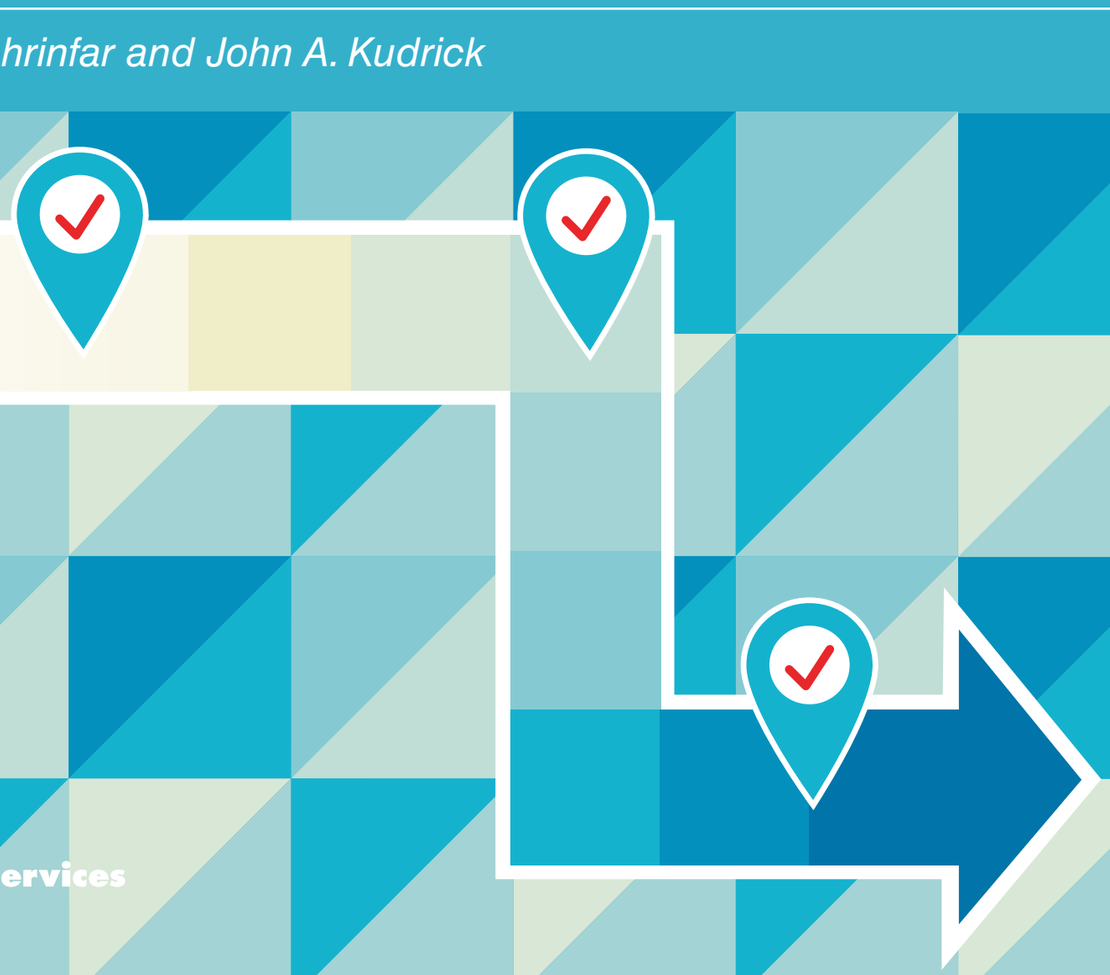
Protecting Your Protocol

Operating a Flawless Clinical Agent Repository

By Mahzad Mehrinfar and John A. Kudrick



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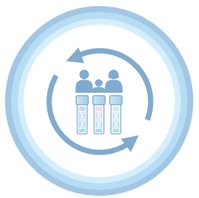

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About the Author

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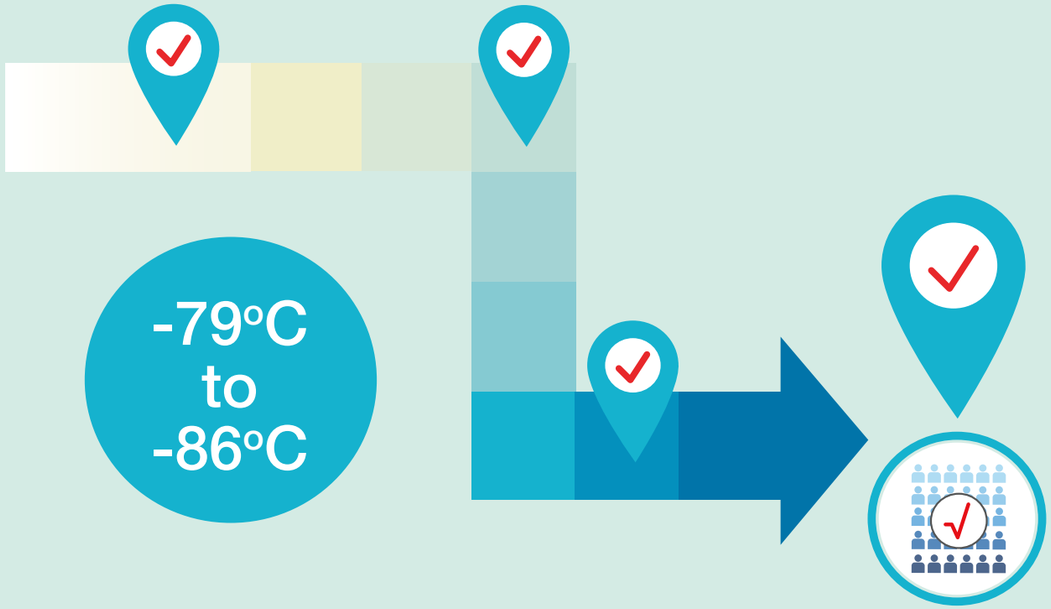
Overview

Introduction



Managing the distribution of clinical agents for large, multi-site, multi-country clinical trials requires a spectrum of expertise and infrastructure, specifically designed to ensure accuracy in order processing and preservation of the integrity of the product from initial receipt into inventory through delivery to the clinical site.

