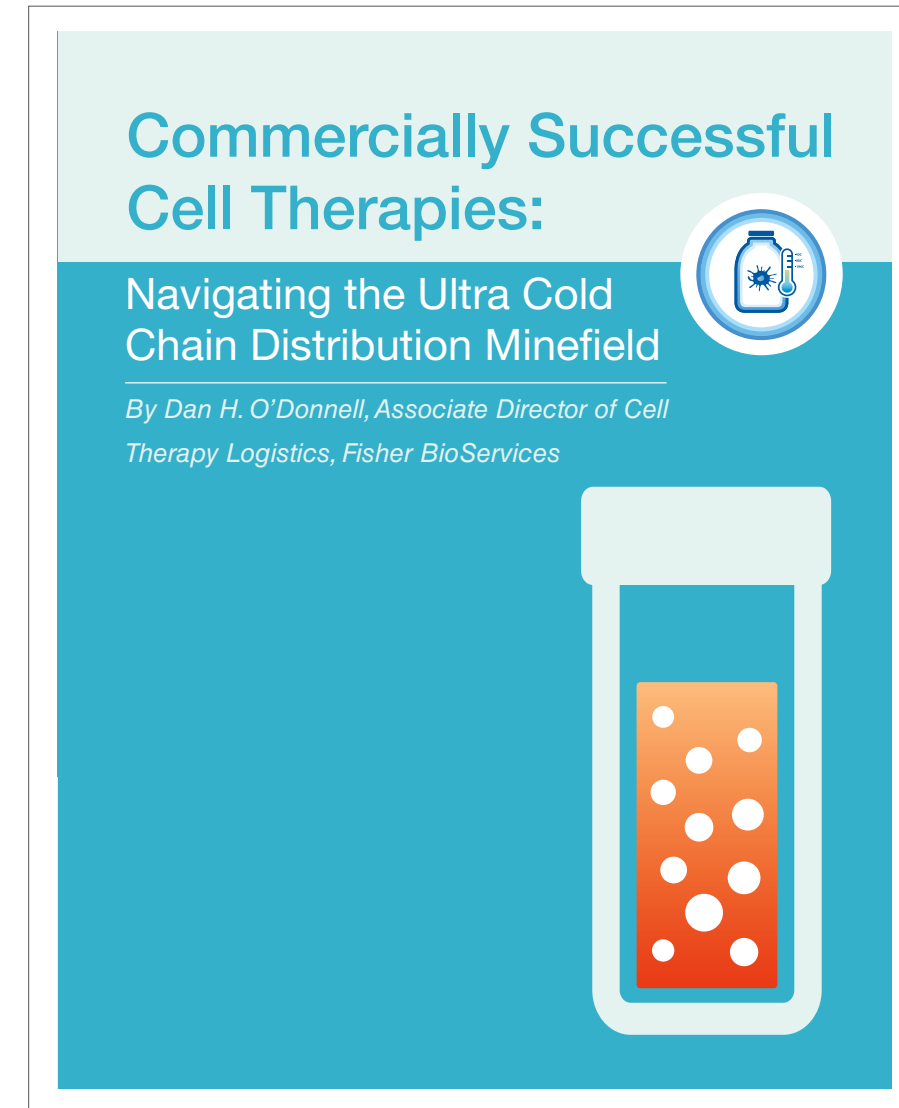
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Introduction

My previous eBook, *Commercially Successful Cell Therapies: Navigating the Ultra Cold Chain Distribution Minefield*, and several of my blogs, have discussed the basics of building a successful logistics strategy for the management of cell-based material. If you read these, then you are aware of the better-known and important factors to consider, such as:

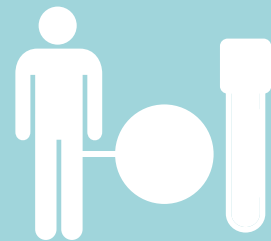
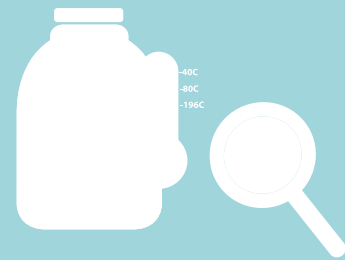
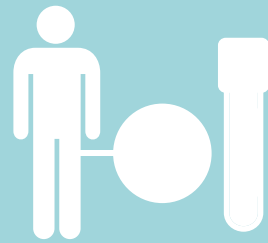
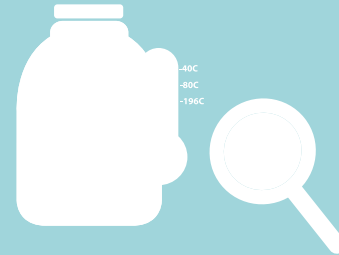
- Selecting the right dry shipper
- Qualifying that shipper to the particular payload and shipping configuration
- Choosing an appropriate data logger
- Creating a chain of custody
- Evaluating a transit carrier
- Anticipating potential problems inherent in shipping at cryogenic temperatures



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Introduction



This eBook goes beyond the basics and acquaints you with some of the lesser known considerations. Although they may be hidden in the background, these factors can play a major role in the success or failure of a clinical trial and the long term efficacy of a cell-based commercial product. They are:

- Standardization
- Package and shipping qualification
- Equipment validation
- Process qualification
- Documenting the chain of custody

I am focusing this eBook on the unique logistical challenges of autologous cell-based therapies, that is, therapies that use a patient's own cells for the manufacture of a treatment that is then administered only to that patient. The other type of cell-based therapy is referred to as "allogeneic" and is derived from an unrelated donor or donors, and administered to the relevant population of patients. All of the considerations I mentioned above apply to allogeneic as well as autologous therapies.



