ThermoFisher SCIENTIFIC

COLD CHAIN QUALIFICATION

FIVE QUESTIONS YOU MUST ASK WHEN SHIPPING BIOLOGICS

patheon

- API
- BIOLOGICS
- VIRAL VECTOR SERVICES
- EARLY & LATE PHASE DEVELOPMENT
- CLINICAL TRIAL SOLUTIONS
- LOGISTICS SERVICES
- COMMERCIAL MANUFACTURING

Introduction

"Cold Chain" refers to the undisrupted series of logistical activities (packaging, shipping, storage, distribution, handling) for products that must be maintained within a given temperature range. And as those of us in the biopharmaceutical industry know well, maintaining cold chain is critical to the integrity of biologically derived therapeutic products.

The Centers for Disease Control and Prevention (CDC) has estimated that $300 million worth of vaccines alone are destroyed each year due to improper storage and distribution; the numbers for other bio-therapeutics are unknown. The scary aspect of that figure is that this includes only the product that was known or suspected to be compromised. Think of the health care implications for administering adulterated medications to patients! The consequences can go well beyond economic losses. Failure at some point in the cold chain can potentially have dire consequences.

Most of us in the biopharmaceutical industry would agree that patient safety and regulatory compliance are the key drivers within cold chain logistical systems. Organizations recognize the growing need for control of the entire cold chain. The ever changing global scenario requires highly efficient processes as a backbone to accommodate the growing needs of organizations.

$300 million vaccines destroyed

Improper storage & distribution

Five questions you must ask

1. **Can you achieve end-to-end cold chain visibility?**
2. **Has that biological therapy been handled properly?**
3. **What is that pre-qualified shipper pre-qualified for?**
4. **What about temperature monitoring?**
5. **How does your shipping system stack up over the entire transit process?**

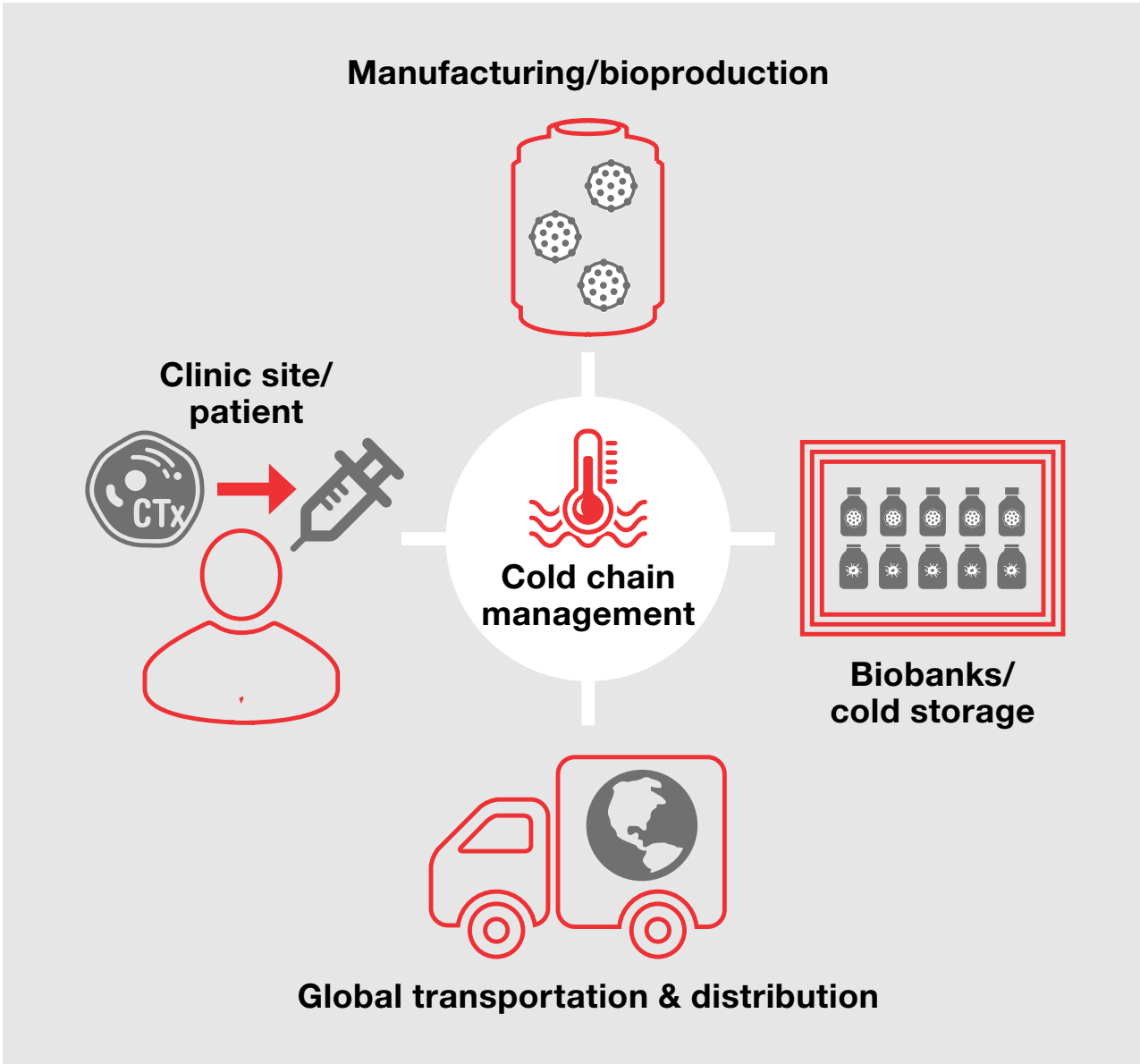
Can you achieve end-to-end cold chain visibility?