These processes are well established for small molecule and other traditional agents. However, the number of cell-based and biologically derived therapies entering clinical trials is increasing exponentially, and includes monoclonal antibodies and other injectable biologics, agents derived from blood products, and cell- and genetically-based therapies, as well as new vaccines and diagnostics. Most of these must be stored and transported within certain temperature ranges—refrigerated or frozen—and may require near-absolute compliance with a specific temperature requirement, such as between -79°C and -86°C. For this reason, managing and distributing biologics for clinical trials involves additional layers of complexity to meet regulatory requirements and collect and manage the associated data.

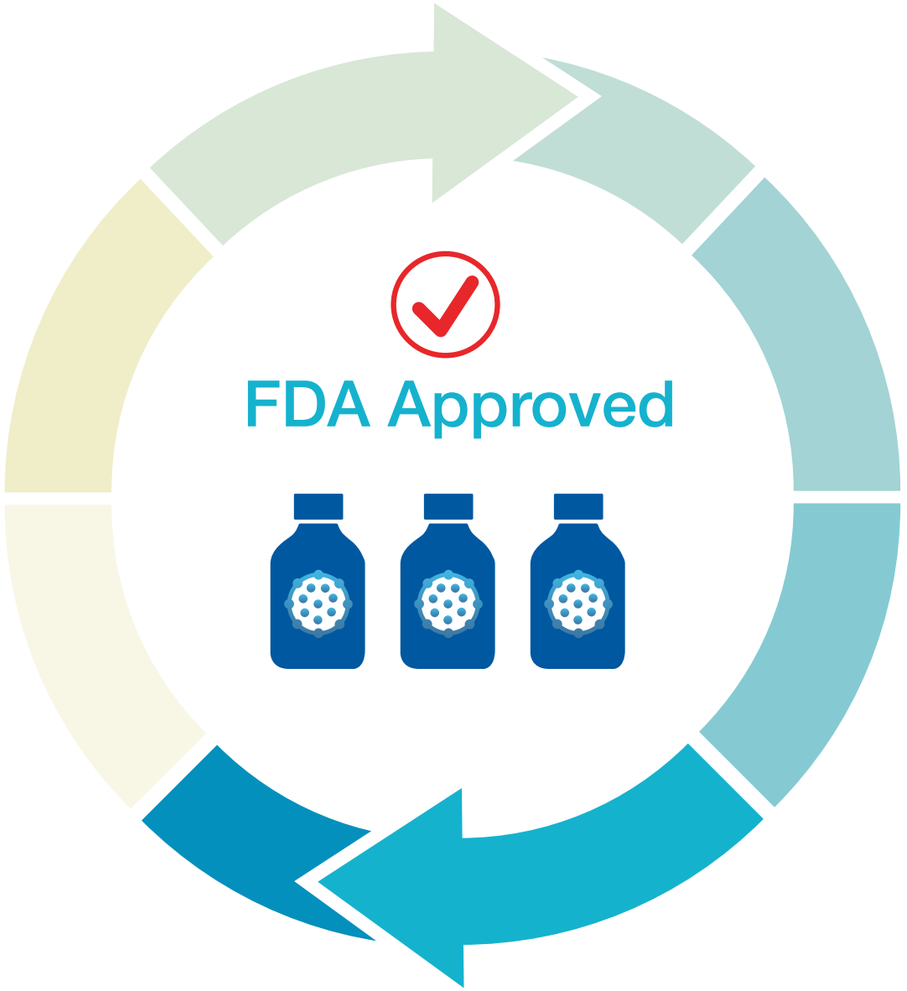
Repositories that manage agents for clinical trials must operate at a level of accuracy that approaches “flawless.” In addition to storage capacity at a range of temperatures, a vendor must have proven processes for handling and management of these specialized products, a robust quality system, and a well trained and experienced staff. If you have such products entering clinical trials, how will you manage distribution to your study sites? Should you outsource or invest capital in infrastructure and staffing? Here are a few insights.

1 Focus on the Protocol

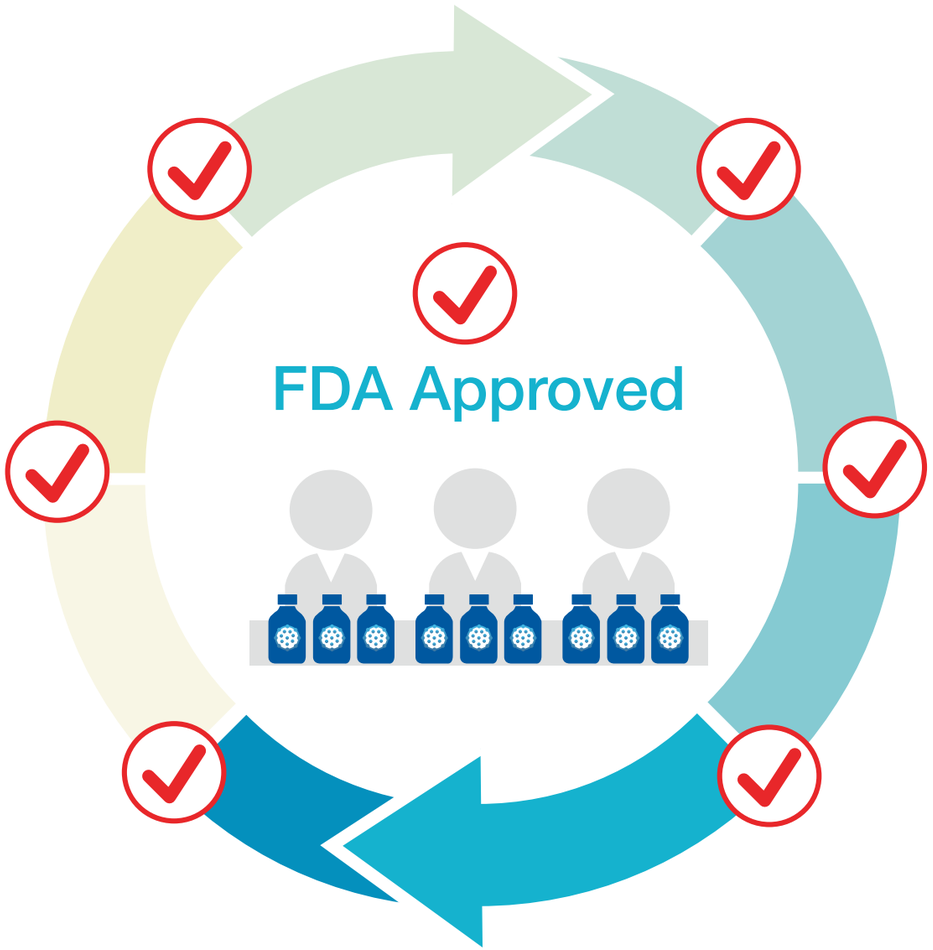
Focus on the Protocol

Pharmacists and facilities that support clinical trials operate very differently than retail pharmacies. A pharmacist in a retail drugstore is concerned that patients are dispensed the correct medication, correct strength, and in the correct quantity. Repositories that support clinical trials, however, are not only focused on the patients receiving the medications, but also the study protocols. This focus on the study protocol, especially in supporting blinded clinical trials, necessitates a far greater level of inventory control on a daily basis.