1

The Unique Complexity of an Autologous Therapy

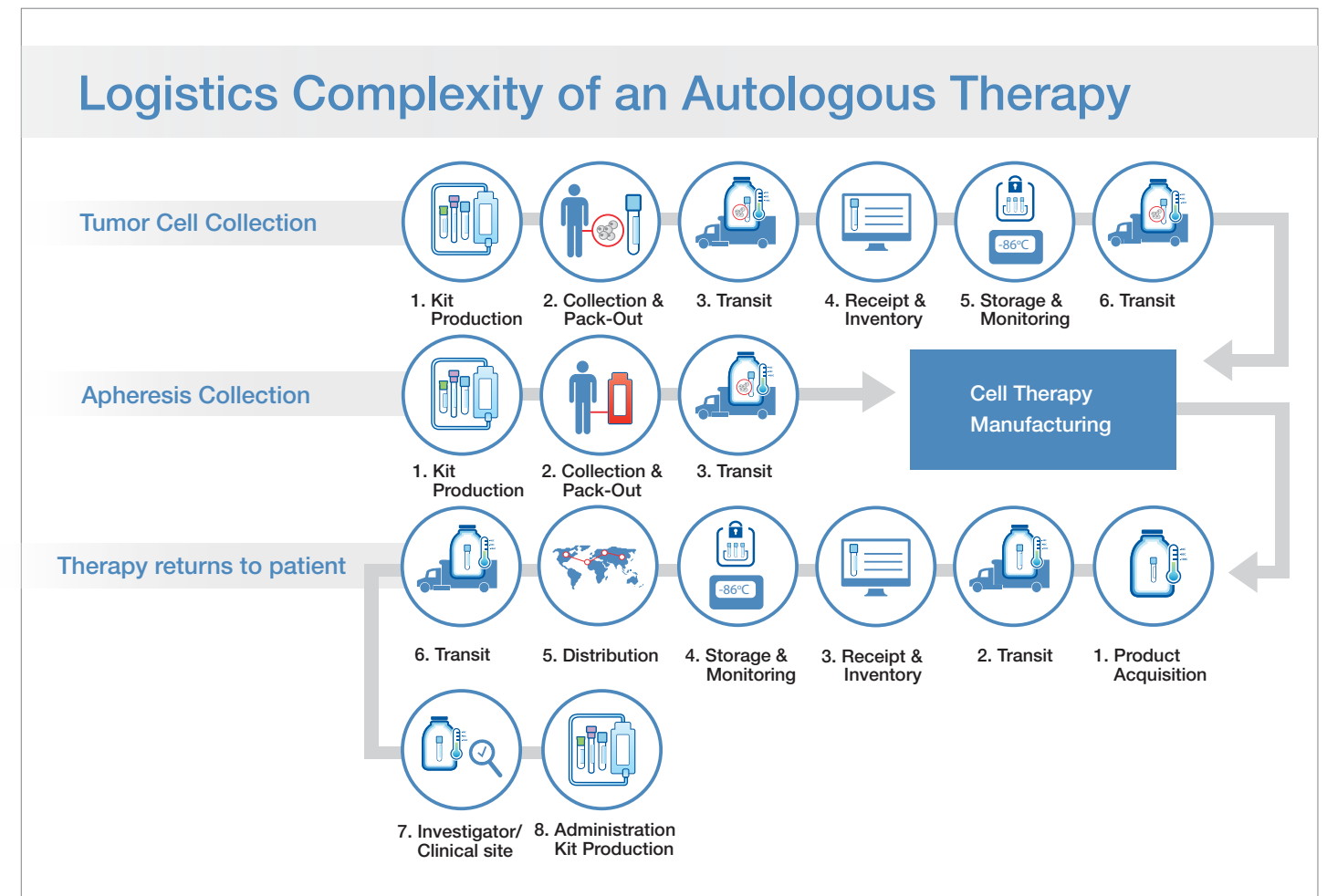


The Unique Complexity of an Autologous Therapy

First, let's map out the multiple paths traveled by the various entities that must come together seamlessly for an autologous cell therapy product to be successful.

The process of creating an autologous therapy, from the collection of base cells through production and back to the waiting patient, has become increasingly complex. This not because regulatory or other demands have intensified, but rather as we have gained more experience, we have discovered additional challenges that must be overcome to ensure success. As a point of reference through this book I will use this flow chart to illustrate where in the chain of custody these challenges occur and need to be addressed.

This chart represents a fairly typical process chain for a cancer-related autologous cell therapy. The therapy requires two separate cell collections from the patient—a tumor and a dendritic cell (apheresis) collection—and a process for the receipt, storage and distribution of the finished product. Let's take a moment to define this chain in greater depth by looking at the three high level processes detailed in the chart.



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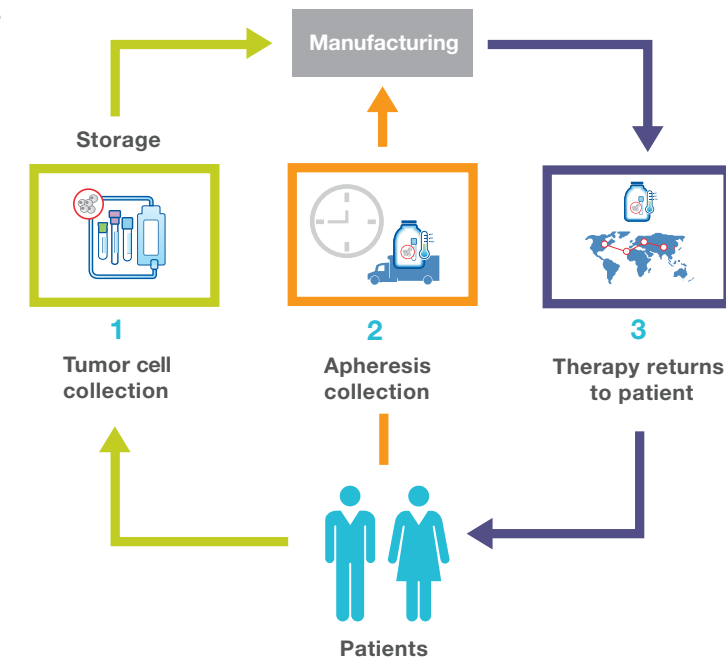


