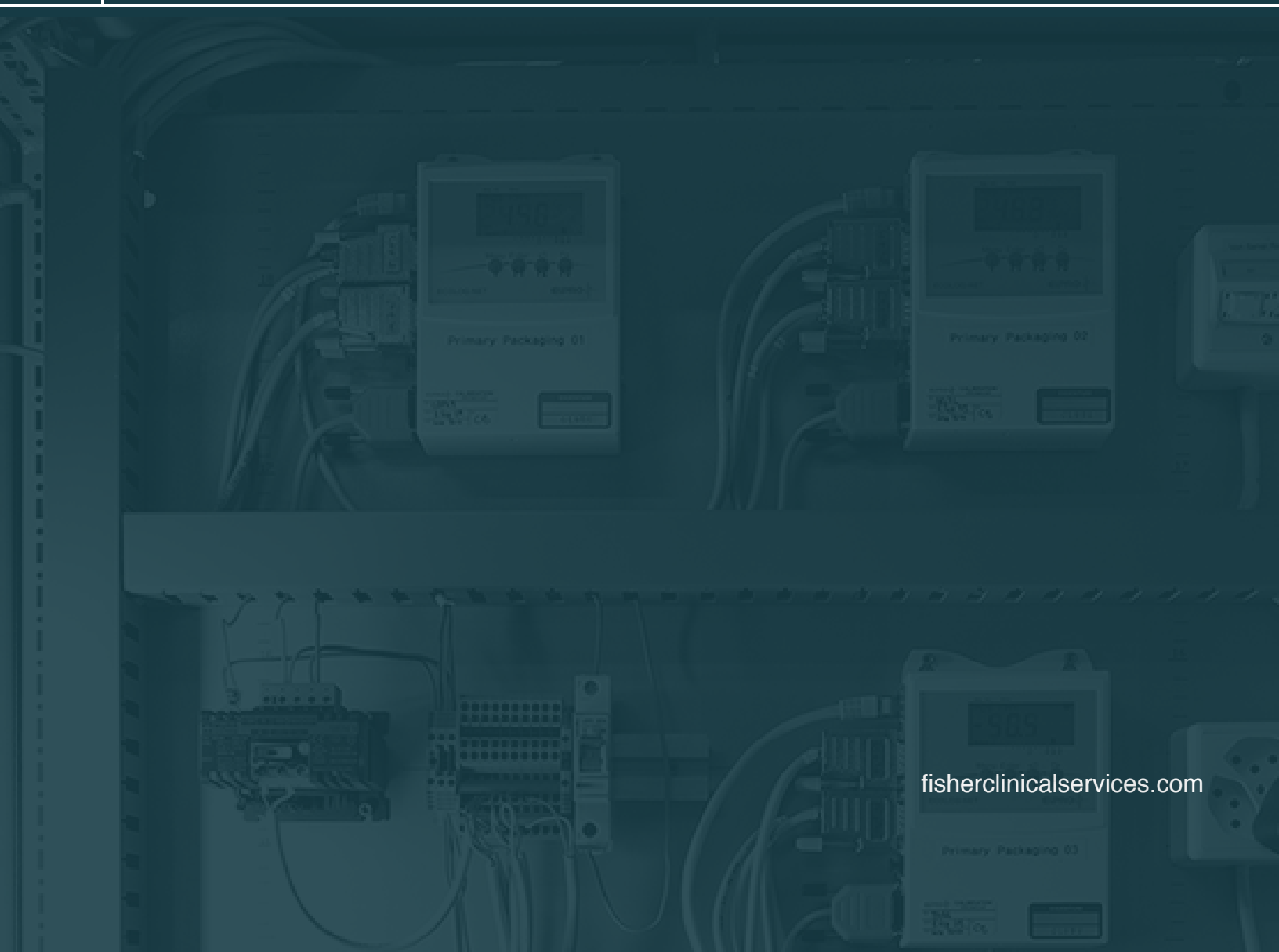
Fisher Clinical Services

Cold Chain Supply:

Top 10 Questions to Ask Your Clinical Supply Vendor about Temperature Sensitive Drugs



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Introduction

Over the years, an entire system called 'cold chain supply (or cold chain transport)' has developed in the food industry to ensure that foods that need to be kept cold are stored and transported in appropriate conditions and are monitored so consumers and regulators can be assured of their safety. Just as certain foods require refrigeration in order to prevent contamination, so do certain medicines. To maintain their therapeutic properties, many pharmaceutical and biotechnology products require specific temperature controls at all points of their life cycle. This includes biologic medicines such as therapeutic proteins, DNA vaccines and monoclonal antibodies.