The advent of global commerce has made the distance between countries appear smaller due to the successful amalgamation of science, process and technologies but the physical separation between geographical entities remains. This is where the enhanced focus on process, end-to-end cold chain visibility and efficient traceability systems come into play.

The good news is that cold chain-related technologies are evolving. Tracking systems, temperature monitoring devices, courier capabilities, and regulations are all changing to accommodate both the increasing numbers of bio-therapeutic products moving through the supply chain and the increasingly stringent criteria for temperature compliance.

How can manufacturers provide end-to-end cold chain visibility and thus satisfy both patient safety and regulatory requirements?

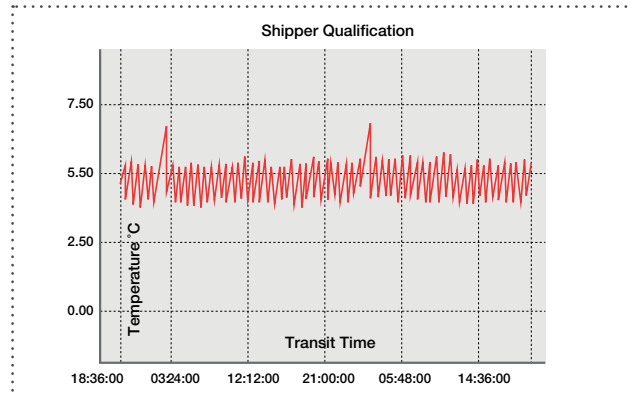
Can you achieve end-to-end cold chain visibility? (Continued)



The Fisher Clinical Services team helps our customers answer this question with “solution-oriented engineering.” We qualify the entire shipping process at a temperature range from X°C to Y°C, for Z hours along the transit lanes. Solution-oriented engineering begins with the components used within the cold chain and extends through the entire shipping/transit lane. An assessment of the materials, suppliers, shipping lanes and methods are part of our process mapping.

The goal is to develop cost effective solutions that are end-user friendly and also ensure performance, established through documented testing. We recognize that cold chains are complex and we work toward reducing this complexity for our clients by incorporating compliance with cold chain requirements into the testing protocols, pack-outs, shipping instructions, quality agreements, and training that we provide.

In short, end-to-end cold chain visibility is achieved by meshing together the technologies and carrier capabilities currently available in the market by mapping them to the supply chain components.