The Unique Complexity of an Autologous Therapy

Tumor cell collection— From a logistics perspective, the entire drug production process begins with the creation of a kit which will be used to collect the tumor and identify the tumor with the patient. This unique identification number is patient specific and will be used throughout the collection, manufacturing, distribution, and administration. This ID ensures the right drug is infused in the right patient. This kit will include a qualified shipper for transporting the tissue to an interim storage point. Using this kit, the tumor sample is collected and packaged for transport (via common carrier) to a storage facility where it is received, inventoried and stored until ordered for manufacture. Once ordered, it will again be packaged in a qualified shipper and transported to the point of manufacture, where it is stored until manufacturing begins

Apheresis collection—Timing and logistics are critical with regard to the apheresis collection, as the manufacturing process begins in earnest with the receipt of the dendritic cells. Unlike the tumor collection process, there is no interim storage step; however, as with the tumor collection, the process begins with a kit with all of the components required for an apheresis collection. The kit includes the patient-specific identification labels and collection containers as well as a qualified shipping container. The cells are shipped via common carrier, with the addition of an important step—notification of the manufacturer that the shipment is on the way. The shipment is received by the manufacturer, the patient ID is confirmed, and the manufacturing process can begin.

Therapy returns to patient—Once manufactured, the dose or doses are cryopreserved and loaded into a qualified dry shipper for transport via common carrier to a distribution facility, where the material is received and inventoried. When the therapy is packaged to leave the manufacturing site, it is “acquired” for distribution and begins the journey of a drug to a patient. At the distribution center, the individual doses are inventoried and stored in vapor phase nitrogen until requested by a clinical/investigator site for patient use. Each requested dose is shipped in a qualified dry shipper by common carrier to the clinical site for administration.



While simplified, this three-step description gives a reasonable overview of the basic movement of the drug and constituent materials required in an autologous drug manufacturing process. Now that we’ve defined the three high level processes, let’s look at the additional considerations mentioned earlier and their impact on the success or failure of a cell-based therapy.



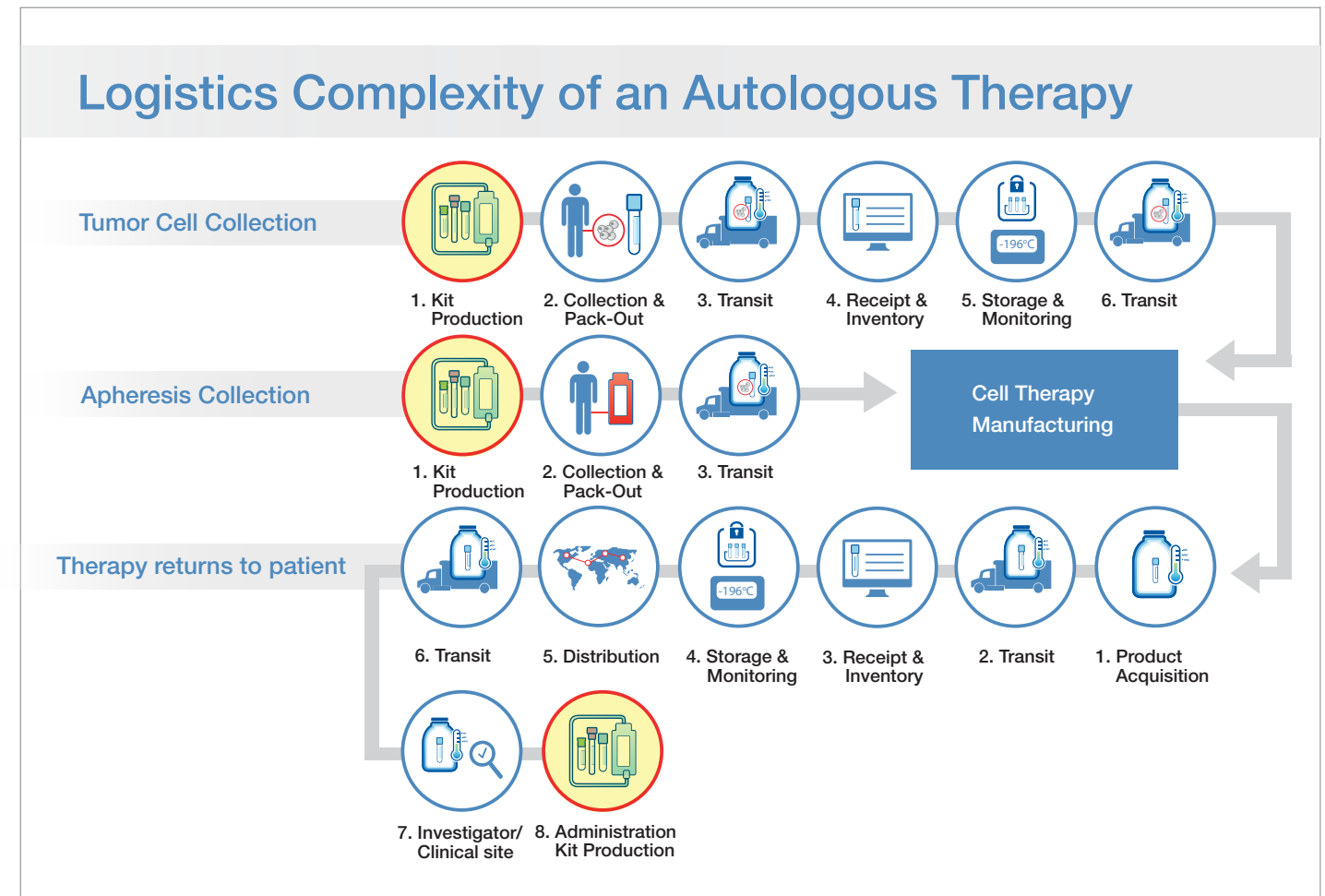
2 Standardization



Standardization

It is important to standardize as many processes and procedures as possible in the development of a logistics strategy. In this particular section I'd like to focus on the management of processes that are outside your direct control. In the cases of cell collection, drug preparation/processing and the administration of the product, kits can be a very effective tool to define the materials used in these processes and drive consistency in their execution. The diagram below highlights the areas where the opportunity exists to employ kits to manage standardization.