The younger cold chain supply industry for pharmaceuticals has borrowed from the food business but has had to implement more controls for its higher-stake endeavor. If these medical agents are exposed to temperatures outside their approved range, they can at best lose their effectiveness and at worst aggregate into particles that can cause serious reactions in patients.

The entire challenge has become a critical topic in the industry as the percentage of pharmaceuticals based on biologics and vaccines has grown tremendously in the past decade. In fact, seven of the top 10 products with the world's highest sales in 2013 were biologics[1]. It is clear that biologic agents will continue to outpace overall pharma spending growth and are expected to represent 19-20% of the total market value by 2017.[2]

Special Considerations for Investigational Medical Products

The cold-chain issue is of special focus within the clinical trial side of the industry because a rising percentage of the drugs in clinical testing today are biologics. Just in the past five years, for example, the number of clinical trials investigating biological compounds has exploded by 900%, increasing from 32 trials in 2009 to 322 studies in 2013 (see Figure 1).

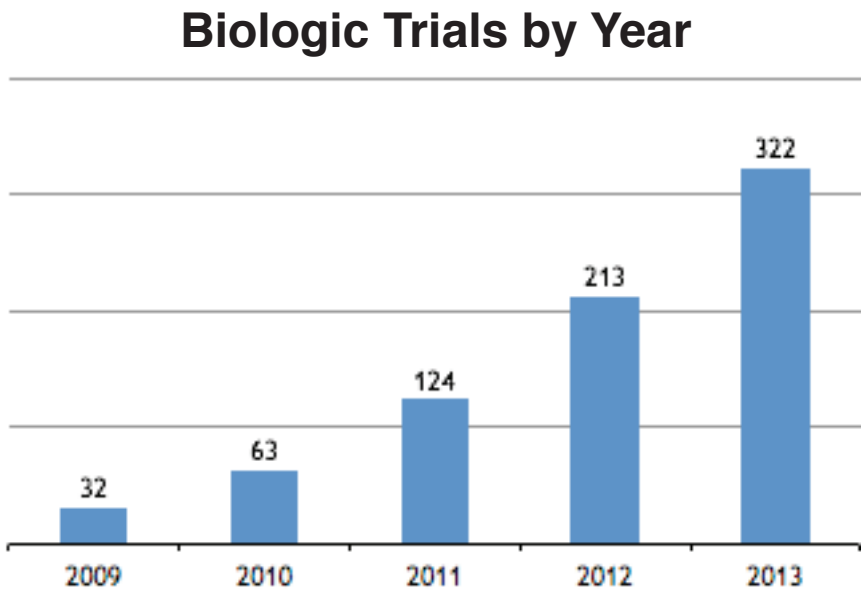

Figure 1 ClinicalTrials.gov shows studies of biological drugs have increased 900% in 5 years.

To manage this growing R&D activity, biopharmaceutical sponsors are increasingly turning to external suppliers to assist them with the packaging, labeling, storage and transport of these temperature sensitive materials. A typical biologic-based product often needs to be received directly into a cold environment. At all times it needs to be stored, prepared for distribution and transported to the investigator site in controlled conditions to maintain the temperature within a narrow range. See Table 1 for typical temperature conditions required for cold-chain supply of Investigational Medical Products (IMPs).

Table 1

Cold Chain Packaging and Distribution Ranges

	Degrees Celsius	Degrees Farenheit
Antibody-based Therapies	-40 to Cryogenic	-40 to Cryogenic
Vaccines	2-8 or -20	36-46 or -4
Special Products	-80	-112

For IMPs, there is the extra requirement that each vial/container of the product needs a specialized label to enable tracking of which patient receives which dose and to reflect the language of the country where the trial is being conducted. The process of labeling the vials/containers becomes more involved for IMPs and sometimes also needs to be performed in controlled conditions. See Figure 2 for all the process flow steps that occur from the time the product leaves the site of manufacture to the clinical trial site.

