ThermoFisher SCIENTIFIC

CELL THERAPY LOGISTICS

ADVANCED THERAPY

fisher clinical services

• API • BIOLOGICS • EARLY & LATE PHASE DEVELOPMENT • CLINICAL TRIAL SOLUTIONS • LOGISTICS SERVICES • COMMERCIAL MANUFACTURING

TABLE OF CONTENTS

INTRODUCTION

Much of the discussion in the cell therapy industry today focuses on the complexity of manufacturing and the unique characteristics of each dose. However, the ultimate success of a cell therapy clinical trial rests on the ability to deliver a viable, potent product to the patient. Ensuring this living drug is delivered to the right patient at the right time, location, and temperature is essential to patient safety and product effectiveness. Having a sound logistics strategy is critical to achieving this goal.

In comparison to small molecule therapeutics and currently available biologics, the logistics management of cell-based material is drastically more complex, requiring ultra-cold temperatures, rigorous quality standards, and coordination between the clinic, biorepository, and manufacturer. Without a comprehensive logistics strategy to manage this and more, the therapy may never get to the patient.

This eBook will walk through key considerations for developing a successful logistics strategy for the management of cell-based material, including:

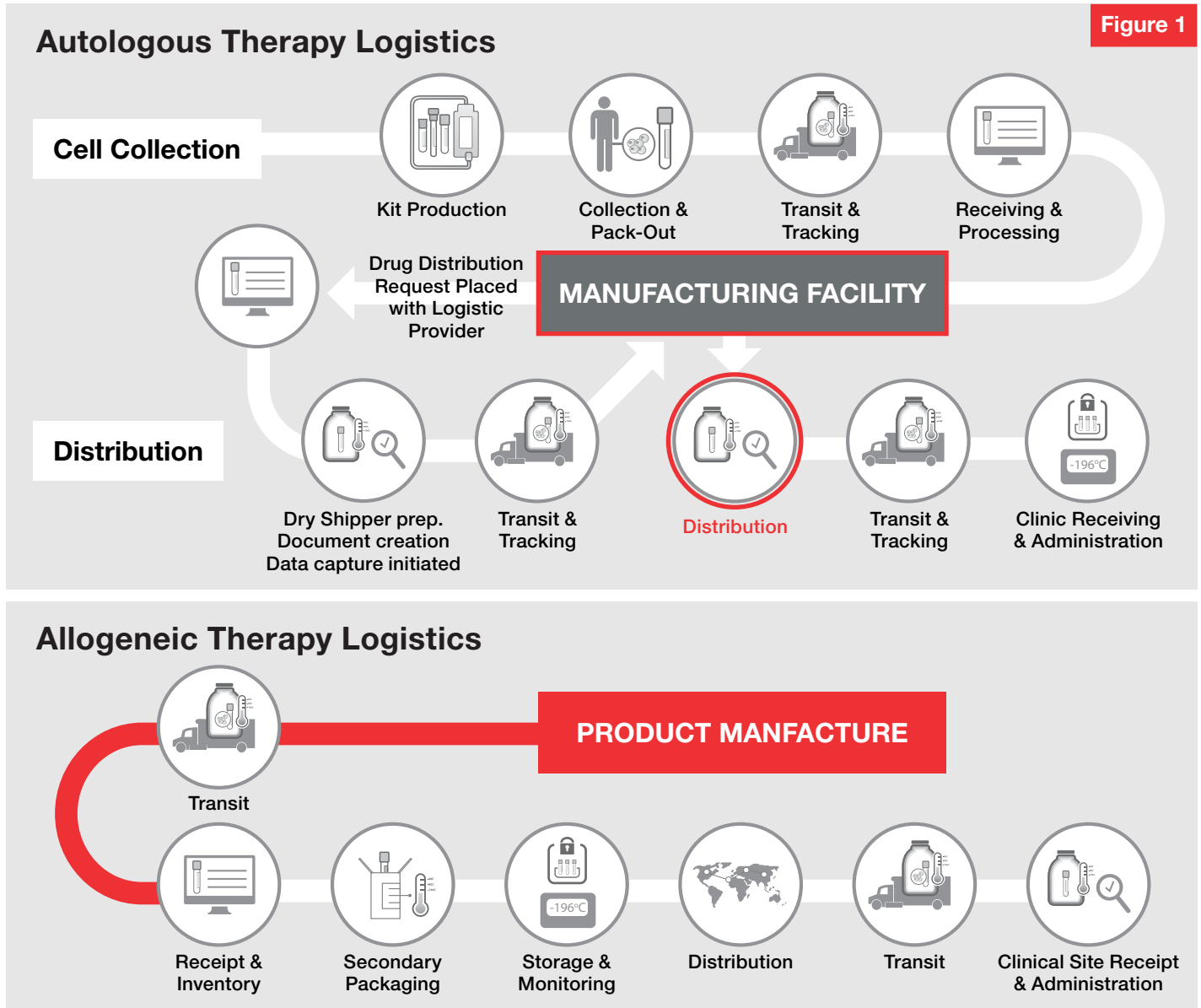
- Process Validation and Standardization
- Shipping and Packaging Qualification
- Storage Equipment Qualification
- Chain of Custody Documentation
- Temperature Monitoring
- Secondary Packaging and Labeling

THE UNIQUE COMPLEXITY OF A CELL THERAPY LOGISTICS STRATEGY

At a high level, manufacturing a cell therapy product requires that patient or donor cells be collected and transported to a manufacturing facility, where they will be processed and developed into a drug product, and finally distributed to the clinic for patient administration. The movement and storage of cells and drug product is conducted at various temperatures, from 2°C to 8°C to cryogenic temperatures, depending on the material. The supply chain will look slightly different for autologous therapies, which uses the patient's own cells in the manufacturing process, and an allogeneic product, which typically relies on donor cells and can be administered to a broader patient population. Combination therapies are also becoming more common, adding another component to the therapy with different storage and shipping requirements. Figure 1 (right) describes the basic supply chain for autologous and allogeneic cell therapies.