The value of kits as standardization tools increases as a drug candidate traverses later trial stages. Early stage (phase 1 and 2A) trials are often done at only one or two clinical sites. The limited number of sites allows close coordination with the developer to ensure that the handling of the material is coordinated and consistent.



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Standardization



The challenge arises as the product moves through phase 2B and 3 trials. These trials often include 20 to 50 clinical trial sites, and it becomes far more difficult to ensure each site follows the exact same procedures for cell collection, product preparation, and administration. One key way to standardize is to use a specially designed kit for cell harvesting (collection kit) and for delivering the finished drug to the patient (administration kit).

The use of a kit ensures that the same materials are used in each process, instructions are available for each procedure, labeling is consistent, and in the case of collection kits, also makes certain that a qualified shipping solution is used for the transit of the critical patient cells following their collection.

The degree to which premade kits impact the outcome of the trial is driven by the complexity of the process it addresses; providing an administration kit for a product that requires surgical implantation is far more critical than for a product that is introduced via IV administration. However, in every case the goal is to reduce variation of process and ensure that the clinical results reflect the efficacy of the drug and not variations in handling.

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③ Package and Shipping Qualification



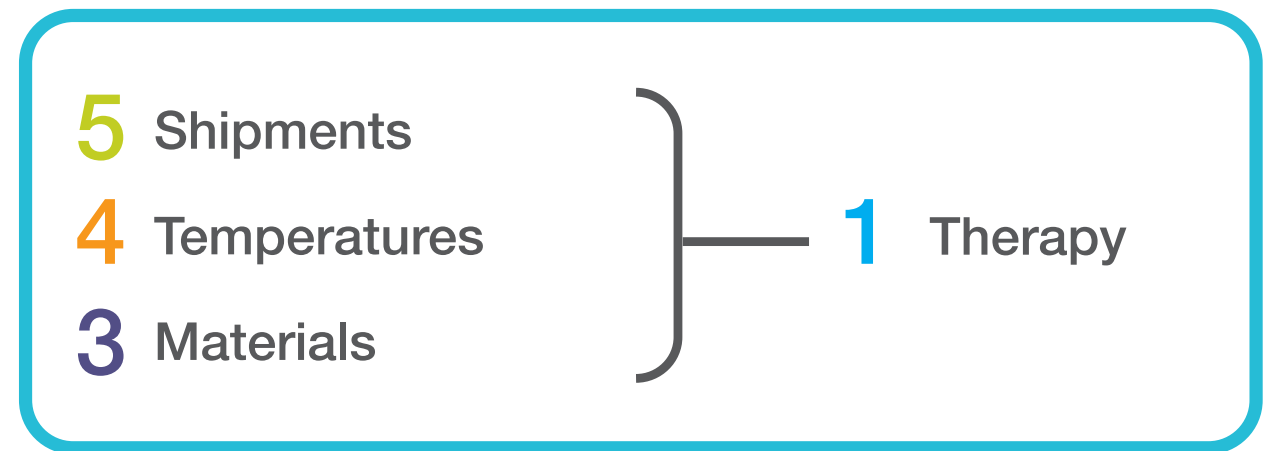
Package and Shipping Qualification

The successful transit of material is a primary objective of any logistics strategy.

Consider that our simple flow diagram contains five different shipments of three different materials at four different temperatures. Let's review:

- The patient's tumor or other applicable tissue is collected and shipped at controlled ambient to a storage facility for preservation at -80°C.
- When needed, the patient tissue is then shipped on dry ice to the manufacturing facility;
- The patient's apheresis collection is shipped under refrigeration (between 2°C and 8°C) directly to the manufacturing facility;
- The finished therapeutic doses are then shipped in bulk from the manufacturing facility to a storage/distribution point in a dry shipper at cryogenic temperatures; and
- Doses are then shipped, again in a dry shipper, a final time to the clinical site for administration to the patient.

For each of these five transit points on our diagram, it is critical to use qualified shipping solutions that are designed to the specific requirements of each individual payload, temperature, duration and the environmental and handling extremes that will be encountered during transit. This is not to be confused with blanket qualifications issued by the manufacturers of shipping solutions. These blanket qualifications can be useful in choosing possible solutions for testing but fall short of the rigorous testing needed to make sure the material being shipped reaches its destination in perfect condition.