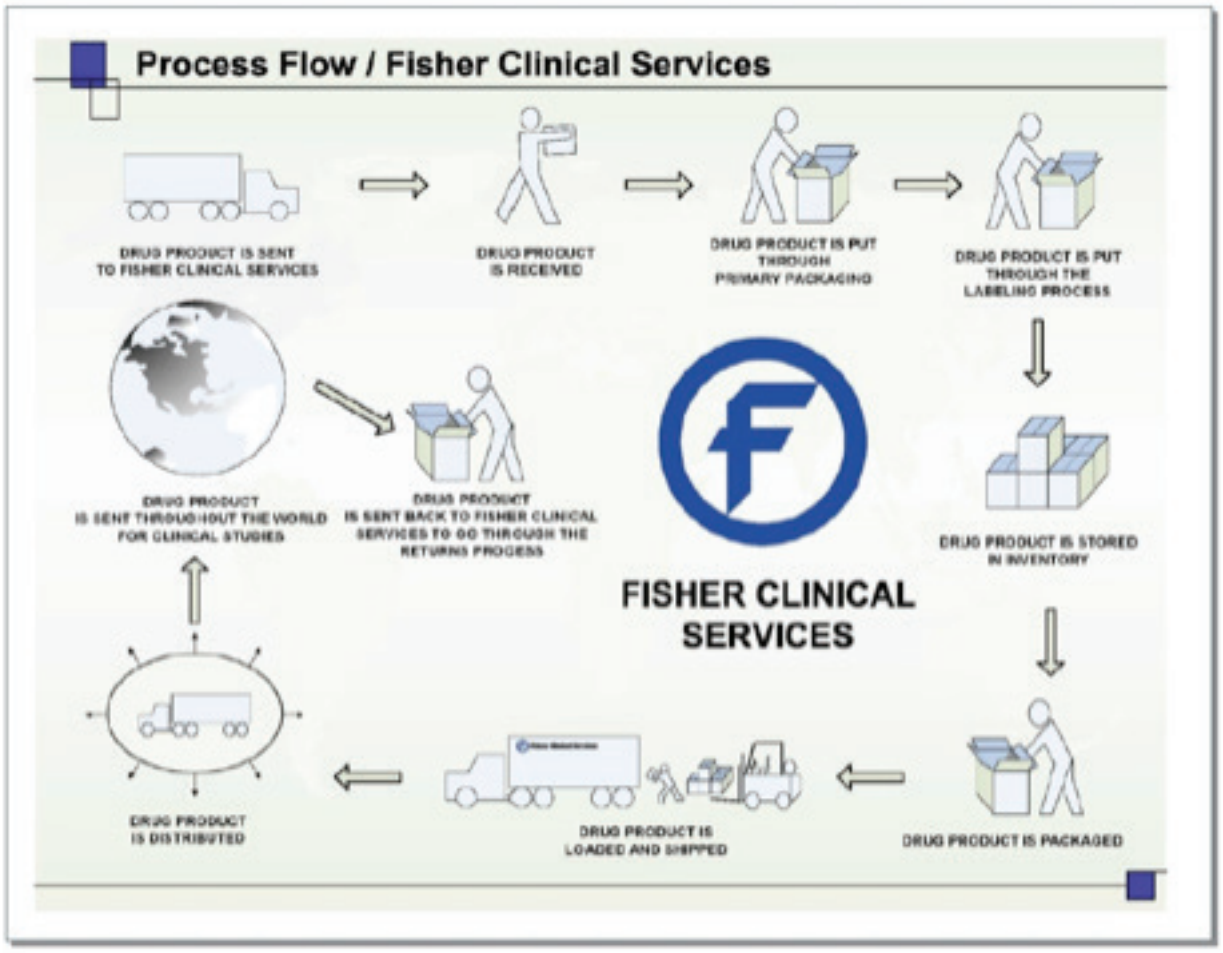

Figure 2

Adding to the challenge of cold chain supply of IMPs is the migration of clinical trials to an ever-expanding network of sites all over the world. The follow-the-patient trend to placing clinical trials in regions with large pools of treatment naive patients has driven trial locations to an increasing number of countries, where the climate is hot. Clinical Trial sites are often located in remote areas where infrastructure is less developed. Instances of shipments waiting on an unloading dock under temperature extremes during power outages or labor strikes are not uncommon.