The danger of a mistake in dispensing medications does not need to be explained. The consequences of an error in dispensing to a single patient are readily understood, but a mistake in managing inventory that supports a clinical trial can harm both the patient and the protocol, and also endanger the outcome of the entire clinical trial. Agents are frequently supplied at no cost, and an error that results in unreliable data or compromises the results can cause the manufacturer to pull out of the trial and the protocol canceled. This may result in a therapy that may have otherwise shown great promise not continue down the pathway towards FDA approval.



Focus on the Protocol



Errors in dispensing medication in retail and hospital settings come from many directions and include such factors as similar drug names, poor label design, small print, crowded shelves, and distracting environments. Much has been done to help prevent errors in dispensing medication in retail and hospital pharmacies. These include efforts by manufacturers to make the print on labels clear and easy to read, use of color and innovative design to distinguish products with similar names, and prominent display of critical information such as the strength.

However, packaging that helps prevent errors in retail situations is generally not an option for organizations supporting clinical trials. This is either because of cost (in the case of open-label trials) or because variations in packaging must be completely eliminated (in the case of a blinded trial) to prevent distinguishing between the active agent and its placebo.

In the absence of distinguishing labels and packaging to help differentiate clinical agents, repositories must rely on proven processes and well-trained, experienced people to achieve the level of accuracy needed to successfully support clinical trials.

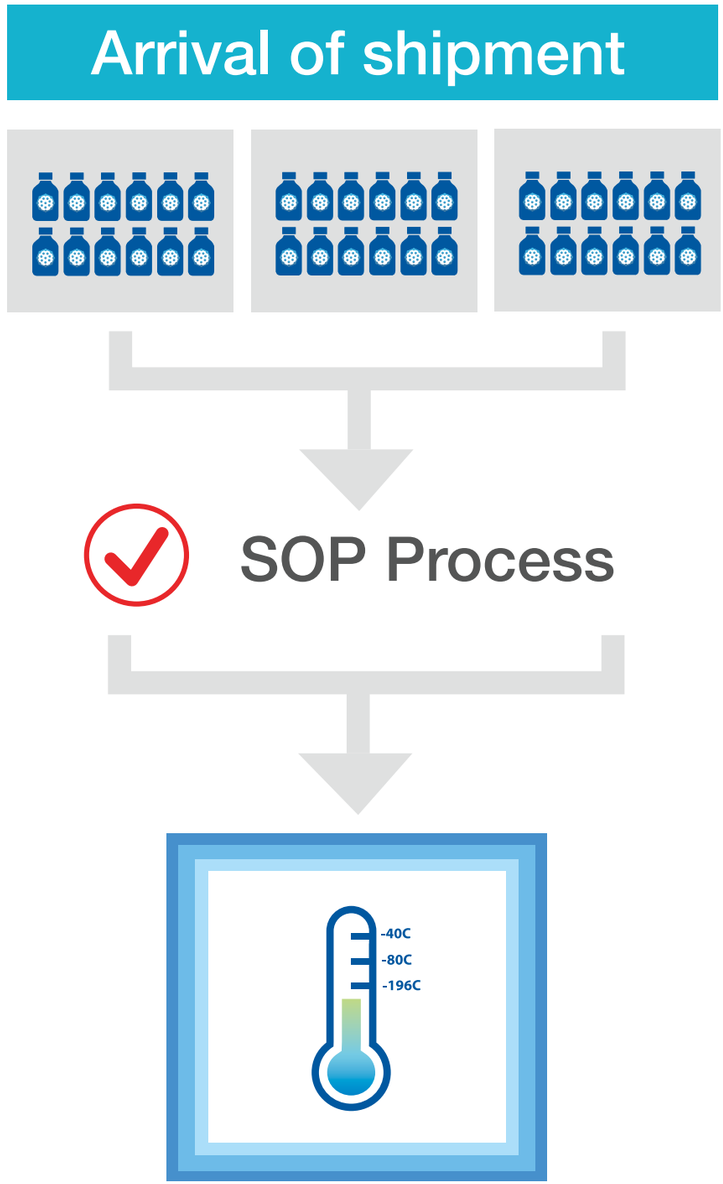
2 Process is Critical and Begins When the Agents are Received

Process is Critical and Begins When the Agents are Received

Every aspect of a regulatory-compliant distribution facility should be governed by a controlled, written, process—a Standard Operating Procedure, or SOP—and every step in every process should have a specific purpose: accuracy in handling the products and preserving their integrity.

Receiving the clinical agents into inventory, as expected, follows a specific process for establishing accuracy and maintaining temperature compliance. For instance, Fisher BioServices has clinical repositories that receive multiple pallets of bottled and packaged agents at a time. Many of these facilities have refrigerators and freezers that allow a forklift to remove a pallet from the truck and place it directly into the cold storage unit.

Multiple processes are needed to ensure complete accuracy in managing inventory, and vary with the client, the contract, and/or the volume of material involved. Compliance with SOPs begins with the arrival of the shipment and process continues to be followed until the quantity received is confirmed, all other details checked, and the data is added to the inventory management system.