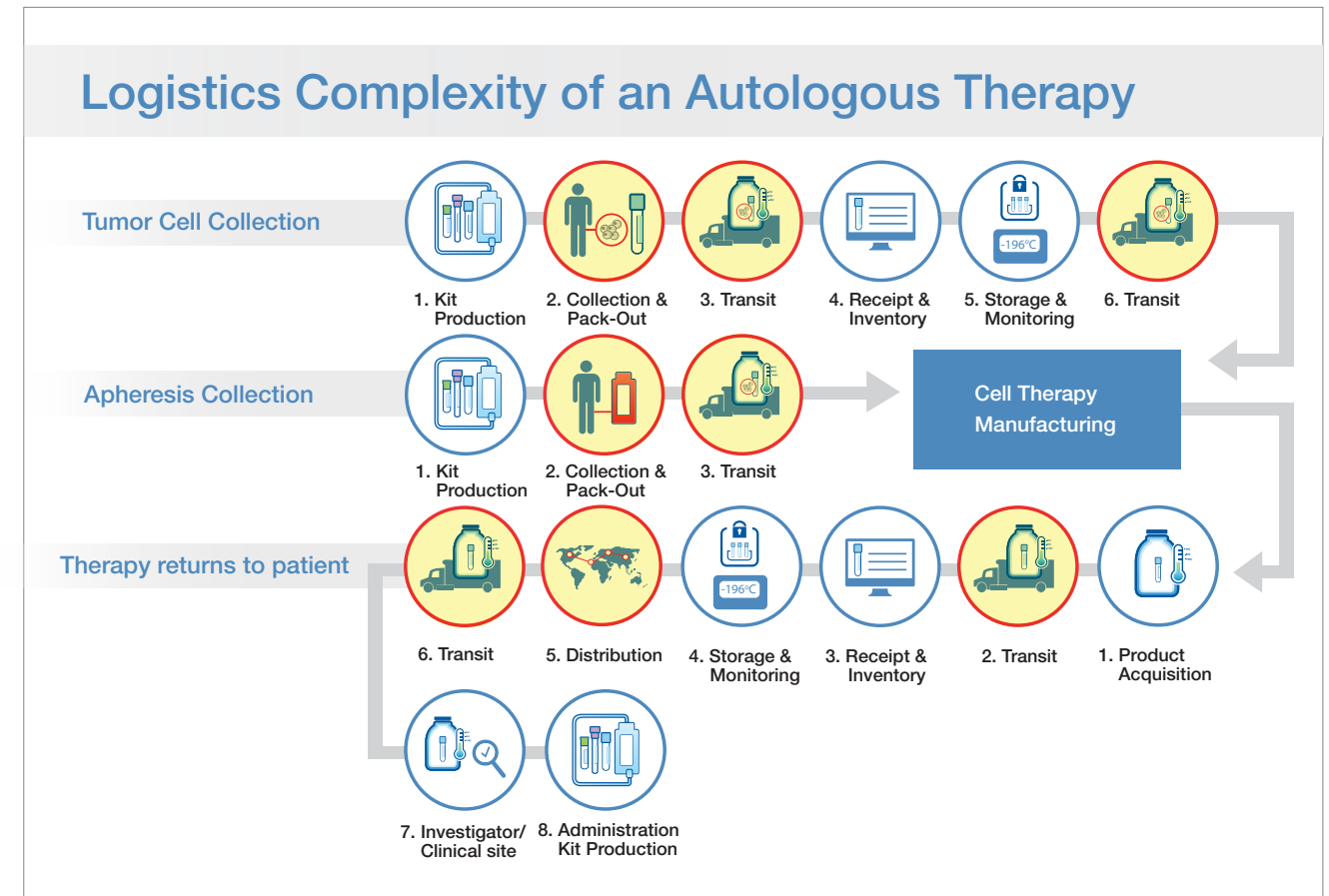
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Package and Shipping Qualification

A qualified shipping solution is a critical element for ensuring that your therapy is judged on its clinical efficacy and not by deficiencies created by packaging or shipping failures. The points where shipping and packaging qualification are needed are highlighted on our diagram to the right.

It is imperative that each individual dry shipper be tested. There can be significant variation from dry shipper to dry shipper. This is not just the case when looking at different makes and models but when gauging performance of the same model and same lot. To illustrate, consider the graph on the next page. This graph displays the static hold time for 20 dry shippers, all brand new, same model, and same lot.

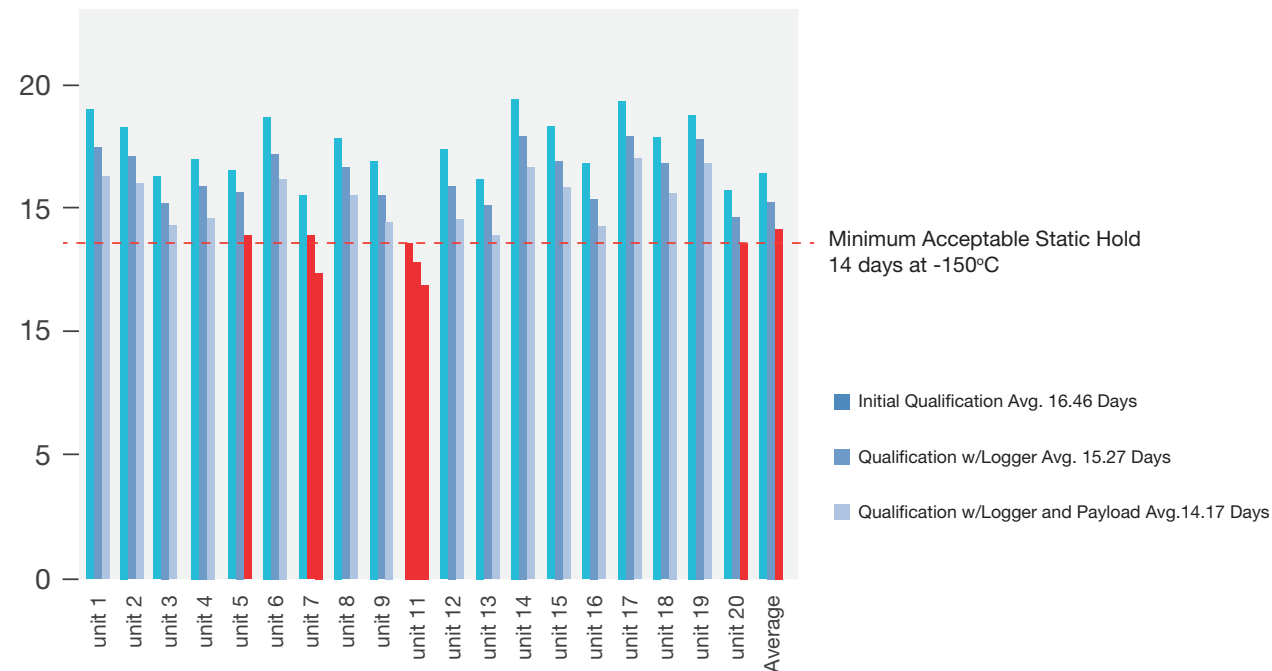


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Package and Shipping Qualification

When 20 pre-qualified new shippers were tested after installation of the data logger and addition of the payload, five failed to meet minimum hold static time.