To distribute an IMP to sites in multiple countries means juggling a variety of requirements such as import and export rules, local regulatory requirements, varying courier and carrier performance, knowledge of local temperature and transportation variations. All the while, the supplier must be able to maintain the integrity of the expensive product within strict temperature controls. With these realities in mind it is easy to see how ensuring an IMP stays within its relevant temperature range is an involved process and requires careful planning. The IMP needs to be handled carefully from the time it leaves its site of manufacture to arrival at the clinic and reaches for the correct patient in the right dosage amount in a controlled and documented fashion.

While packaging and distribution used to be considered a fairly routine and automated process and rarely required significant interaction with clinical teams, the changing face of today's products have outdated that approach. Multi-national clinical testing now requires the management of many moving parts. Clinical teams need to collaborate early on in the process with their clinical supply chain partners to discuss potential risks and sources of delay and proactively develop a risk mitigation strategy to ensure those challenges are avoided. Listed below are some of the recommended approaches to ensure that the cold chain partner you select is capable of supporting your program.

Top 10 Questions to Ask a Cold Chain Clinical Supplier

1. Do you specialize in investigational medicines?
2. How do you plan the cold chain logistics?
3. Do you have any new technologies that help the process?
4. Do you have staff that specializes in cold-chain supply?

5. What are your storage facilities like?
6. Do you have specialized labels?
7. What are your green shipping options?
8. How far is your global reach? Do you partner with any 3rd party networks?
9. Do you have flexibility in how to partner?
10. How well do you know the regulations of the destination countries?

1. Do you specialize in investigational medicines?

Supplying investigational medicine differs greatly to supplying commercial, approved medicines. There are many unique nuances that apply to supplying investigational medicine. For this reason, most supply/logistics companies do either one or the other. Supplying IMPs involves keeping track of who gets what, manufacturing and placing labels that specify different doses in a 'blinded' way so neither the patient nor physician knows which patient received which dose, yet it can be tracked. The stakes are a lot higher too for supplying IMPs. Quantities are more precious as there are not typically large amounts of drug made for a clinical trial. Also, if mistakes are made in labeling or if a batch of IMP 'spoils' by being out of its temperature range for too long, the whole trial can be affected since interpretation of the data is based on a certain number of patients receiving specific doses of the medicine.

It is important to understand not only a cold-chain supplier's capability to manage a cold product, but at what stage of the process they help. If they provide cold storage and distribution, do they also provide packaging and labeling services, and can those services be conducted in a variety of temperature controlled settings? It is preferable to minimize the number of handoff and transitions the product needs to make. It is also critically important to ensure that the supplier is well versed and compliant in good manufacturing practices (GMP) regulations and certifications.

2. How do you plan the cold chain logistics?

A vendor that specializes in cold-chain clinical supply needs information to plan how the IMPs should be packaged and transported. They should be asking the client these basic questions:

- Allowable excursion range – how long can the IMP be outside of its temperature range?
- Where are the clinical trial sites/final destinations?
- What is the range of materials available to ship the product, based on budget and location of final destinations and who are the shippers?

- Does the client have a preference for cold chain specialty shippers?
- How large are the shipments?
- Is re-icing an option if there are expected delays along the supply chain?

3. Do you have any new technologies that help the process?

Temperature Monitors

One of the main tasks in cold chain supply of pharmaceutical products is to have ways to monitor and assure that a product remains within its prescribed temperature range and in the case of any deviation, to understand how long a product has been outside of its prescribed temperature range. Biologics typically need to stay within 2-8°C, which means refrigeration is required. Inactivate vaccines need to be maintained 2-8°C or live vaccines at -20°C, which is usually accomplished by special packaging or storing in special freezers.

There are various devices that track if a bottle/vial/syringe has left its cold environment. Typically, they include a 'clock' that 'ticks' when the product is out of its cold location and provides a read-out of when and how long the IMP was out of its temperature range. The ticking clock is well suited to working with material that is unstable or where the stability is unknown. It allows the packaging and distribution team to understand the limited time that is available to work with the material outside of its stable environment. The drawback to the ticking clock, however, is that it limits what can be done with the material outside of a specified range – making material handling overall a more complex process.

Some of the newer technologies enable easier access to the read-out of the clock. The personnel at the clinical trial site can determine right away whether an IMP has remained cold and is ready to use or whether it has been out of its temperature range and needs further analysis to determine if it is still effective.