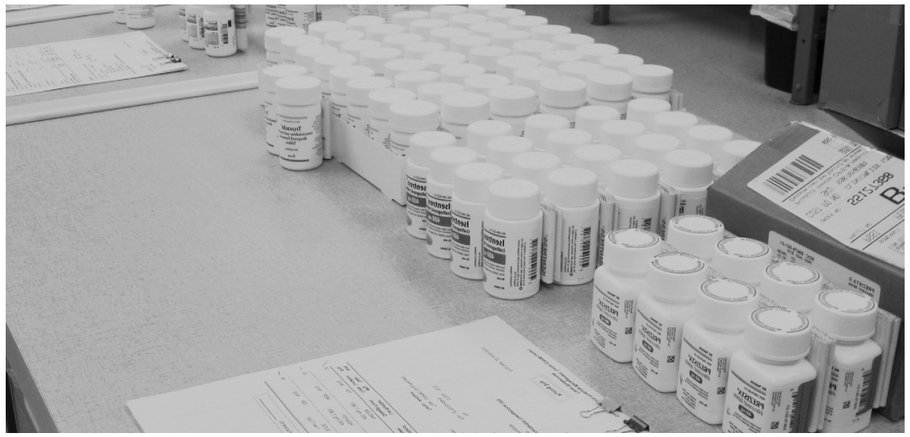


Process is Critical and Begins When the Agents are Received

We may request an electronic copy of the shipment manifest in advance, so that an incoming shipment can be uploaded into the inventory system and staff prepared for its arrival. Depending on client preferences, we may also use a Receipt Notification Form to request shipment information from the sender in advance. In this case, nothing is entered into the inventory management system until the shipment arrives and undergoes inspection, according to SOP.

Inventorying, repackaging, and other steps in the process may be performed inside a cold storage unit if applicable, to be sure the product is maintained at the correct temperature at all times. Cryogenically frozen (-130°C through -195°C) materials are placed and handled in a liquid nitrogen-equipped cryocart to keep them at the proper temperature. Statistical sampling may be applied to perform cost-effective checks, or complete accuracy verification may be performed depending on client specifications. The accuracy of the data in the database and complete agreement between the database and physical inventory is paramount. Standard receiving process also includes an inspection of labels and other elements, verifying the accuracy of all data entry and paperwork, and even systematically checking the packing and shipping cartons to confirm they are empty before they are recycled.

The management of the facility also follows process: the inventory must be stored according to temperature and other criteria, segregated into clearly labeled shelves and spaces, and protected by extensive risk mitigation infrastructure (temperature monitoring, emergency power generators, back-up storage areas, dry chemical fire suppression systems, and others). The integrity of the agents under investigation must be carefully protected. Fisher BioServices operates clinical repositories that support thousands of clinical sites, and we also rely as much as possible on our inventory management system. Agents are tracked by agent information (such as lot numbers, strength, and other data) and managed electronically rather than manually to the extent possible.



3 People are Paramount

People are Paramount

A flawless operation requires solid, proven processes. However, processes are only as good as the people who execute them. The importance of a well-trained, experienced, and well-managed clinical repository staff cannot be overemphasized.

At Fisher BioServices, staff members at each site are thoroughly cross-trained, to allow for great flexibility in filling orders, handling workflow surges, and covering staff absences, as well as for allowing employees variety in tasks. In these cases, staff members may pull and prepare orders on both blinded and open-label studies, but are under the supervision of the departmental managers. These managers know employee strengths and are also knowledgeable of the studies they are supporting and can assign staff members accordingly.

Variety in tasks is key to helping prevent errors; our cross-training means that staff members perform different activities throughout the day—pulling shipment orders, then working on receiving shipments, as well as spending time doing back-up checks. Cross-training and built-in variety in workload keeps staff members mentally fresh and able to maintain the attentiveness to detail needed for operational accuracy. New hires are trained and closely supervised for at least a month and typically longer. At least six months of experience is needed for a new staff member to begin to master the basic details of clinical repository operations.

4 Process Continues – Filling Orders for Clinical Pharmacies

Process Continues – Filling Orders for Clinical Pharmacies

Dispensing of agents for clinical trials also follows detailed SOPs and multiple quality control (QC) checks, each with a specific focus. The steps taken in the preparation of an order vary, depending on whether the agent is for use on an open-label study or a blinded study, but a formal process is followed in both cases.

Open-Label Studies

Open label studies refer to studies in which everyone—the participants, clinical site staff, statisticians, and others—know what is being administered. There is no need to conceal the nature of the agent, although in general, due to associated cost, clinical trial medications may not have special packaging such as that used for commercially available drugs.

At most Fisher BioServices facilities, orders for open-label studies are shipped on the same day they are received. Clinical repository staff members download orders from the clinical coordinating centers in batches at timed intervals throughout the day, and the orders are processed in stepwise manner according to SOP.

For instance, every order is reviewed by a qualified staff member before the items are retrieved from inventory. One order is filled at a time, and in a dedicated space. The space is completely cleared between orders. Depending on the study or contract, staff may inventory the agents left on the shelf as a back-up check.

Process Continues

Review by a qualified staff member before the items are retrieved from inventory.

One order is filled at a time. The space is completely cleared between orders.

Orders for open-label studies are shipped on the same day they are received.

Process Continues – Filling Orders for Clinical Pharmacies

Blinded Studies

Blinded studies are more formally known as randomized clinical trials, and may involve a complex study design. The integrity of the study protocol demands that all participants—patients, doctors, nurses, everyone—is "blind" with regard to which patient is receiving what agent. For this reason, the repository/distribution staff must ensure both accuracy and absolute uniformity among the various agents. A variation in labeling and/or packaging between the agent and the placebo could compromise the protocol.

For this reason, the agents to be dispensed under a blinded protocol are defined and managed not only by the agent identifiersr and strength, but also by lot number. Blinded studies may run for several years, and in order to prevent clinical site staff as well as patients from speculating which patient is receiving which agent (and potentially skew study results), every detail of the bottle, label, and formulation must remain uniform throughout the entire study duration.