Static Hold Time for New Units (Days at or below -150°C)

This graph illustrates the variance in new shippers, right out of the box. It should be noted that each element of the shipping configuration (data logger, rack, baffles, packaging, and the product) will influence hold time. In order to get a true understanding of the expected performance of a dry shipper it must be validated with all elements in place.

Beyond the shipper itself, there are three key variables that influence the amount of temperature hold time required for each shipment:

The first is the time needed for an international shipment to clear customs. While in most cases customs can be cleared in 24 to 48 hours, in some countries it can be considerably longer. Clearance times vary not only by country, but also with the volume being processed on a given day, delays caused by documentation problems, local holidays, weekends, and inexperience on the part of the agent, just to mention a few. A safety margin must be calculated into the temperature hold requirement.

Secondly, these dry shippers are often used for temporary storage at the site of administration. How much time is needed to prepare and administer the therapy to the patient once it arrives at the clinical site?

Finally, you need to consider the amount of temperature hold lost in mishandling. Dry shippers are designed to be used in an upright orientation. Any deviation from straight up and down will rob the shipper of valuable hold time. For example, a shipper that is tipped over on its side for eight hours can lose as much as 50 percent of its hold time. Given these variables it is important that you choose shippers that allow for the longest reasonable hold times, and that you validate them in both static and dynamic conditions.

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Package and Shipping Qualification

While the shipping of cryo-preserved materials may be the most challenging it is of equal importance to insure that all biologics are shipped in qualified containers designed to meet the temperature and duration requirements of that material. The key to success is finding a solution that meets temperature and duration requirements in a procedure that can be easily implemented by the individuals performing the pack out. Remember, in late stage trials the pack out of vital component biologics may be done in hundreds of locations by individuals with limited experience in the transport of these materials. The best solutions are those that are the least complicated. The more complex the process, the more likely you will have deviations and failures. Unfortunately the easiest solutions are often the most costly, and you will need to evaluate this cost versus the risk of loss for each shipping requirement.

It is also important to consider where you are shipping and when. A qualified solution that works in Maine in January may not work in Phoenix in August. There are several options but the two most common include creating a summer and winter shipping profile or creating a universal shipping solution. Summer and winter profiles are generally the most cost effective but can require tricky decisions during the change of seasons and weather patterns. The universal solution can be more costly but is considerably easy to manage.



The final consideration is volume. Autologous drugs are unique in that the primary active pharmaceutical ingredient are human cells that must be harvested, shipped and incorporated into the drug manufacturing process with a very tight time window. While this is generally a manageable process during the clinical trial phase it becomes a monumental logistical challenge in commercial production. In Autologous drug production the manufacturing process begins when the cells are harvested. This means you will need an effective scheduling and tracking system in addition to an effective way to transport viable material. There is no way to manage production without a tight scheduling and tracking process in place. It is wise to begin laying this ground during your phase II trial and it is imperative that you are testing a commercial volume solution by phase III.