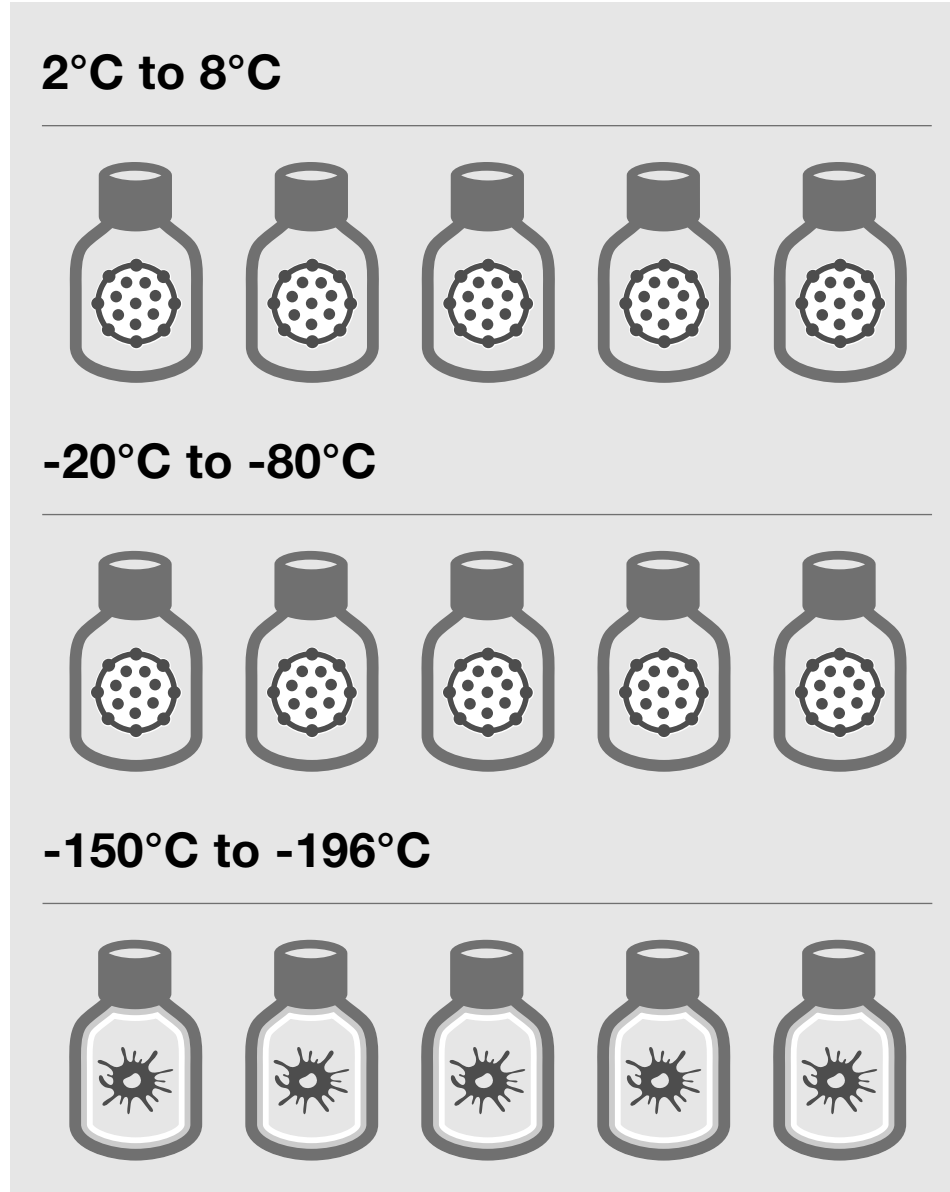


Has that biological therapy been handled properly?

The Biologically derived therapies have varying temperature requirements, ranging from cryogenic, ultra-low, frozen, and refrigerated. Maintaining refrigerated temperatures may be the most challenging.

The majority of vaccines require storage and distribution under refrigeration (2°C to 8°C), and exposure to both warmer and colder temperatures may affect their potency. The negative effects of warming above 8°C are usually more gradual, predictable, and smaller in magnitude than losses from temperatures that are too cold. However, exposure to freezing temperatures rapidly diminishes the potency of most vaccines, and according to the CDC[1], the potency of a dose of vaccine can be reduced even though there are no visible signs of freezing. For this reason, maintenance of correct temperature of vaccines is especially critical, as well as challenging, be it during storage or distribution.

Biologics that must be kept frozen, whether at around -20°C or -80°C, are typically shipped in dry ice, and these shippers and pack-outs are well defined in the industry. The more recent challenge is the shipping and distribution of cell- based therapies at cryogenic temperatures (<-150°C) in liquid nitrogen.