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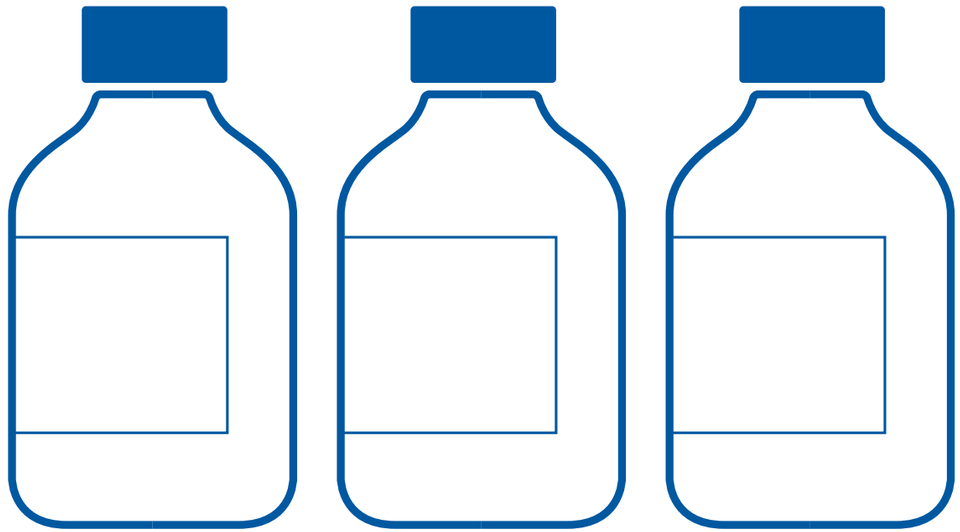


Process Continues – Filling Orders for Clinical Pharmacies

In filling orders for blinded studies, all the quality control and accuracy checks performed for open-label studies are also performed for blinded studies, plus additional steps as well. The (QC) check for blinded studies is conducted by at least one pharmacist, in addition to a pharmacy technician.

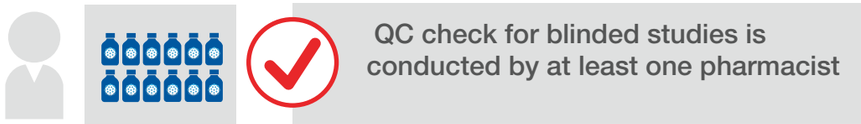
Blinded agents are patient-specific, and if the repository is responsible for applying the labels as well as distribution, then the labels are printed and undergo a separate set of (QC) checks prior to being affixed to the agents.

The orders associated with the blinded studies are generally shipped the day after the orders are received. Our process calls for a complete physical inventory of the active and placebo agents used on the study before the orders leave the repository, as another accuracy check.

In addition, shipping staff will check to be sure someone is available at the clinical site to receive the agents. This involves not simply checking the delivery schedule, but also for holidays and other local circumstances at the destination site. If the agents must be kept at a certain temperature, the shipping staff may verify that someone will place the agents in a refrigerator or freezer as needed.

Ms. Mehrinfar's group processed and shipped more than 24,000 orders in 2013 with zero errors.

SOP Process



orders for open-label studies are shipped on the same day they are received

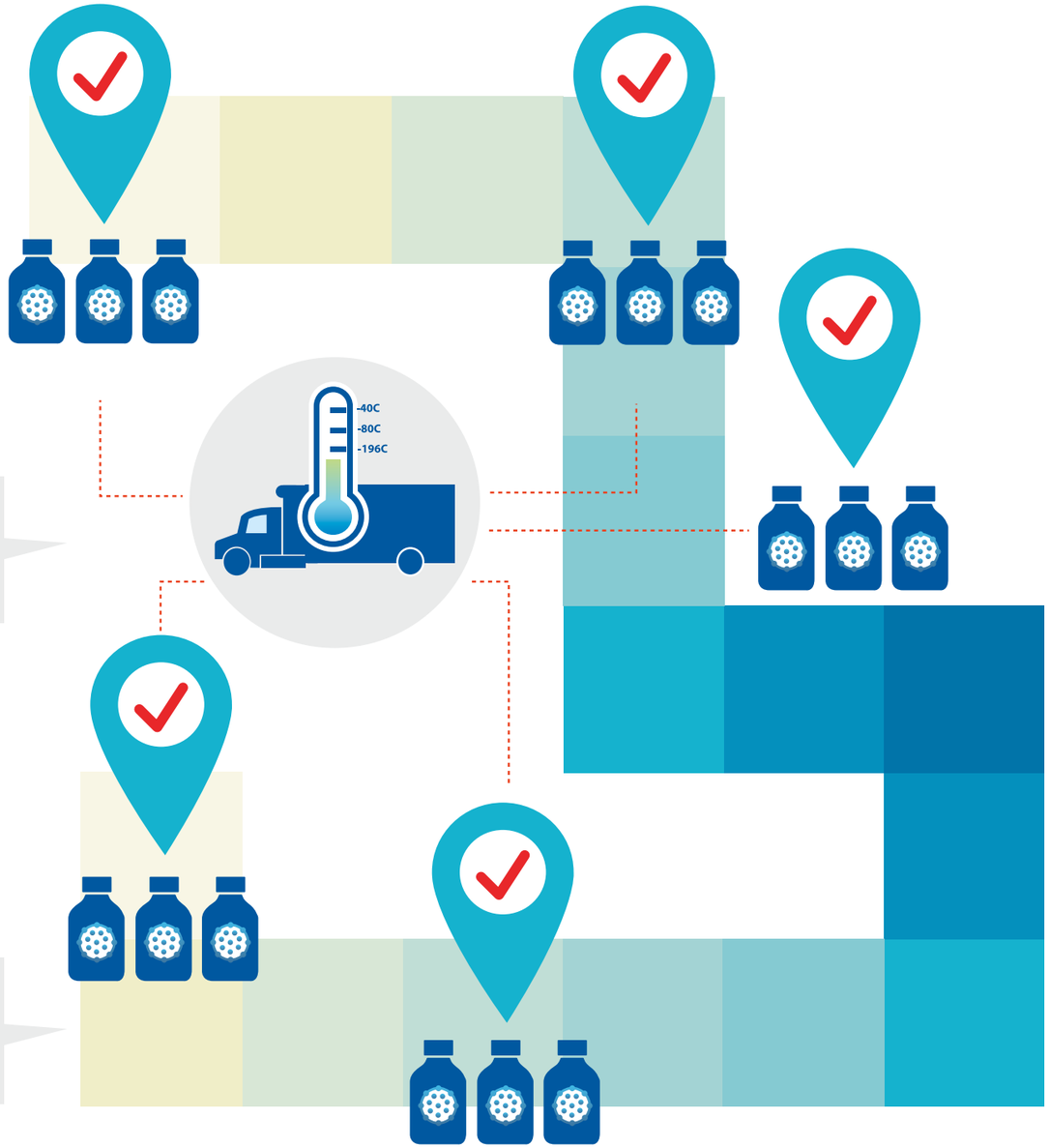
5 The Critical Issue of Delivery and Cold Chain