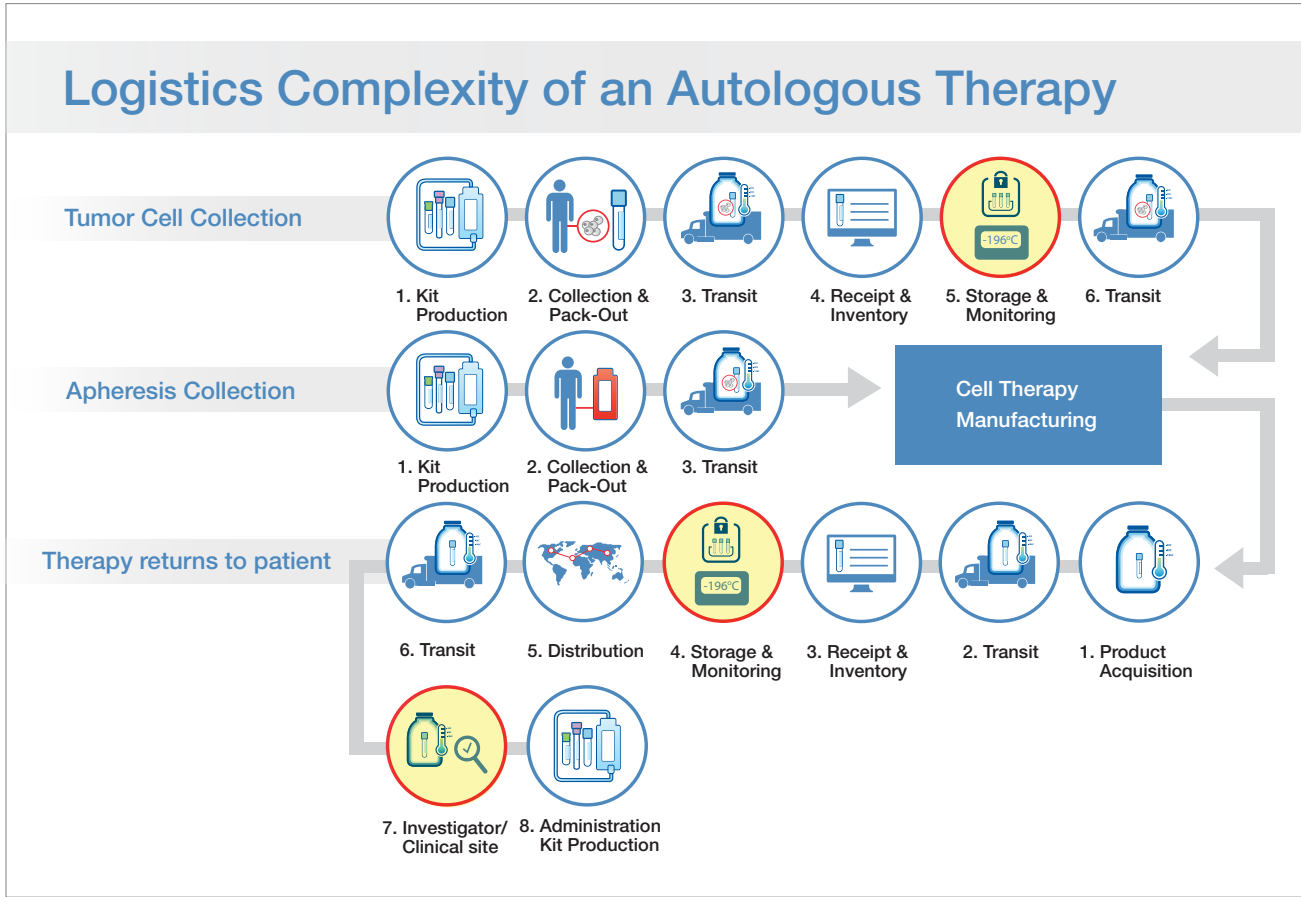


4 Storage Equipment Validation



Storage Equipment Validation

It goes without saying that validation of the equipment used to maintain such valuable material is an absolute requirement of any trial. What I would like to emphasize here is that just as the shipper can vary in performance and must be qualified, the storage equipment must also be validated to perform in the specific way it is to be used relative to the material. The need for equipment validation is highlighted in this version of our process flow diagram.



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Storage Equipment Validation

As an example, let's say the finished drug product has a maximum storage temperature of -150°C and will be stored in a vapor phase dewar. As you may know, there are variations in the temperature of any vapor phase vessel; the temperature is always colder at the bottom and warmer at the top. In order to determine the optimum storage location in the tank we must validate with multiple probes to determine the temperature gradient of the vessel. See the illustration to the right.

We can see that only a portion of the vessel, the area at or below the -150°C level, is appropriate for storage of the finished product. It also indicates that a custom probe will have to be placed in that location in order to monitor the material appropriately. Specific equipment validations should be performed on all equipment used for the storage and handling of the drug product or any of the constituent cell products. This would include freezers, refrigerators, LN_2 vessels and cryo-carts.





5 Process Qualification

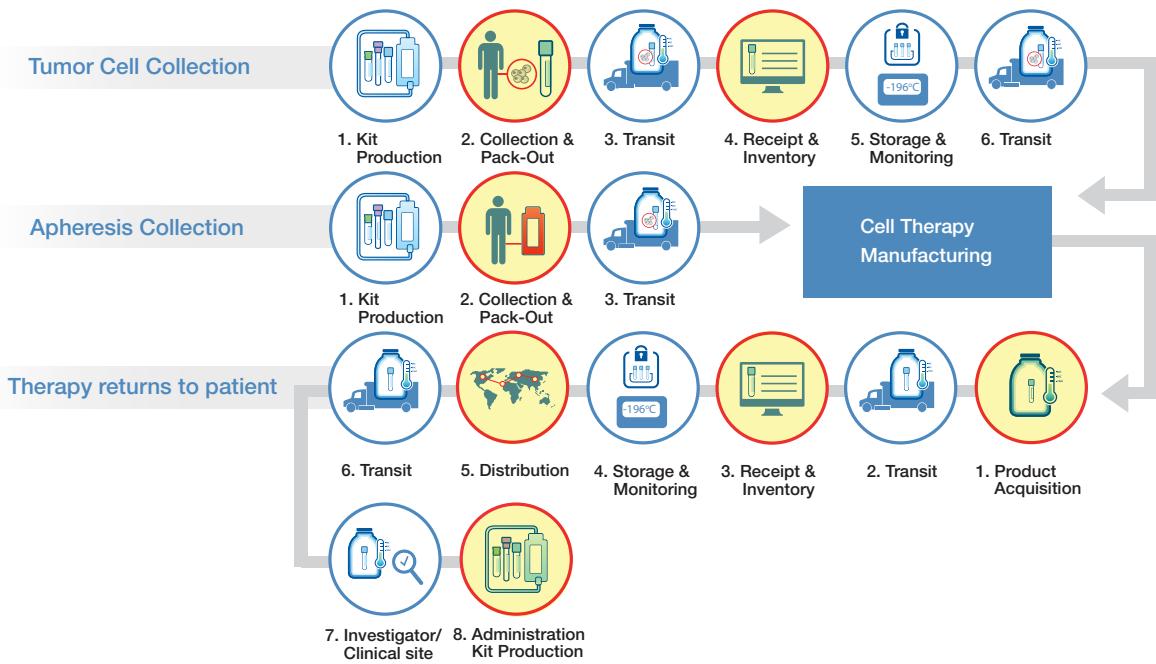


Process Qualification

In much the same way we validate equipment to ensure it will meet requirements, we must also test the procedures used for handling. At any point where temperature-sensitive material is physically handled, a process qualification should be considered. The flow chart shows the areas where process qualification needs to be evaluated.



Logistics Complexity of an Autologous Therapy



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Process Qualification

In general, process qualification ensures that the integrity of the material is maintained while it is outside qualified/validated equipment and being handled by people. Process qualification ensures that it is maintained within acceptable temperature ranges as well as within time-out-of-temperature standards. Process qualifications are always a good idea but are strongly recommended when:

- The volume of material is small (less than 2ml)
- The temperature windows are particularly tight (for instance, no warmer than -150°C or colder than -180°C)
- Significant handling is involved, such as re-packaging or labeling in large batches

It is also important to consider the cumulative effect of temperature variation on your product. Let's take the example of a product stored in cryovials; assume these vials are stored 50 units to a box, and stacked four boxes to a rack. Each time a dose is removed from storage, the rack is lifted into an ambient environment. All the vials in the rack—not just the one removed—are briefly exposed to a (short duration) temperature excursion.