Fisher Clinical Services has worked to leverage such leading technology and to simplify the instructions and requirements so that the risk of a user error is reduced or eliminated. For example, sometimes the clock read-out is effective but the user requirements are not that simple, resulting in some false alerts where it may appear as though the product was out of range and is no longer usable when in fact it was simply incorrectly disabled at the investigative site.

The company has also worked to develop real time read-outs of the transit temperature history, allowing the product to be used immediately. This saves the clinical trial site a few days in getting the trial started. In the past, the site had to send the monitor back to their

vendor so they could extract and analyze the data to get the IMP's temperature tale and then send it back to the clinical trial site to let them know if the IMP could be used or if it needed further investigation.

Probe Monitors/RFID Logic Tags

Another innovation allows the clinical site to see the temperature tale monitor without opening the box. In the past, all monitors were placed inside the box with the IMP. Often upon arriving at the clinical trial site, the box was opened to transfer the Investigative Medical Product into the site's controlled storage, but the monitor was not turned off. That led to mistakenly thinking an IMP was 'spoiled' because its monitor was not turned off when it should have been. More recent designs place the probe and monitor outside the box, providing ease of access and reducing the chance of an accidental reading.

Though usage of Radio Frequency ID (RFID) has yet to gain widespread adoption within clinical trial sites, its growth has been substantial in the commercial market. Radio-frequency identification (RFID) is the wireless use of electromagnetic fields to transfer data, for the purposes of automatically identifying and tracking tags attached to objects. According to a recent market study, the RFID pharmaceutical and biomedical cold chain segment earned total revenue of $78.5 million in 2012 and grew 37.2% over the previous year[4]. This segment is likely to have a CAGR of 43.1% and become a $471.6 million market by the end of 2017.

Phase Change Materials

Typically some vaccines that need to be kept below -20C would be shipped on dry ice in Styrofoam containers. However, recent developments in phase change materials provide several significant advantages over dry ice shipping[5]. First, systems using these materials are lightweight, often using plastic polymers as insulation, meaning that they can cut the weight of the overall shipment. Secondly, these systems last longer than dry ice, with some phase change materials able to maintain temperature for up to 120 hours. In terms of clinical trials, this means that clinical materials can be delivered to more remote trial sites with lower risk of a temperature excursion. Pharmaceutical companies will be better able to access rural patients in both developed and emerging markets with these temperature control systems. In addition, avoiding dry ice saves on shipping costs because dry ice is considered a hazardous material. Finally, using phase change materials enables reusable boxes to be used rather than Styrofoam.

4. Do you have staff that specializes in cold-chain supply?

Having dedicated cold-chain personnel who know how to work in refrigerated conditions, know how to handle IMPs and label them in the cold, and know the specifications of the

pack-out material, helps reduce errors and increases speed. Whilst adequate training is imperative, experience comes with the volume of orders.

5. What are your storage facilities like?

When the IMP leaves the pharma/biotech manufacturing site, the cold-chain supplier keeps it in its warehouse until it is ready to be sent to a clinical trial site. It labels and packages the IMP at this warehouse or at a depot closer to the trial site right before it is ready to be sent to the site.

Size matters when it comes to the storage facilities. Throughout its company owned manufacturing sites and depots, Fisher Clinical Services maintains more than 1.4 million cubic feet of refrigerated and frozen storage space. Storing vaccines in ultra low or deep freeze/cryogenic conditions requires stand up freezers. Most of Fisher Clinical Services' warehouses and facilities can accommodate large volumes of refrigerated and frozen drugs. In the biologics cold chain, having space for walk-in fridges is desirable because that enables the labeling to be done in the cold, so the IMP does not have a temperature excursion during the process.