Both require cell collection from multiple sites, shipments at multiple temperatures, and strict chain of custody documentation throughout the entire process, but each cell-based product will require unique adaptations of the supply chain in order to ensure successful delivery to the patient.

Figure 1



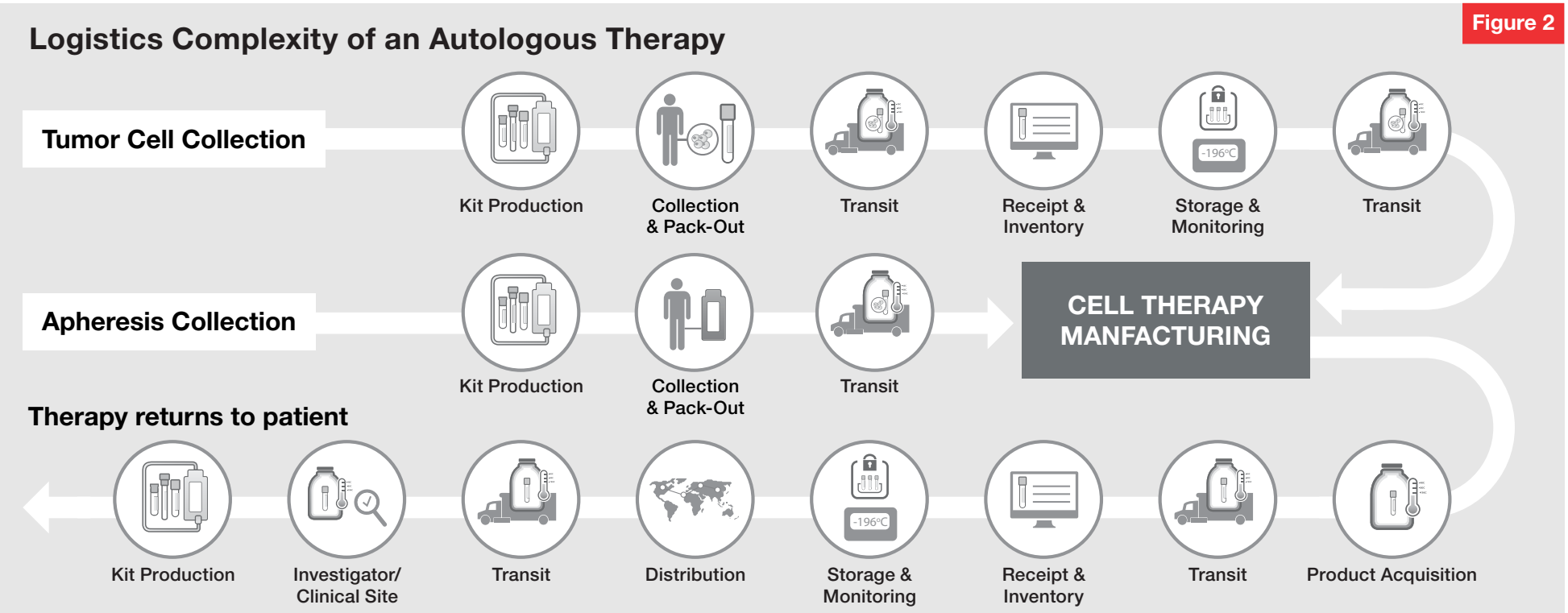


Figure 2 illustrates this complexity using the example of a cell therapy that involves the collection of both tumor samples and apheresis (dendritic cells).

- 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 vapor phase liquid nitrogen dry shipper or dewar at cryogenic temperatures; and
- Finally, doses are shipped, again in a dry shipper, to the clinical site for administration to the patient

In this example, there are five different shipments of three different materials at four different temperatures. The remainder of this eBook will use this unique example to highlight the critical decisions that will ensure the integrity of this cell-based material throughout the supply chain.

5 Shipments
4 Temperatures
3 Materials
1 Therapy

PROCESS VALIDATION

As previously stated, generally cells will be collected from the patient and sent directly to the manufacturing site (usually at 2°C to 8°C).They will then be processed into a drug product, and finally transported back to the patient in a dry shipper or placed into cryogenic storage pending distribution. But what about the steps in between? What happens when the drug product is taken out of storage to be prepared for shipment? What happens when the drug product arrives at the clinical site? In general, process validation ensures that the integrity of the material is maintained while it is outside qualified equipment and being handled by technicians.

Process validations are always a good idea but are strongly recommended when:

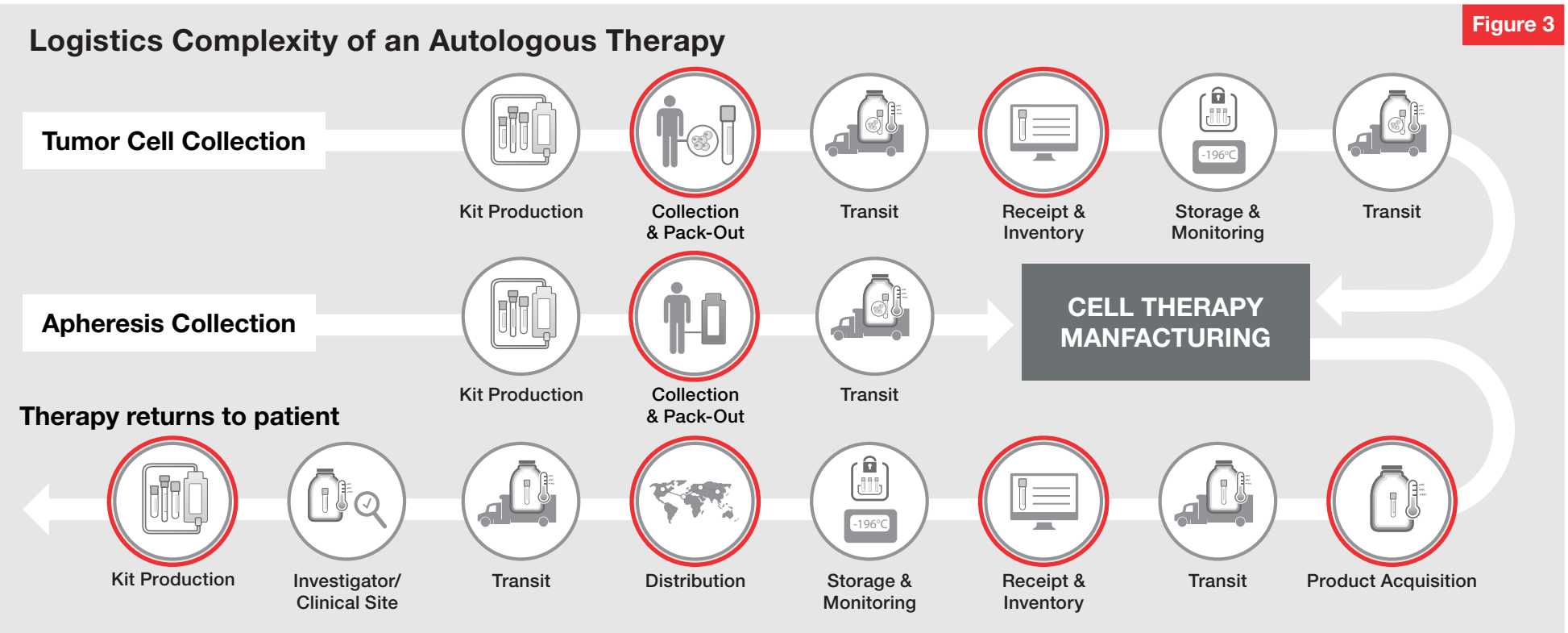
- The volume of material is small (less than 2 ml)
- The temperature windows are particularly tight (for instance, no warmer than -150°C or colder than -180°C)
- Significant handling is involved, such as complex packaging or labeling requirements

It is important to consider the cumulative effect of temperature variation on the product. Using an example of a product stored in cryovials, assume these vials are stored 50 units per box, 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 warmer temperature.

A validated process will minimize any time out of temperature. 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 ensure that they meet the specifications.

The flow chart in Figure 3 shows the areas where process validation needs to be evaluated.

Figure 3



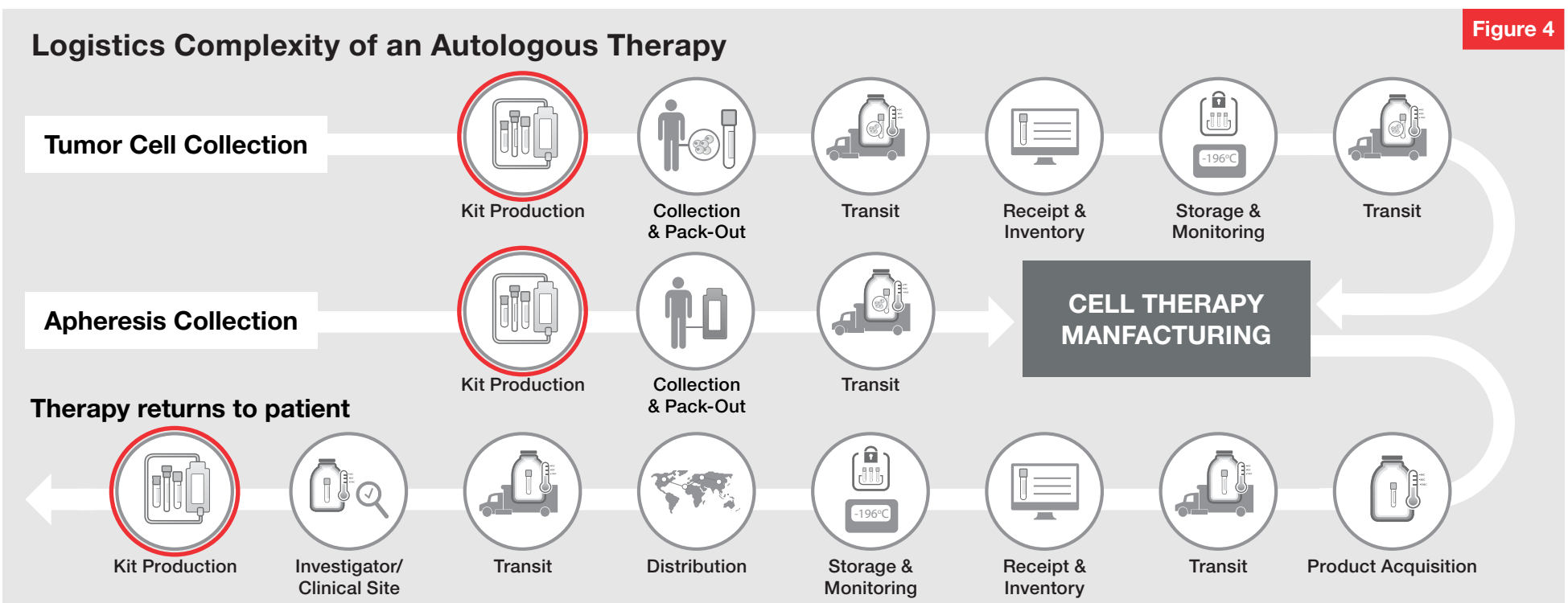
STANDARDIZATION OF PROCESSES AND PROCEDURES

The supply chain may involve outside actors such as contract manufacturing organizations (CMOs) or clinical sites across different geographies. Within the validated workflow, it is important to standardize as many processes and procedures as possible to avoid unwanted variation throughout the process.