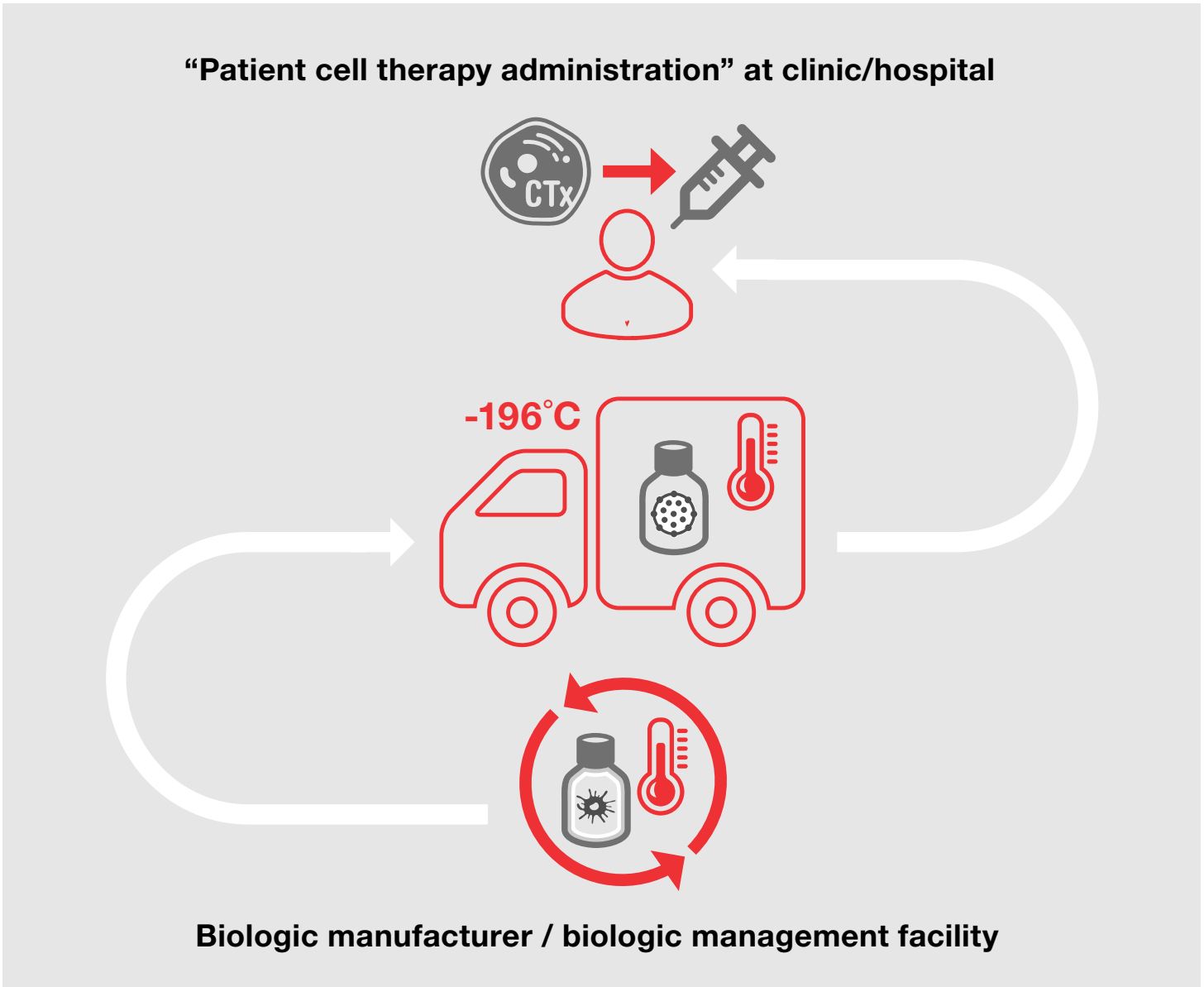


1. Galazka, A.; Milstien, J. & Zaffran, M. (1998). Thermostability of Vaccines. World Health Organization, Global Programme for Vaccines and Immunization, Geneva, Switzerland: Publication No. WHO/GPV/98.07.

Has that biological therapy been handled properly? (Continued)

The most challenging issue in the distribution of cold chain materials is the clinical site. For instance, an assessment of 721 primary care physician offices showed that an estimated 17 to 37 percent of the staff members responsible for managing the vaccine had exposed their vaccine inventory to improper conditions[2,3], including refrigerators that were set too warm or too cold, placing vaccine in the refrigerator door, placing food in the same unit, leaving inventory on a table during group vaccination events, and returning unused doses to the refrigerator.

Managing cell-based therapies at the clinical site is especially challenging, as these products must often be thawed and administered using a specific protocol, and clinical site staff must be trained in handling the shipper as well as the therapy.

