

Choosing A Supplier for Temperature-Sensitive Investigational Medicines

Introduction

Just as there are certain foods that require refrigeration in order to prevent contamination, so are there medicines. Many of the newer pharmaceuticals require specific temperature controls at all points of their life cycle. They include some blood products, vaccines and biologics such as antibody-based therapies. 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.

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. 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 endeavour. 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.

Special Considerations for Investigational Medical Products (IMPs)

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. 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 **Side Bar 1** for typical temperature conditions required for cold-chain supply of IMPs.

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 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 1** for all the steps that occur from the time the product leaves the site of manufacture to the clinical trial site.

Cold Chain Packaging and Distribution ranges:

Antibody-based therapies:

2 to 8 degrees C
(36 to 46 degrees F)

Vaccines:

-40 to -20 degrees C
(-40 to -4 degrees F)

Special products:

-80 degrees C
(-112 degrees F)

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, many where infrastructure is less developed and where the climate is hot. Instances of shipments waiting on an unloading dock under temperature extremes during power outages or labor strikes are not uncommon.

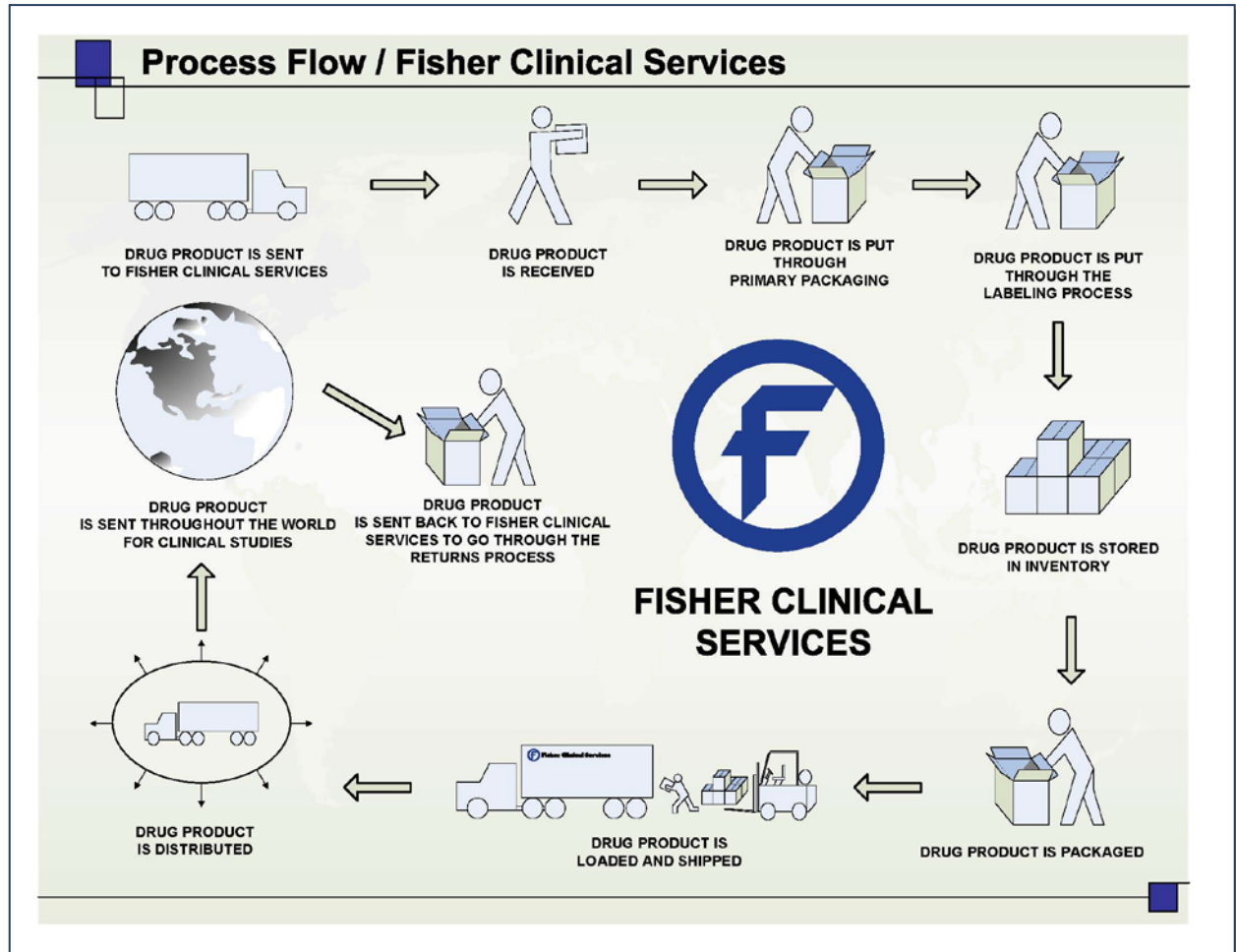


Figure 1.

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 from the time it leaves its site of manufacture to arrival at the clinic and reaches the correct patient in the right dosage amount in a controlled and documented fashion is an involved process and requires careful planning.

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, and 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 (summarized in **Side Bar 2**).

Top Ten Questions to Ask of a Cold Chain Clinical Supplier

1. Do you specialize in investigational medicines?

Supplying investigational medicine is a completely different ball game from supplying commercial, approved medicines. 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 on 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 quantities 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 trials 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 GMP regulations and certifications.

Top Ten Questions to Ask of 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?

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 in, 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?*

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 degrees C, which means refrigeration is required. And vaccines need to be below -20 degrees C, which is usually accomplished by packaging with dry ice or storing in special freezers.

There are various devices that track if a bottle/vial/medicine 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 very 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 investigation to determine if it’s still effective.

Fisher has worked to leverage such leading technology but to simplify the instructions and requirements so that the risk of a user generated 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 useable when in fact, it was simply incorrectly disabled at the investigative site.