As an example (Figure 4, highlighted), kits can be a very effective tool to identify the materials used in these processes and drive consistency in their execution. In the case of apheresis, collection kits can be particularly important as they ensure standardized collection and pack-out product and procedure, which is a key consideration to an effective package qualification. The value of kits as standardization tools increases as a drug candidate traverses later trial stages. Early stage (phase I and IIA) trials are often conducted at only one or two clinical sites. As the product moves through phase IIB and phase III trials, the number of patients and clinical sites increases, and it becomes far more difficult to ensure each site follows the exact same procedures for cell collection, product preparation, and administration. The use of a kit ensures that the same materials are used across sites, instructions are available for each procedure, labeling is consistent, and in the case of collection kits, makes certain that a qualified shipping solution is used for the transit of the critical patient cells after 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 process variation and ensure that the clinical results reflect the efficacy of the drug and not variations in handling.

Figure 4



SHIPPING AND PACKAGING QUALIFICATION

Just as important as a standardized, validated workflow and standardization is a qualified shipping solution. It is a critical element for ensuring that a 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 in Figure 5.

Figure 5

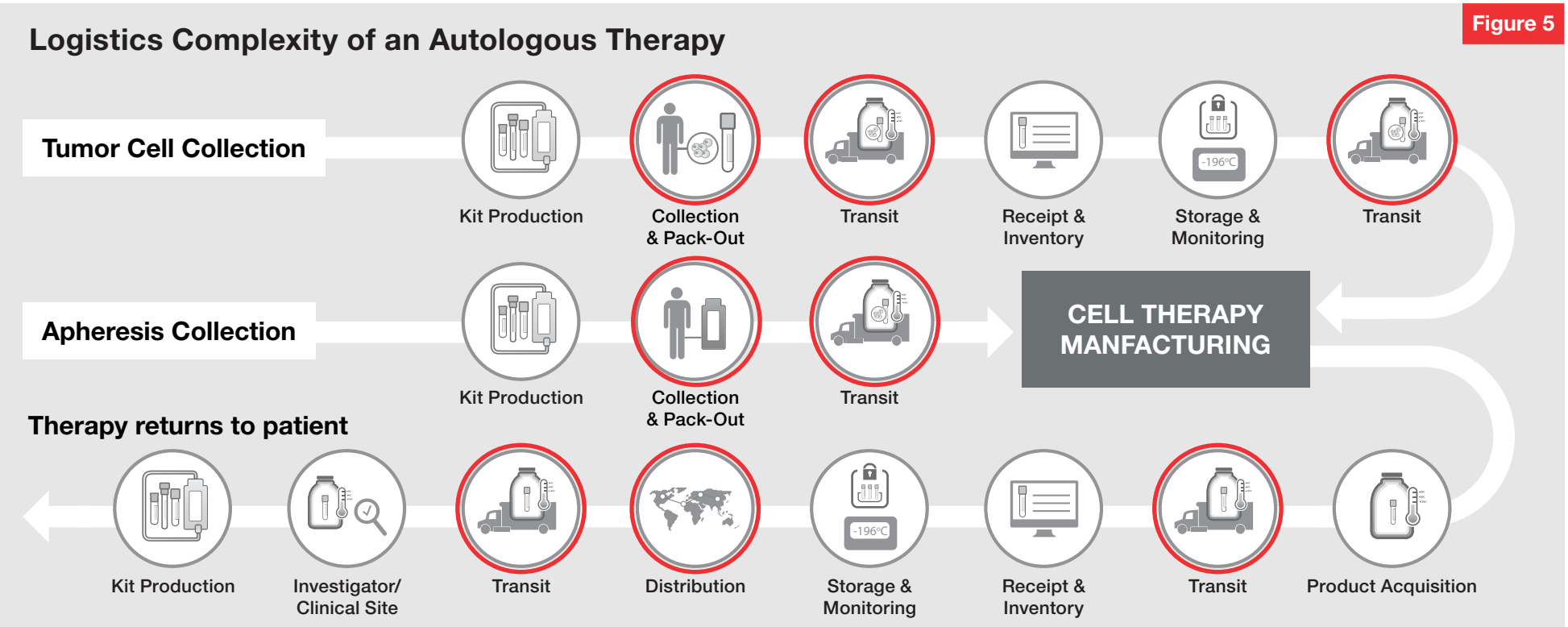
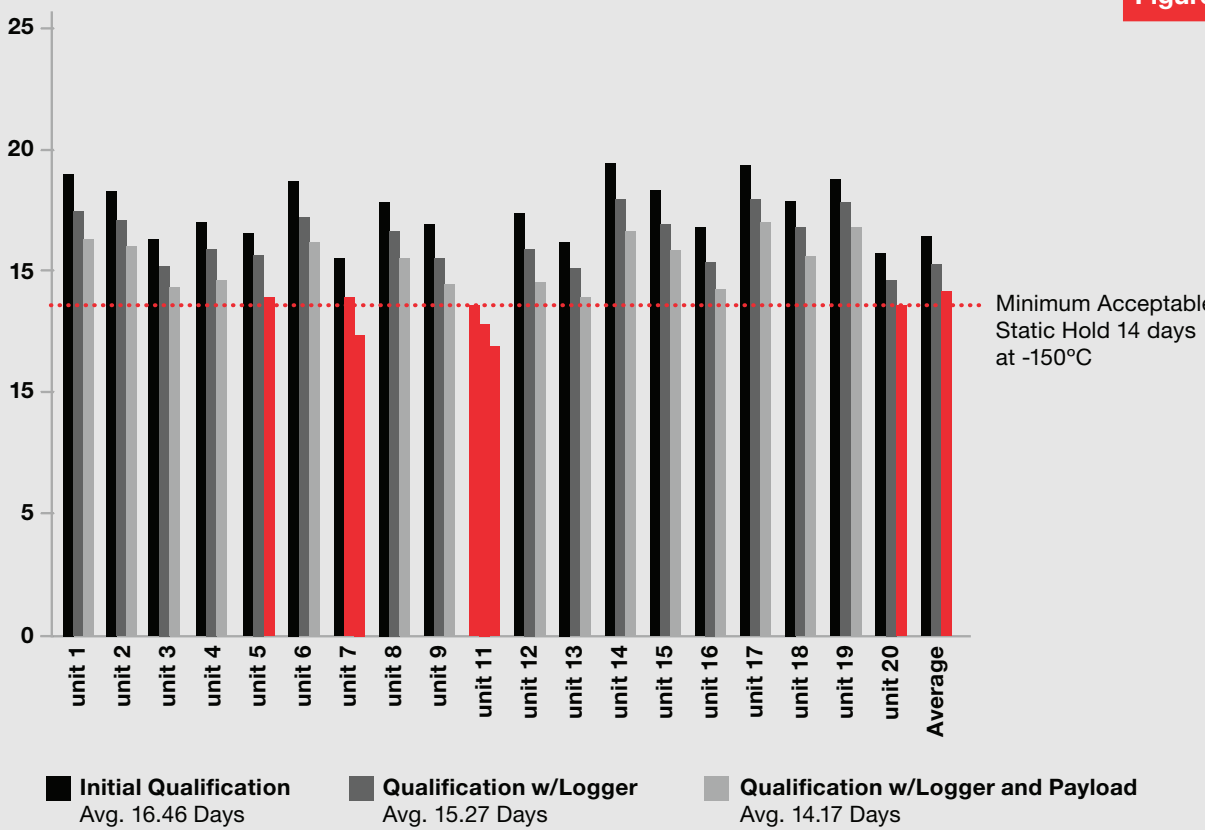