The Critical Issue of Delivery and Cold Chain

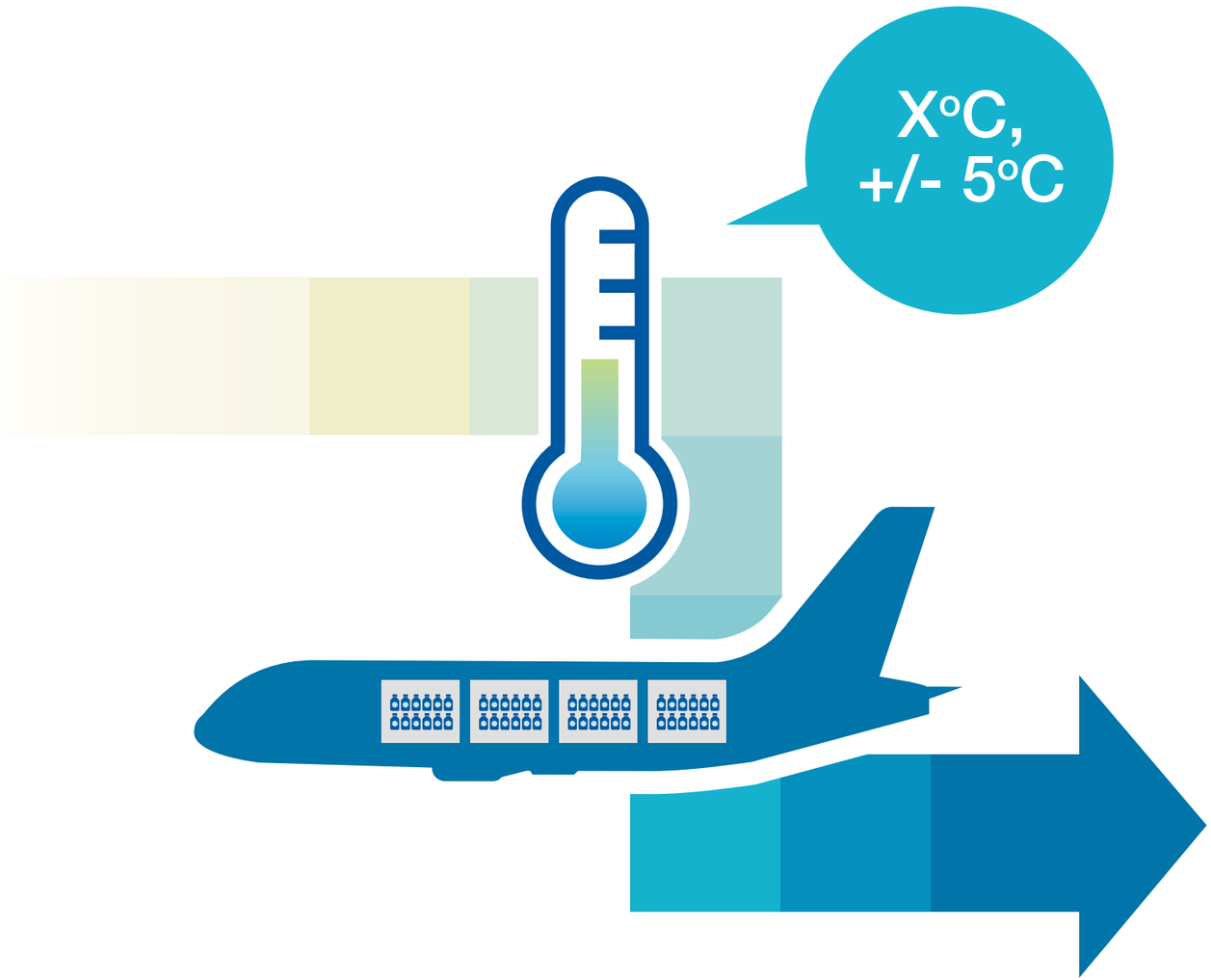
This final distribution leg is another critical element that differentiates repositories supporting clinical trials from pharmacies in the community. Unlike retail or hospital based pharmacies, where the patient is standing across the counter or in a room of the hospital, the end users enrolled in a clinical trial may be thousands of miles away. Maintaining consistent, on time, and accurate delivery of clinical agents to many different clinical sites is a challenge. This challenge becomes more complex when the clinical agents must be maintained at a specific, narrow temperature range during transit.

The patient may be thousands of miles away

Proper temperature must be maintained during transit



The Critical Issue of Delivery and Cold Chain



Managing Temperature

Within the past 10 years there has been an increase in investigational therapies that do not come in the more traditional solid and liquid oral dosage forms. These include vaccines, injectable biologics, agents derived from blood products, cell- and genetically-based therapies and other immunological agents, and nearly all have to be kept refrigerated or frozen, within a narrowly defined allowable temperature range, at all times. These agent must be handled with the same accuracy as the more traditional dosage forms as well as delivered at the correct temperature. In addition, the FDA requires documentation of temperature compliance all along the cold chain, so the repository must have the means to collect temperature data in a manner that complies with the applicable regulations. These temperature and documentation requirements are a primary reason to outsource distribution of clinical agents, particularly biologics.