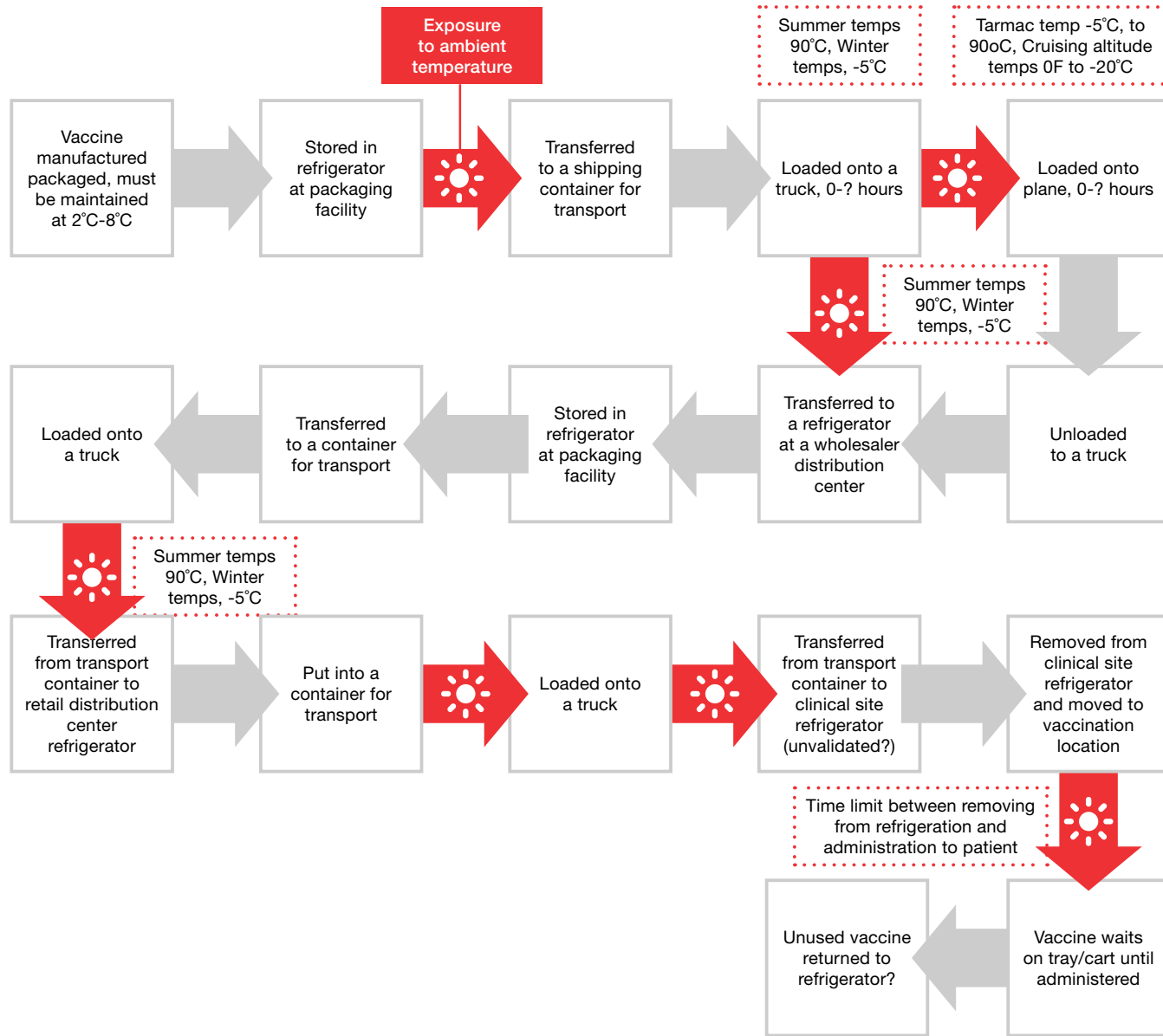


2. Gazmararian, J.A.; Oster, N.V.; & Green, D.C. et al. (2002). Vaccine stor- age practices in primary care physician offices. American Journal of Pre- ventive Medicine, 23(4):246–53.

3. Bell, K.N.; Hogue, C.J.; Manning, C. & Kendal, A.P. (2001). Risk factors for improper vaccine storage and handling in private provider offices. Pedi- atrics 1:107:E100.

Has that biological therapy been handled properly? (Continued)

The Fisher Clinical Services team has years of experience in qualifying these dry shippers and is also working inside clinical sites to provide the training, infrastructure, and implement best practices in handling bio-therapeutics all the way to a patient's bedside. Ensuring the correct handling of biological therapies and creating a fully transparent distribution system means extending the cold chain not to the clinical site door, but to the patient.



What is that pre-qualified shipper pre-qualified for?

The cold chain distribution process is an extension of the good manufacturing practice (GMP) environment that all drugs and biological products are required to adhere, and is enforced by the Food and Drug Administration (FDA) and other similar regulatory bodies in the US and overseas.

Most manufacturers and distributors of vaccine and other biological therapeutics turn to pre-qualified shippers, and there are many choices available. We do not manufacture shippers, but we test and qualify shippers and pack-outs for our clients, and these units do not always perform as specified. There are a number of reasons why shippers may not perform to the manufacturer's specification, and before purchasing a pre-qualified shipper, you need to investigate how the testing was conducted.

For instance, shippers can fail because of:

- **Inadequate stressing:** The environmental stressing profile standards typically employed to qualify these shippers come from ISTA (International Safe Transit Association), which are not representative of most transit conditions and should only be used as a starting point for more rigorous and true-to-life temperature simulations.
- **Issues with pre-qualification:** We have found instances where the testing profile selected helped to ensure a successful run, either through lack of temperature extremes or prolonging the duration of compliance by alternating the heat and cold stress to keep the package within the targeted temperature range.
- **Orientation was not maintained:** Shippers can fail because they were turned on their side, in spite of signage to keep the item right side up. Pre- qualification should include orientation testing in order to demonstrate the shipper's ability to maintain temperature regardless of the orientation.
- **Damage:** Shippers must be strong enough to ensure the security of the payload under worst-case handling conditions. Pre-qualification testing should capture drop-testing and related cold chain applicable stresses.
- **Variations in Payload:** Compare the payload tested as part of the shipper qualification and relate it to your own payload requirements. The introduction of previously untested sizes or amounts of payload can alter performance, and pre-qualification should include variations in the number of units and the overall volume of the contents.