Figure 6



The qualification of a shipping solution should not be confused with blanket qualifications issued by the manufacturers. Manufacturers' 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. To illustrate, consider Figure 6.

This graph displays the static hold time for 20 brand new dry shippers, all the same model and lot. When these 20 manufacturer-qualified new shippers were tested after installation of the data logger and addition of the payload, five failed to meet minimum hold static time.

Beyond the shipper itself, there are situations that need to be considered when determining the hold time that is needed:

- **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 can be caused by documentation problems, local holidays, weekends, and inexperience on the part of the agent. A safety margin must be calculated into the temperature hold requirement.
- **Using dry shippers 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? What if the patient misses his or her appointment and has to reschedule for several days later?
- **Amount of temperature hold lost in mishandling.** Dry shippers are designed to be used in an upright orientation. Any deviation 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% of its hold time.

It should be noted that each element of the shipping configuration (data logger, rack, baffles, packaging, and the product) will influence hold time. To get a true understanding of the expected performance of a dry shipper it must be validated with all elements in place.

Given these variables it is important to choose shippers that allow for the longest reasonable hold time and to validate them under both static and dynamic conditions. Equally important is using a pack-out procedure that can be easily implemented by the individuals performing the task. In late stage trials, the pack out of materials may be done in hundreds of locations by individuals with varying experience in the handling and preparation of materials for transport. Devising a simple process will help to limit deviations and failures.

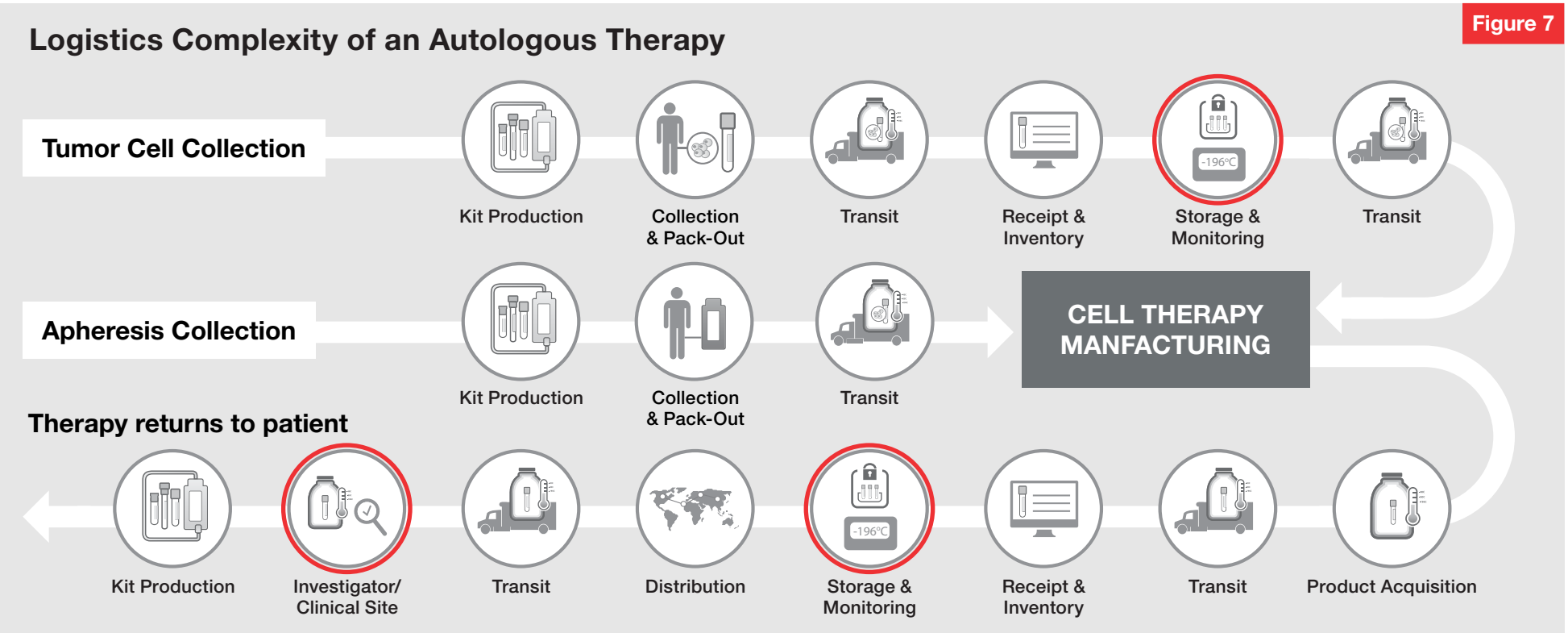
It is also important to consider when and where shipping will take place. A qualified solution that works in Maine in January may not work in Phoenix in August. There are several options, but the two most common include creating a summer and winter shipping profile or creating a universal shipping solution. 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 costlier but is easier to manage.