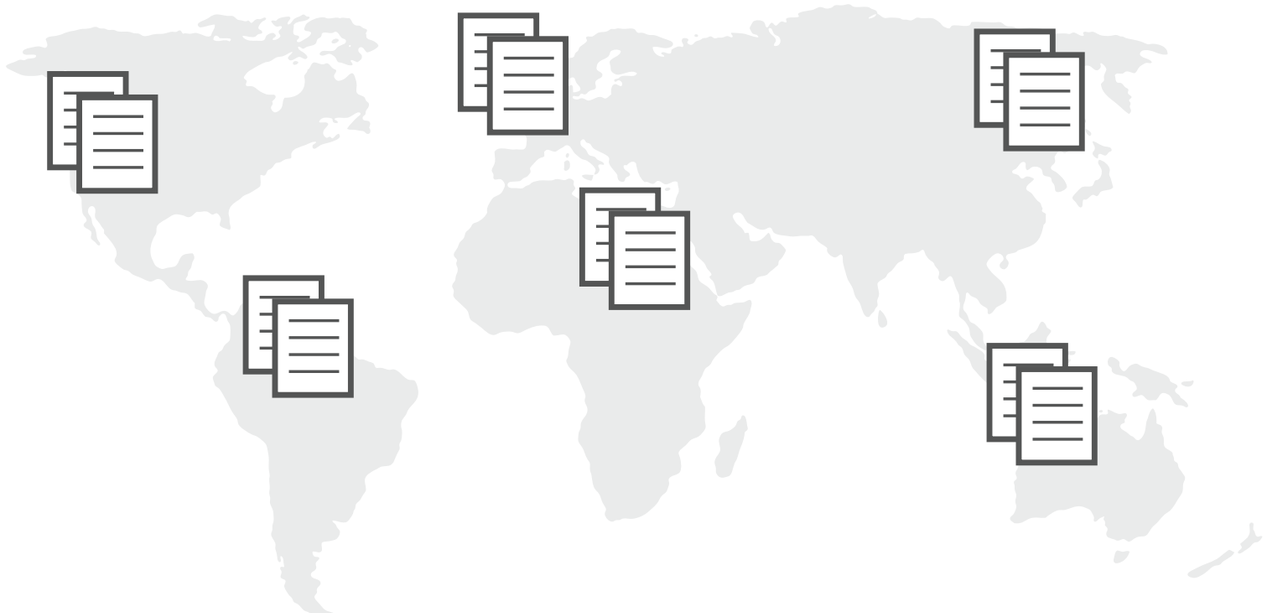
Precise cold chain management can be challenging, particularly when shipping internationally. The agents must be correctly packed in the shipping container and the pack-out configuration must hold the material at the correct temperature well beyond the anticipated delivery time to allow a generous margin for error. The pack-out should include a temperature monitoring platform so the recipient can be sure the agents were maintained at the correct temperature, or alerted to an excursion, as even the most robust shippers and pack-outs can fail under extreme circumstances. Management of these agents requires not only proven processes, but extensive experience with shippers, pack-outs, and data collection.

The Critical Issue of Delivery and Cold Chain

Managing Customs Documentation

An extensive knowledge of import and customs requirements is also critical, especially when shipping to challenging countries such as Canada, Japan, and Israel. The documentation required may include (but is not limited to) pro forma invoices, Commercial invoices, donation letters, Certificates of Origin, Certificates of Analysis (CoA), Safety Data Sheets (SDS), No Objection Letters, Certificate of Pharmaceutical Products, Shipper's Export Declaration (SED), Import permits, and waiver of duty and taxes statements. The requirements vary from country to country, by number of copies needed, originals vs. copies, notarization, consulate authority, official language, ink color, and so on. In addition, these requirements change constantly, often every month!

Customs documentation requirements vary from country to country and change constantly.



The Critical Issue of Delivery and Cold Chain

Managing Logistics

A clinical agent repository has to know which logistics company can provide consistently reliable delivery in any given country (and region within a country). A good courier knows the best transit routes and appropriate shipping times and can assist with clearing customs and other issues. These companies have varying strengths and weaknesses with regard to geographic area served, temperature ranges, and support infrastructure. Distributors of biologics for clinical trials need partnerships with multiple vendors and must know which vendor to use for each specific shipment.

Above all, the shipment should be actively tracked and receipt verified. In the event of a delay or failed delivery, a manager should follow up immediately to determine the nature of the problem. There is no substitute for good business relationships with courier services, customs brokers, and others who are involved in ensuring safe and timely delivery of agents needed for clinical trials.

6 Risk Mitigation – Promoting Accuracy Downstream

Risk Mitigation – Promoting Accuracy Downstream

Operations that support clinical trials need to not only take extensive measures to ensure accuracy in their operations, but also to consider what happens after the agents are safely delivered to the clinical sites. The primary focus of a clinical agent repository is the integrity of the protocol, and an excellent provider understands what happens at the clinical site and will work to minimize risk all the way to the patient. This is a value-added service and should not be minimized: the dispensing organization has an opportunity to spot disasters waiting to happen and should alert the client.

This can include such services as designing, printing, and applying auxiliary labels to highlight differences in agent strength or handling instructions (i.e. “shake well before use” or “external use only”).

As an example, when receiving vaccine into inventory for a comparator study of different dosage strengths, staff members noticed that the strengths were marked in very small print, and that all the labels were similar in appearance and design. This was an invitation for errors to occur at the clinical site. The problem was brought to the attention of the client, and because it was an open-label trial, it was ultimately decided to place color-coded stickers on the outer box of the vaccine, to make the various strengths easier to spot.

Errors can easily occur when distinguishing information (such as dosage) is in small print and labels are uniform.

Risk Mitigation – Promoting Accuracy Downstream

Kit design and layout helps mitigate errors at the clinical site.