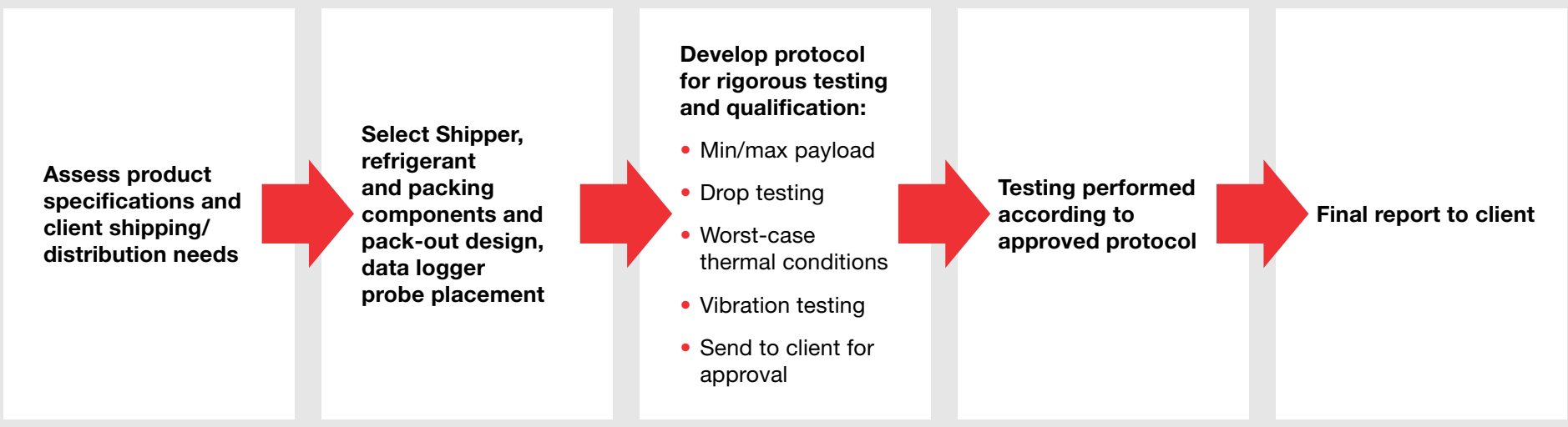
What is that pre-qualified shipper pre-qualified for? (Continued)

Be sure to thoroughly review the qualification report. Since there could be some bias in the in-house testing of a product line, you want to be sure that the testing was sound, rigorous, and comprehensive in scope and quality. Ask the vendor to supply you with a certificate of conformance.

In addition to providing a high degree of patient safety, a well- qualified shipper and pack-out leads to cost savings by eliminating the ongoing re-supply of adulterated material, and expediting FDA approval of BMLA, IND, and NDA submissions.

If shipping costs are of a concern then you may want to perform a cost-analysis to determine whether a pre-qualified shipper with a tare weight of 36 lbs, for instance, is sufficient or overkill for your needs. We typically design and qualify packaging configurations at half that weight including the product payload. We can qualify shippers and pack-outs that will allow more economical distribution modes, such as shipping ground or two-day rather than overnight.

Shipper qualification

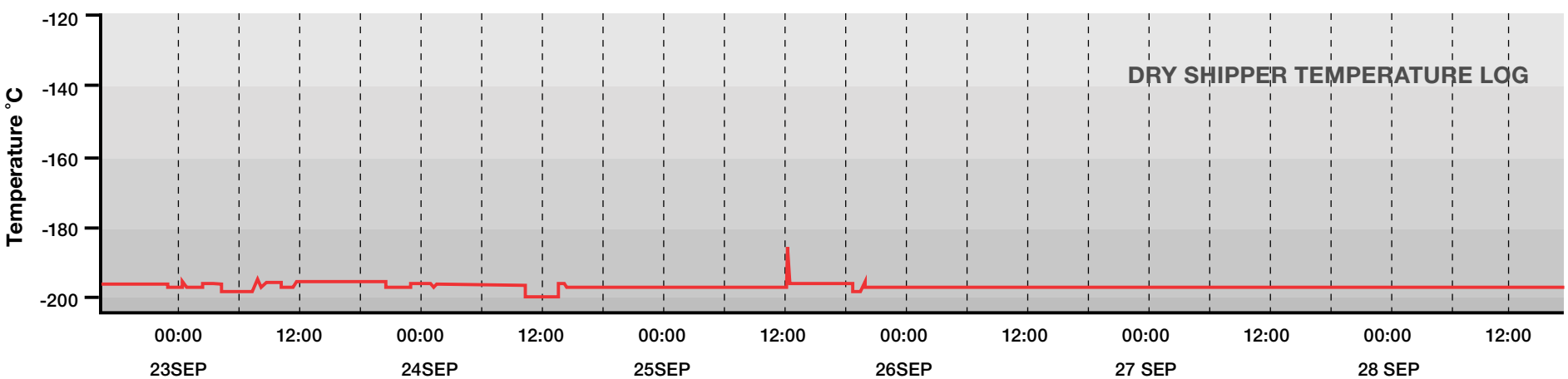


What about temperature monitoring?