The final consideration is volume. Cell therapies are unique in that the primary active pharmaceutical ingredient are human cells that must be harvested, shipped, and incorporated into the drug manufacturing process within a tight timeframe. While this is generally a manageable process during early phase clinical trials, it becomes a monumental logistical challenge in commercial production. In autologous drug production the manufacturing process begins when the cells are harvested from the patient. Incorporating a scheduling and tracking system could be beneficial to streamline production and transport early on and drive efficiency as the clinical trial advanced.

STORAGE EQUIPMENT VALIDATION

The qualification of the equipment used to maintain such valuable material is a baseline requirement of any trial. Similar to the aforementioned reasons for qualifying a shipper, storage equipment must also be qualified to perform in the specific way it is to be used relative to the material. The need for equipment qualification is highlighted in this version of our process flow diagram (Figure 7).

Figure 7



Storage Equipment Validation (continued)

As an example, say a finished drug product has a maximum storage temperature of -150°C and will be stored in a vapor phase dewar. However, there are variations in the temperature of any vapor phase vessel; the temperature is always colder at the bottom and warmer at the top. To determine the optimum storage location in the tank, it must qualify with multiple probes to determine the temperature gradient of the vessel.

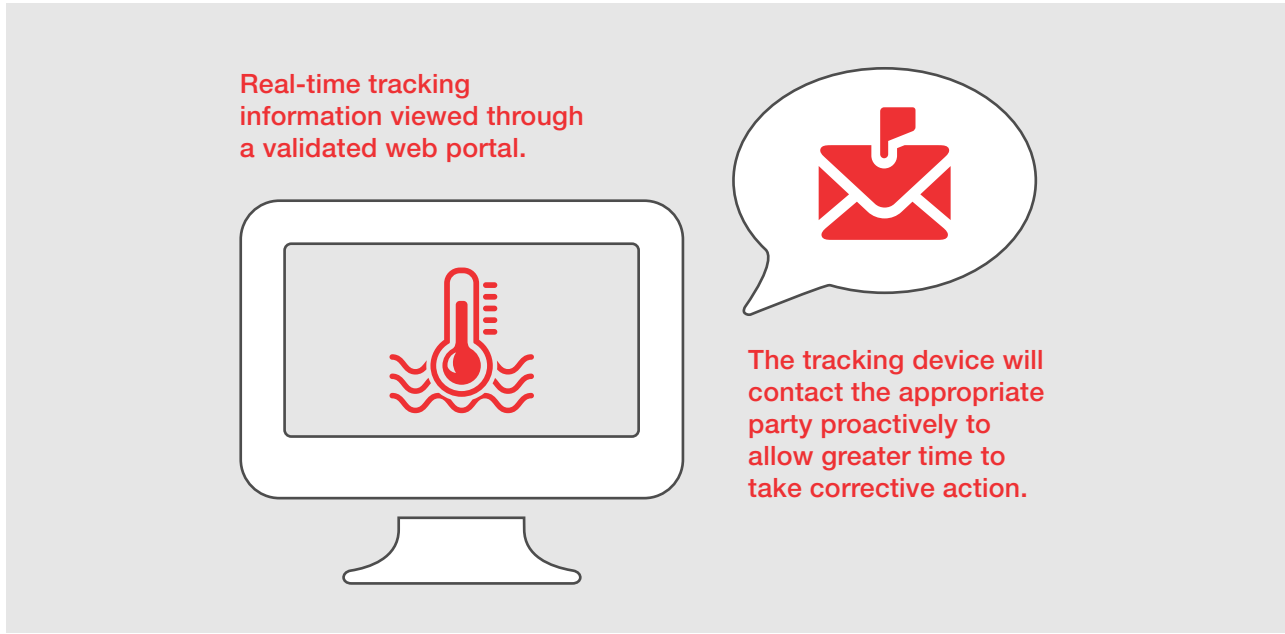
Only a portion of the vessel, the area at or below the -150°C level, is appropriate for storage of the finished product. It also indicates that a custom probe will have to be placed in that location to monitor the material appropriately. Specific equipment qualifications should be performed on all equipment used for the storage and handling of the drug product or any of the constituent cell products. This would include freezers, refrigerators, LN2 vessels and CryoCarts.

REAL-TIME TEMPERATURE MONITORING

As previously mentioned, verifying that the appropriate temperature has been maintained throughout the supply chain is an important aspect of chain of custody documentation. There are data loggers available that will provide real-time tracking information viewed through a validated web portal. Sophisticated tracking technology can be set up with exception criteria. Exception criteria will allow acceptable windows to be set for conditions critical to the wellbeing of the product. If a parameter exceeds its critical window, the tracking device will contact the appropriate party proactively to allow greater time to take corrective action.

Corrective action could involve a phone call from a project manager to the airport personnel or courier to set the shipper upright, or it could involve preparing a second shipment so the patient does not miss a dose. Corrective action is not always possible, but can be attempted with the help of real-time monitoring.

Geo-fencing allows the clinic or manufacturing site to prepare to receive the material. Through an online web portal, a radius around the delivery site is created. Once the shipment enters this radius, a specific person or group of people is notified. This will help ensure that the treatment is not left out on a loading dock and is processed immediately.



SECONDARY PACKAGING AND LABELING

Secondary packaging and labeling is an integral element in the product distribution chain. The following are several considerations for choosing the right label and packaging.