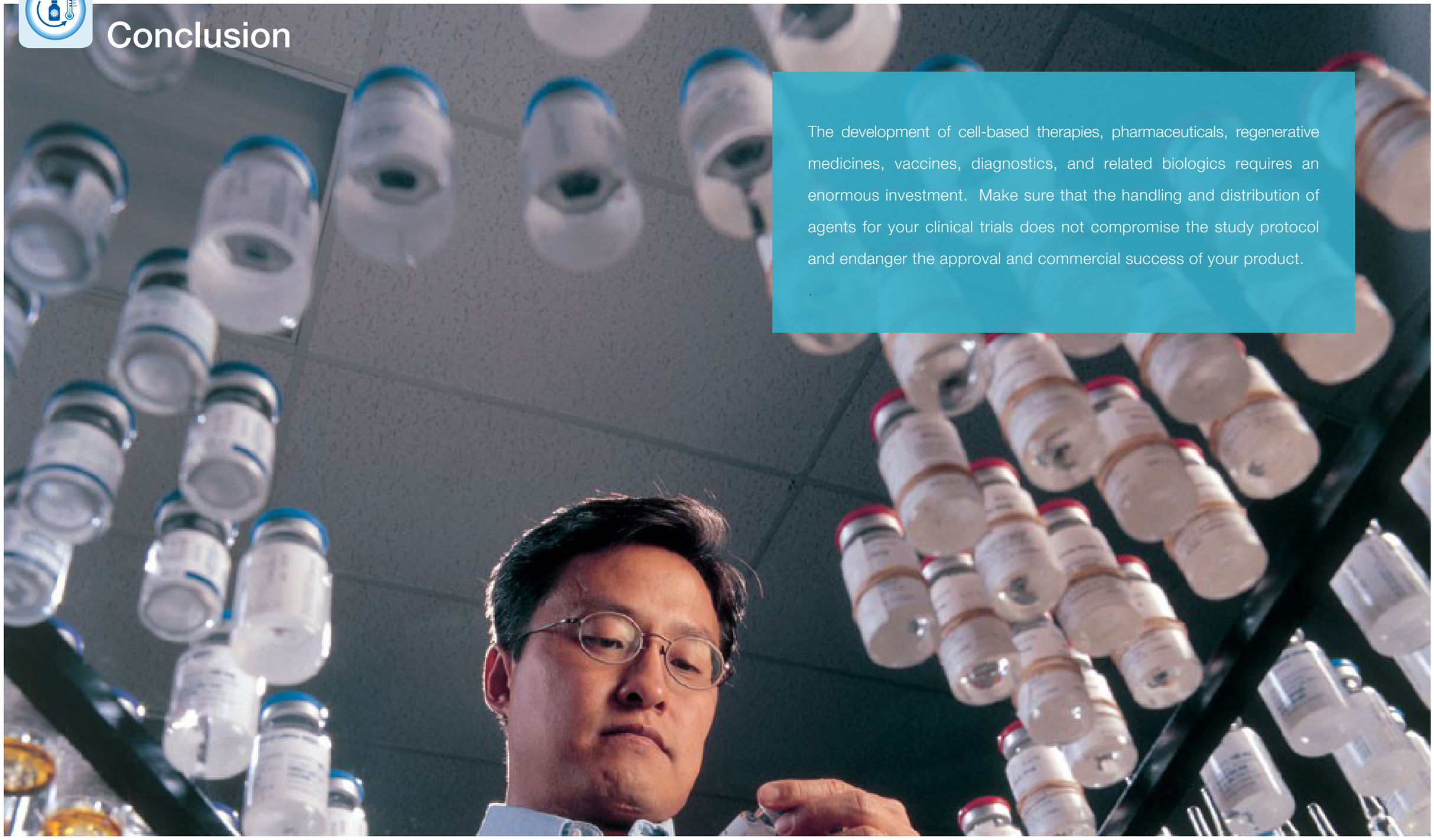
If the repository is tasked with labeling of clinical supplies it should use precisely the same strength and volume nomenclature that are used in the protocol, manual of procedures and the investigator's brochure. This will prevent confusion from variations in terminology at the clinical site. Label design should be as uncluttered as possible and all critical information either bolded or printed in a different color to highlight its importance.

Another area where the repository can help mitigate errors at the clinical sites is in kit design and layout. An excellent repository can package multi-component therapies so that items are arranged in their order of use, or to provide all ancillary items needed to complete the administration of the agent e.g., alcohol swabs with injectables.

When constructing multi-step kits the repository should either package all the components for each step together in clearly marked plastic bags or containers or place the items needed in the first steps at the top or front of the kit and pack the rest of the kit components in order of need. This lessens the need for clinical site personnel to shift through the entire kit to find the next item needed and picking the wrong component by accident.

7 Conclusion

Conclusion



The development of cell-based therapies, pharmaceuticals, regenerative medicines, vaccines, diagnostics, and related biologics requires an enormous investment. Make sure that the handling and distribution of agents for your clinical trials does not compromise the study protocol and endanger the approval and commercial success of your product.

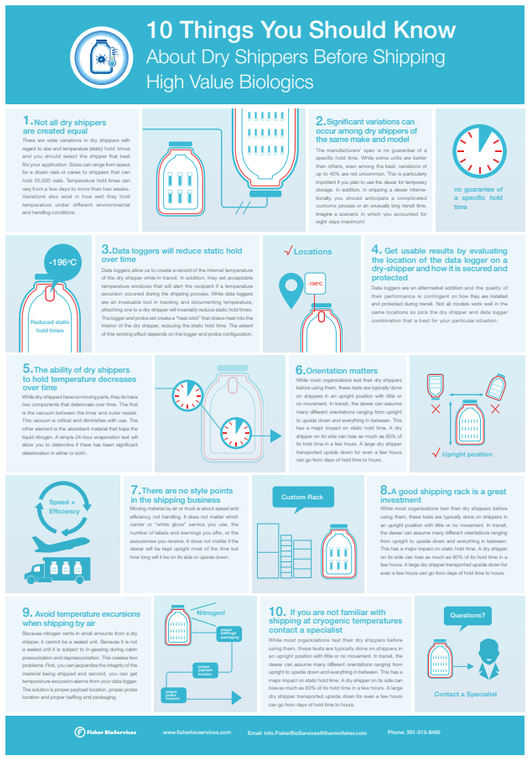
Additional Resources

As a worldwide provider of biobanking and biologic-API management.

- Simple to complex sample collection kit design and production
- Sample processing, global biobanking, and data management
- Online access to inventory for data searching, requesting samples, and exporting reports

Explore Your Solutions

Additional Resources



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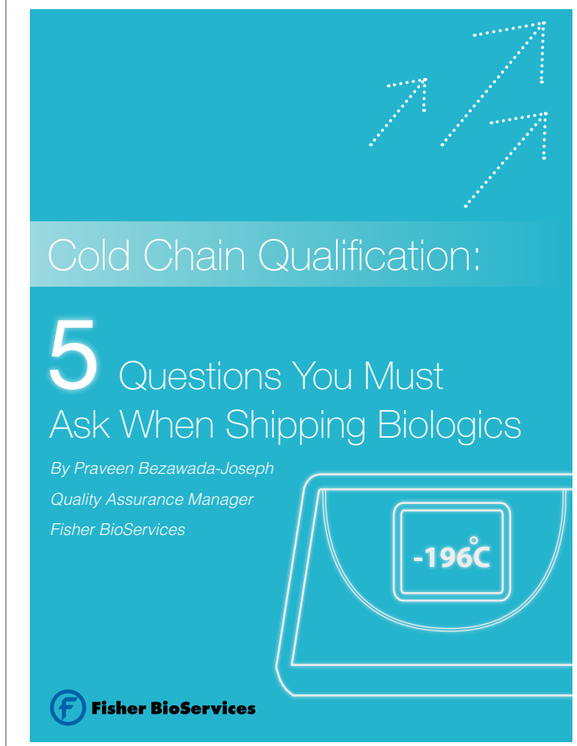

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