We have 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 needed further investigation.

Probe monitors/ RFID log-ic 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 take out the IMP and put it 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. New designs today, place the probe and monitor outside the box, providing ease of access and once again reducing the chance of an accidental reading.

Phase change materials

Typically a product such as vaccines, that needs to be kept below -20C, would be shipped on dry ice in Styrofoam containers. Now there are special materials that can maintain low temperatures without dry ice. Avoiding dry ice saves on shipping costs because dry ice is considered a hazardous material. Using the phase change materials also 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 the cold refrigerator, 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. 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. Storing vaccines in ultra low or deep freeze/cryogenic conditions requires stand up freezers. Most of Fisher's warehouses or depots can accommodate a large number (60 to 70) of freezers. For biologics, 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 additional products. 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, 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 plays 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 gets 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 have a long term budget, 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 company that has depots in many countries that the product can be held at on its way to its final destination has more control over ensuring the product remains cold in case of any unexpected delays or occurrences.

If the supply company does not have a depot 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? Fewer handoffs in the entire clinical supply chain help prevent against temperature excursions.

Having a local presence is important so that your supplier can send trained, known staff to locations to trouble shoot in the 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 provide insight to plan for and overall transit times and to ensure that the shippers selected can maintain the integrity of your product. 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. Using a clinical supply company that works with a variety of shipping vendors and can custom design a distribution plan for you is helpful. Custom-designed plans can end up providing the best outcomes and help you manage your budgets more effectively.

If the client doesn't 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. A good clinical supply cold chain company will know these and will have people at the destination countries to call in if necessary to facilitate the materials getting through customs while having their cold conditions maintained.

Authors:

Tim Brewer

Tim Brewer is Vice President, Global Distribution for Fisher Clinical Services. Tim has more than twenty five years of packaging and distribution experience where he has worked across functions in quality, operations and management.

Prior to joining Fisher, Tim founded Acculogix, a packaging and distribution vendor that pioneered paperless operations in the industry. Today Tim is focused on developing best-in-class and green solutions.

Dave West

Dave West is Manager, Clinical Supply Chain for Fisher Clinical Services and has more than ten years of experience in clinical supply chain services. Dave has worked at Pfizer and across multiple functions such as engineering, inventory management and strategic sourcing.