While a great deal of time is expended determining the effect of a single temperature excursion, far less is paid to the effect of cumulative exposure. In the example above, the first dose is exposed once while the last dose may be exposed two hundred times. While the actual handling times will vary with each product it is a good practice to develop processes that minimize product exposure and validate those processes to insure that they do indeed meet your specifications.





⑥ Chain-of-Custody Documentation



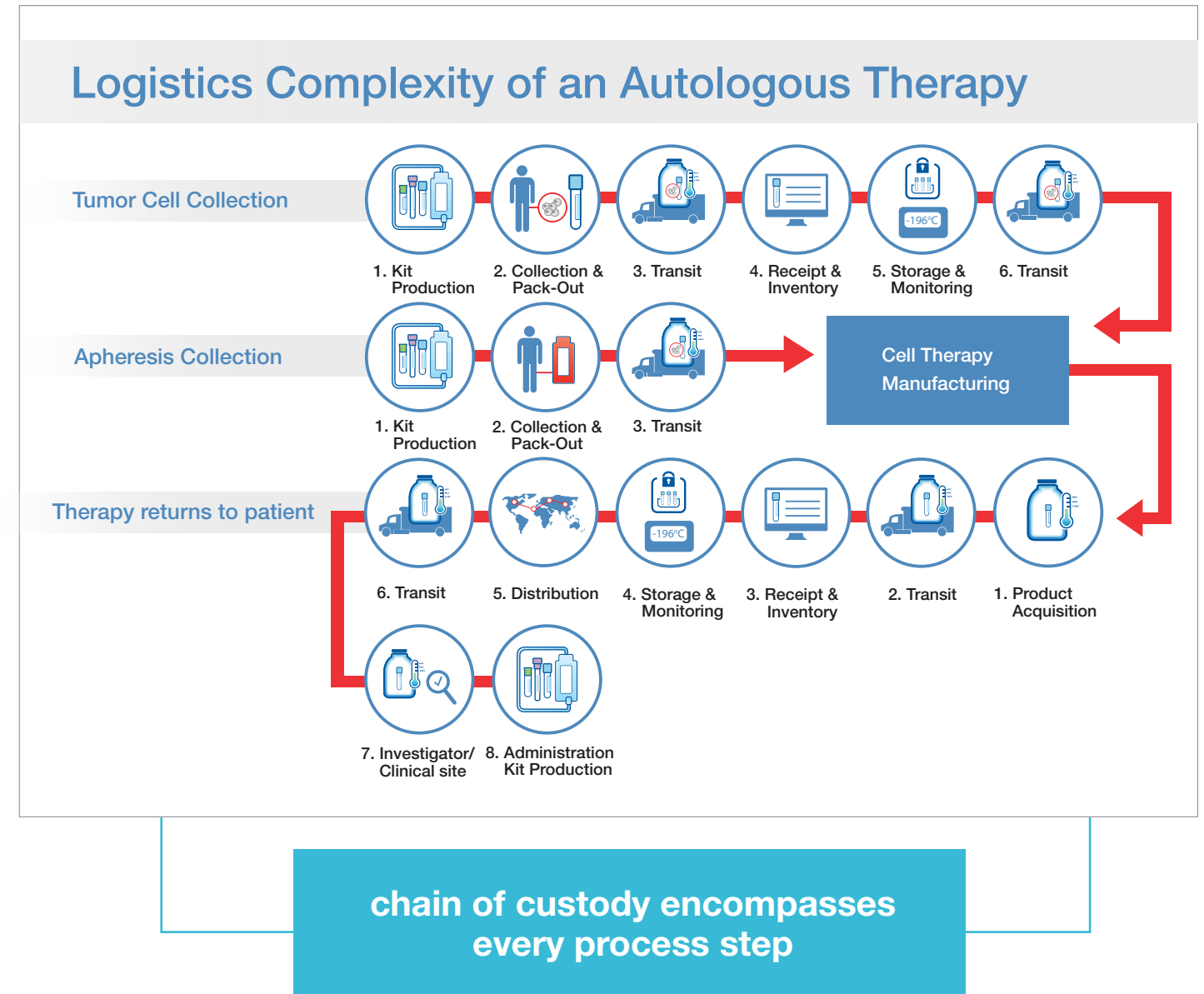
Chain-of-Custody Documentation

In the case of any cell therapy drug product, the chain of custody begins at the point of manufacture and concludes with administration into a patient. Autologous drugs require that the chain extends backwards, to the collection of the constituent cells used for drug production. In all cases, the chain of custody documentation has to capture the location, security and temperature of the material at all times: this chain of custody encompasses every process step in our diagram.

Given that a chain is only as strong as its weakest link, documenting chain of custody necessitates that all processes be given equal weight with regard to collecting and documenting accurate and complete data. A loss of documentation at any point renders the chain inadequate.

Maintaining suitable documentation of a chain can be far more difficult than it first appears. Because processes occur in different settings and by multiple individuals and organizations it is imperative that a robust procedure be in place to ensure that the requisite data is compiled and collected in a standardized fashion. This documentation must be maintained at a per dose level and be readily available for review when necessary.

Special consideration must be given to the last link in this chain—the point of administration. The clinical site, where the final leg of storage, processing and administration occurs, is invariably the most difficult area for collecting the necessary documentation on a consistent basis.



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7 A Final Word



A Final Word

If the logistical challenges I have discussed here give you pause, then I have done my job. We want your cell therapy to be successful, and by informing you well in advance about the issues you will face in delivering a cell-based therapy to a patient, we hope to help prevent unnecessary delays and costs downstream. An experienced logistical partner can help smooth the entire round trip from the initial collection of cells to the delivery of the finished dose back to the waiting patient.



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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