Secondary Packaging:

Secondary packaging has two functions: protect the product and hold the label. Most secondary packages are custom built to meet the specifications of the drug and trial. The packaging can hold as many drug containers as is deemed necessary for delivery to a single patient or center. A shipment may contain a single vial or 400 vials. Alternatively, a single shipment could contain one to 10 cassettes if cryo-bags are the container of choice. Secondary packaging is generally made of cryo-compliant cardboard and is cut to custom fit the vial. The cost difference between 100 and 10,000 units is marginal, so if one is currently in a phase I or II it may make sense to purchase the number of cartons required through phase III.

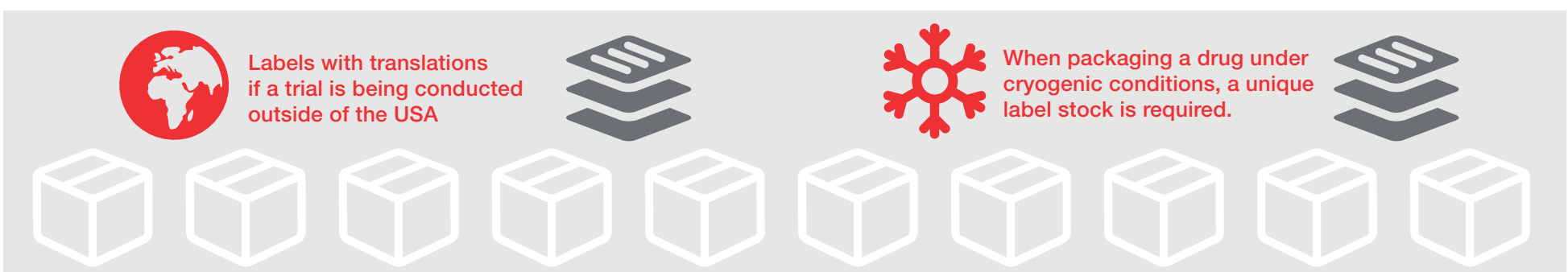
An important companion to the carton is the transit rack for the dry shipper. While standard options are available on the market, custom transit racks can be developed to fit the carton and provide maximum protection during transit. Like the dry shipper, the rack is reusable and considered part of the total shipping solution.

The final step in the process is the marriage of container and vial. Because this is a cryogenic drug product, the actual packaging procedure must be executed under cryogenic conditions. The best method for this operation is to perform the process in a CryoCart at a temperature no warmer than -130°C. This process must be conducted under a Batch Record process. The Batch Record process begins with the creation of Master Batch Record (MBR). The MBR is the set of instructions that are approved prior to execution. The MBR governs the actions, temperatures, equipment, relevant SOPs, and documentation of the process. Each individual instance of packaging and labeling will be documented through an individual Batch Record whether it is a lot of 10,000 or a single autologous dose. Batch records are issued based on Quality-approved MBRs. The conditioning of the carton, removal of the drug from storage, quality checks and vial insertion are all performed based on MBR instructions and batch record documentation. Once packaged, the drug product can be inventoried as packaged product or sent to distribution for transit to a clinic.

Secondary Labels:

Labels must meet the requirements of the regulatory agencies in the countries where the trial will be conducted. Once this requirement has been met, the size of the label needs to be considered. This is dependent on both the size of the secondary package and the volume of text. Note that if a trial is being conducted outside of the United States, labels will need to be printed in the local language, and some countries require multiple languages. Each language should be translated and retranslated, preferably by a different source, and a proof should be made for each version. All translations need to fit on the same size label, which can be particularly challenging if booklet labels are used.

The next step is to choose the label stock. When packaging a drug under cryogenic conditions, a unique label stock is required. There are several options, so asking the label service provider how their chosen label stock has performed under cryogenic conditions, is critical. The label should be applied at least 48 hours prior to cryogenic packaging to ensure the adhesive has adequate time to cure and adhere to the package.



PUTTING IT ALL TOGETHER

The final section of this eBook will take a comprehensive look back at the example of a cell therapy requiring both tumor cell and apheresis collection and describe how each of the considerations outlined thus far contribute to the successful delivery of drug to patient.

Tumour Cell Collection

The drug production process begins with the creation of a kit that will be used to collect the tumor. The kit will have a unique patient ID that will be used throughout the collection, manufacturing, distribution, and administration of the drug product. The unique ID will ensure the right drug is infused in the right patient. The kit will also include a qualified shipper for transporting the tissue to an interim storage point, where it will be received, inventoried and stored at -80°C until ordered for manufacture. The -80°C freezer will have been qualified to ensure that it will remain within the correct temperature range when storing these critical materials. Once ordered, it will again be packaged in a qualified shipper and transported at temperature to the point of manufacture, where it is stored until manufacturing begins.

Apheresis Collection

Unlike the tumor collection process, there is no interim storage step for apheresis collection—the cells must be shipped at a temperature of 2-8°C from the clinic to the manufacturing facility within 24 to 48 hours. Like tumor collection, kits are essential in the collection process, both in ensuring standardized collection and standardized pack-out for transportation to the manufacturing facility. The kit includes the patient-specific ID labels and collection containers as well as a qualified shipping container to keep the cells at the correct temperature. The cells are shipped with the addition of an important step—notification from the logistics manager to the manufacturer that the shipment is on the way. This way, the manufacturer will be ready to process the cells immediately upon arrival. Once the shipment is received by the manufacturer and the patient ID is confirmed, the manufacturing process can begin.

Therapy Returns to Patient

Once manufactured, the dose or doses are cryopreserved and loaded into a qualified LN2 dry vapor shipper for transport to a distribution facility, where the material is received and inventoried. The material will go through a process of quarantine, and it will ultimately be packaged and labeled. At the distribution center, the individually packaged doses are inventoried and stored in LN2 vapor phase until requested by a clinical/investigator site for patient use. Each requested dose is shipped in a qualified dry shipper to the clinical site for administration. Again, pack-out should occur under cryogenic conditions to ensure minimal time out of environment. The qualified shipper should be equipped with a temperature monitoring system to allow for continuous visibility of the product until it reaches the clinic.