The common adage that proper temperature monitoring is the key to accurate cold chain management is true in this context, but not necessarily all encompassing. The need for real time data and zuse of multiple temperature gathering platforms has created its own challenges. Most of the entities in the supply chain are working toward simpler, more manageable ways of determining temperature compliance.

Even with a qualified package, on-board data loggers should be employed to provide time/ temperature information during transit. It is nearly impossible to test for and protect against all contingencies, like extended shipping delays and handling. However, data loggers have their limitations. Loggers capture a single location inside the shipper and cannot account for the entire cavity temperature. If the pack-out was not done properly, the difference between the temperature reading at the location of the probe and temperatures elsewhere in the cavity can be upwards of 7°C.

As mentioned above, temperature monitoring is evolving. Dry shippers have temperature monitors built into the lid, while for vaccine, bulky data loggers are being replaced by thermo-chromic labels in short Vaccine Vial Monitors (VVM). These provide an instant answer to the ultimate question of whether or not an individual dose was maintained at the correct temperature at all times.



Temperature of dry shipper with cell therapeutics-001 from Maryland, USA to UK

How does your shipping system stack up over the entire transit process?

Due diligence in cold chain means not simply using a qualified shipper, but qualifying the shipper to perform within the conditions of the entire shipping process, whether overnight to the Midwest, or four days to the Far East.

Commissioning a transit study to qualify your shipping system will lower costs in a number of ways. These include dramatically reducing loss of material and the repetitive testing of suspect material. A transit study will allow you to identify when a more expensive shipper combined with a less expensive transport option, such as two-day ground vs. overnight, is more cost effective than a less expensive shipper, combined with occasional use of a specialized courier service (such as FedEx White Glove service).

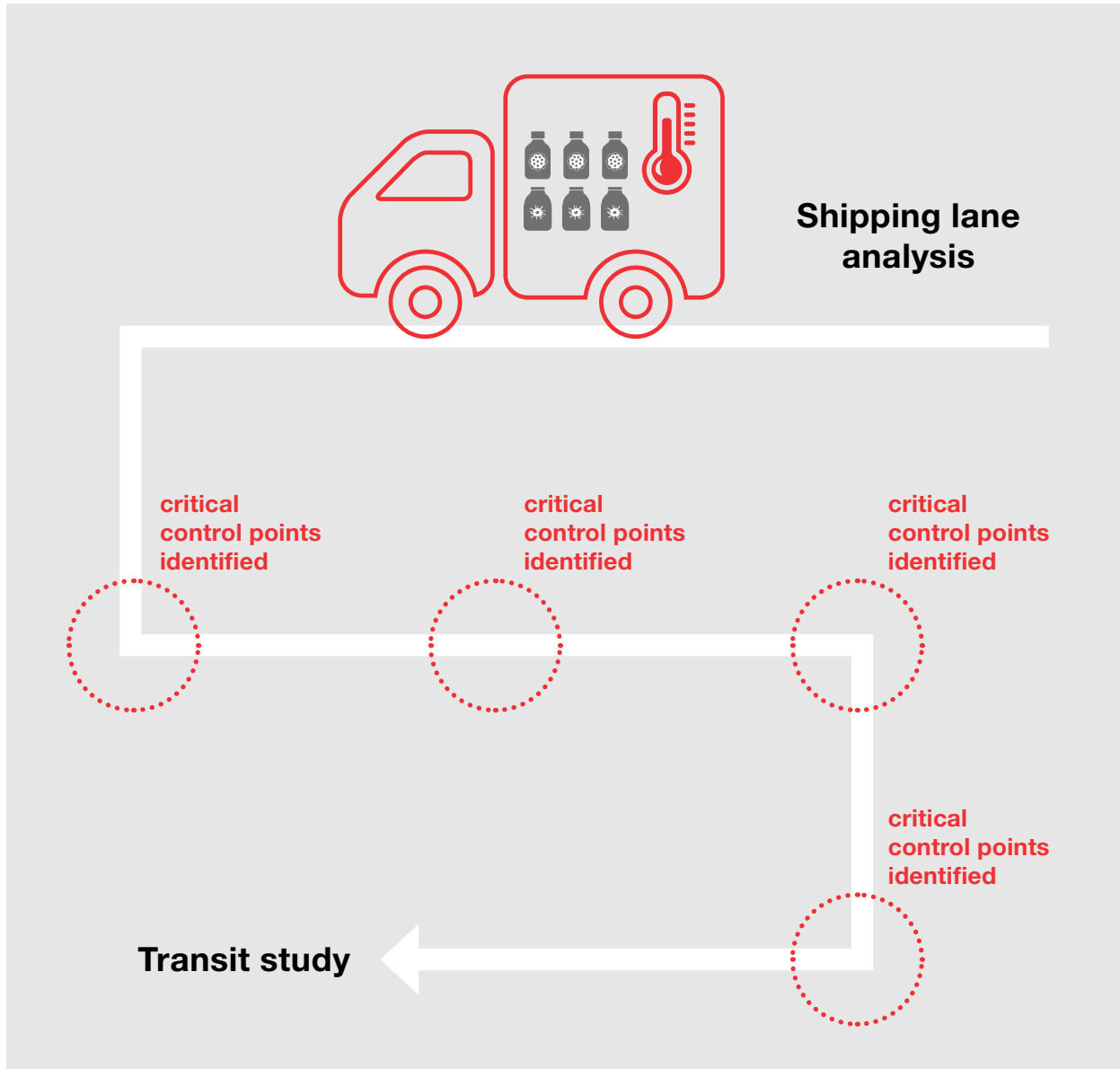
Choosing the right shipping system begins with:

1. a thorough shipping lane analysis,
2. determining critical control points, and
3. performing a transit study—testing the shipper and configuration to the highest degree of performance during transit.

How does your shipping system stack up over the entire transit process? (Continued)

What does shipping lane analysis entail? This is where we identify critical elements such as the package carriers operating within the shipping route and the environmental/ temperature trends affecting the geographical locations along the route. Critical control points include but are not limited to the shipper, coolant, pack-out, size of your payload, the stability and allowable temperature range of the materials, and storage and handling requirements.

Once the shipping lane analysis is completed, and critical control points identified, we design a transit study. When performing a transit study for a biologic, we devise multiple pack-out configurations and test them to see which best meets your needs with regard to performance and cost. For instance, we test a payload of a single dose up to, for example, 100 doses so that the end solution will perform reliably regardless of the number of doses placed in the shipper.



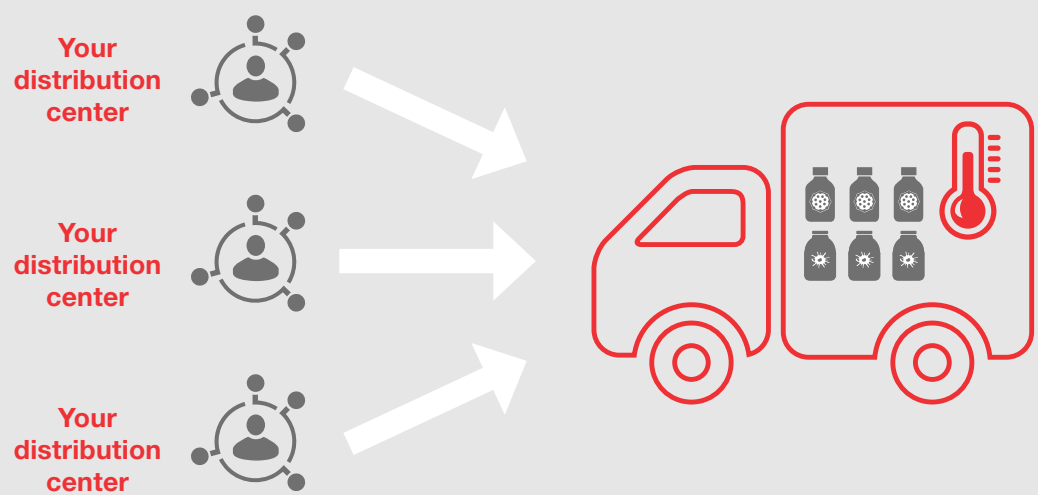
How does your shipping system stack up over the entire transit process? (Continued)

The transit study is performed in triplicate with mock material to verify how the validated configuration works in live conditions, by shipping to sites deemed worst case in terms of environment (e.g., Minneapolis, Minnesota for cold and Tucson, Arizona, for heat). Transit studies test for temperature, relative your distribution center humidity, CO2 exposure, preferred couriers and courier transport methods, minimum and maximum payloads, distribution center conditions, recipient capabilities, and any other applicable variables. We deliver qualified pack-outs and can provide materials for training across all your distribution centers, so that your process is standardized for a higher degree of product integrity throughout the entire cold chain.

If you have asked and answered these five questions, and are using a rigorously designed and qualified shipping system, then the data will provide an objective affirmation that you performed due diligence and significantly advanced the commercial success of your product.

A transit study tests for...

- Temperature
- Relative humidity
- CO2 exposure
- Preferred couriers / courier transport methods
- Minimum and maximum payloads
- Distribution center conditions
- Recipient capabilities
- Any other applicable variable



Additional resources

As a worldwide provider of ultra cold chain management of biologics and cell therapeutics, we can assist companies looking to validate cold storage equipment, qualify pack-outs and shippers, and conduct cold chain transit studies.

- **Pack-out and shipper qualification**
- **Cold storage equipment validation**
- **Lane qualification and transit studies**

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