It is also important for the facility to have spare capacity. That way it can handle fluctuations in demand. If, for example, a local site loses power and the IMP needs to be kept at the warehouse longer, or if the clinical trial protocol ramps up at the last minute, then the capacity is available. The storage facilities also need the following:

- Back-up power source
- Fire protection systems – each location/rack in the walk-in fridge should have sprinkler protection
- GMP compliance – check how frequently they are audited and by whom

6. Do you have specialized labels?

Cold-chain IMPs need specialized labels – for example, the adhesive has to adhere in the cold. Special consideration needs to be paid to design, stock and type of label. Inks and/or toner used for the label also play a pivotal part in the cold chain packaging model. Some IMPs require frozen or ultra low (cryogenic) storage conditions. Extreme storage conditions have the ability to create numerous label failures – from toner or inks that disintegrate to paper label stocks that shatter from the extreme cold. In addition, the label stocks need to be approved by the FDA to ensure that the adhesives are safe. It is also helpful if the labeling is completed in walk-in fridges. For all IMPs, labeling involves making sure the right IMP gets the right label because the same medicine can be dispensed in many different ways (different doses, different languages on the label depending on which country it is going to, etc.).

7. What are your green shipping options?

The advent of phase change materials and less need for dry ice has enabled the industry to reduce the use of Styrofoam boxes. The phase change materials can be put in boxes that can be reused or sent back to the supplier with pre-paid bills. The Styrofoam may be cheaper initially, but if the client can consider the long term budget implications, the

reusable boxes lead to cost savings within a few years and of course lead to a healthier planet.

8. How far is your global reach? Do you partner with any 3rd party networks?

Because clinical trials are so global nowadays, often the end destination is far from the original warehouse where the IMP is packaged and labeled. A clinical supply vendor that has company owned facilities in many countries will have more control over ensuring the product remains cold in case of any unexpected delays or occurrences.

If the supply company does not have a facility close to the final destination of the IMP, does it have relationships with 3rd party networks that it knows to be GMP compliant? How frequently have they worked with those 3rd parties, and have they audited them? As noted above, fewer handoffs in the entire clinical supply chain help prevent temperature excursions.

Having a local presence is important so that your supplier can send trained, known staff to locations to trouble shoot in case of emergencies (for example, a shipment that is held up at a loading dock during a power failure). Familiarity with local country regulations and customs requirements will help you to plan in advance for potential delays, to appreciate the overall transit time and to ensure that the shippers selected can maintain the integrity of your product for the duration of transport from point of origin to destination. In many cases, a customized plan by region is the best way to go.

9. Do you have flexibility in how to partner?

Some pharma/biotech clients already have a relationship with a certain courier such as FedEx or UPS and refer all clinical shipments through that vendor. However, using a clinical supply company that works with a variety of shipping vendors and can custom design a distribution plan may be helpful. Custom-designed plans can end up providing the best outcomes and help you manage your budgets more effectively.

If the client does not require a specific shipping vendor to be used, the clinical supply company should be able to provide a recommendation on an optimized distribution plan based on regional or country specific performance experience. Check that your supplier can build a plan based on actual performance data in prior distribution experience of temperature sensitive products.

10. How well do you know the regulations of the destination countries?

Each country has its own import/export regulations. Knowledge of the specific requirements in these countries has grown more significant given that 45% of all clinical trials take place exclusively outside of the United States[6]. A good clinical supply cold chain company will be up-to-date on specific country regulations. They will also have people at the destination countries to call if it is necessary to facilitate the materials getting through customs while having their cold conditions maintained.

When conducting trials of biologics, the number of considerations to evaluate within the clinical trial supply chain can be daunting. Keeping investigational products at the right temperature and environmental conditions takes careful coordination of resources and, when required, tight integration with an experienced vendor. But the investment of time and energy pays dividends that are expected to deliver a high return long into the future.

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Fisher Clinical Services

For more than 25 years, Fisher Clinical Services has exclusively focused on serving the packaging and distribution requirements of clinical trials across the world. As clinical trials require increasingly complex supply chain support, the company's purpose-built integrated facilities provide the global presence, information systems, and flexibility to allow unparalleled visibility and control of GMP activities from protocol design through to the investigator site.

Fisher Clinical Services' professional teams bring unsurpassed experience to the challenges associated with supporting clinical trials today. With exposure to large multinational trials and thousands of protocols every year across all therapeutic areas, Fisher Clinical Services has developed the industry's best practices in clinical supply chain management. Fisher Clinical Services is a part of the BioPharma Services Division of Thermo Fisher Scientific, the world leader in serving science, enabling our customers to make the world healthier, cleaner and safer. With annual revenues of $17 billion, the company has more than 50,000 employees and serves over 350,000 customers within pharmaceutical and biotech companies, hospitals and clinical diagnostic labs, universities, research institutions and government agencies, as well as environmental and industrial process control settings.