A Final Word

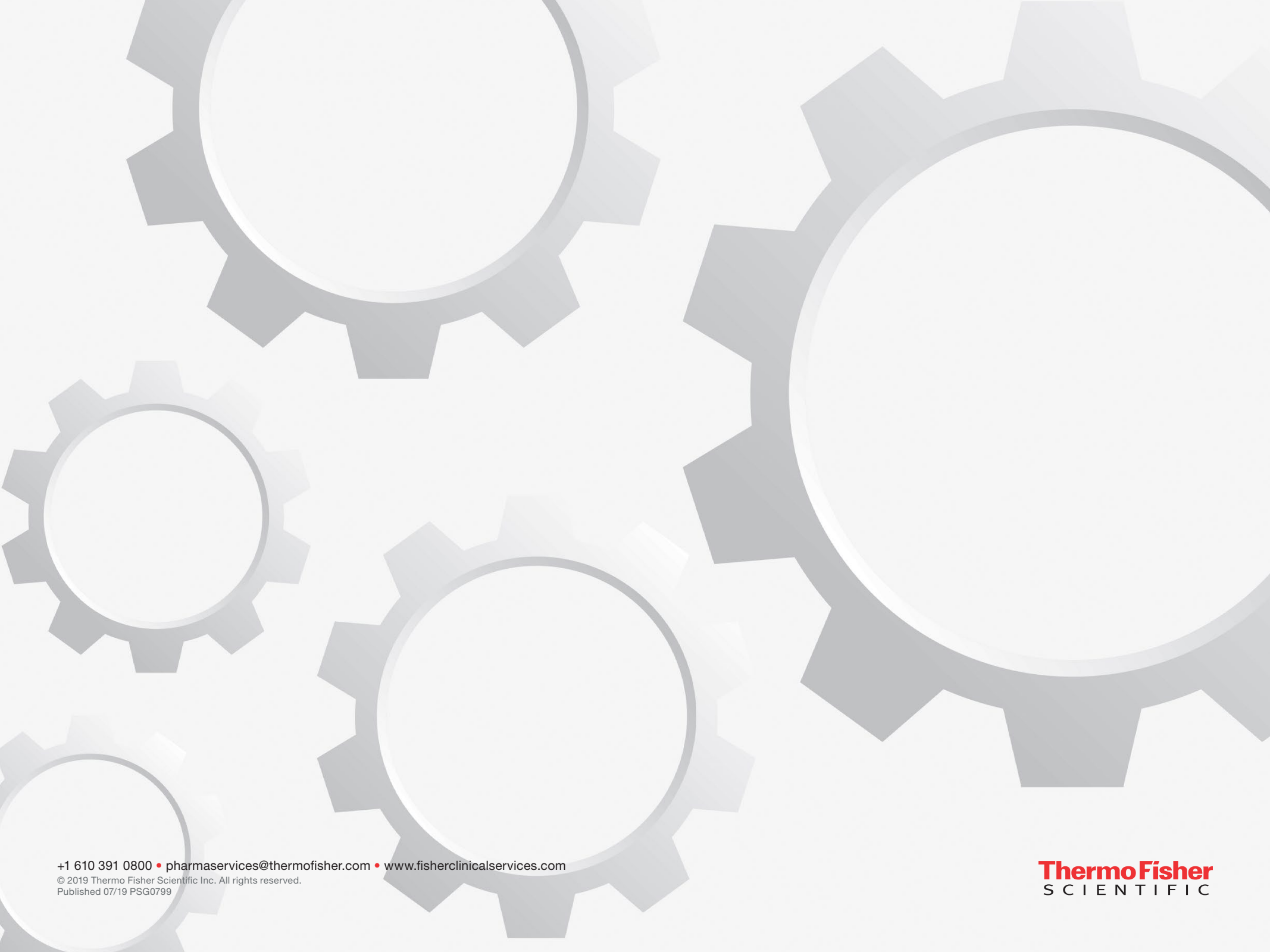
Cell therapy is a challenging space that is constantly evolving, and having a basic awareness of the issues is essential for ensuring the success of your program. An experienced logistical partner can help smooth the entire trip from the initial collection of cells to the delivery of the finished dose back to the waiting patient.

ABOUT US

With unwavering commitment to service, science and process engineering, Thermo Fisher Scientific is powered by people with an exceptional commitment to quality, deeply instilled ethics of personal responsibility and unrivaled expertise.

Thermo Fisher Scientific is the world leader in serving science, with revenues of more than $24 billion and approximately 70,000 employees globally. Our mission is to enable our customers to make the world healthier, cleaner and safer. We help our customers accelerate life sciences research, solve complex analytical challenges, improve patient diagnostics, deliver medicines to market and increase laboratory productivity. Through our premier brands—Thermo Scientific, Applied Biosystems, Invitrogen, Fisher Scientific and Unity Lab Services—we offer an unmatched combination of innovative technologies, purchasing convenience and comprehensive services.

As the leading service provider to the cell and gene therapy community, Fisher Clinical Services, by Thermo Fisher Scientific, is uniquely positioned with the experience, resources, and global expertise to support our customers on their path towards commercialization. Our global infrastructure enables customers to seamlessly conduct clinical trials across multiple geographies while providing patients around the world with access to life changing therapies. Our cryogenic storage and logistics, combined with proven components and validated procedures, allow us to configure and replicate each site to meet the specific requirements of individual clinical trials with minimal variation, regardless of volume or geographic location. This is supported by a global comprehensive and integrated Quality System based on regulatory requirements, industry best practices and highly trained personnel.



+1 610 391 0800 • pharmaservices@thermofisher.com • www.fisherclinicalservices.com

Published 07/19 PSG0799

ThermoFisher SCIENTIFIC