Rx SOURCE
Clinical Services

Article

Considerations for shipping temperature-sensitive products for clinical trials

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Over the past couple of decades, we have seen a significant growth in the need for temperature-controlled shipping. More and more drug products are becoming both time and temperature-sensitive. While a growth in the proportion of large molecule biologics in biopharma pipelines has driven a growth in the need for refrigerated and frozen shipments, GDP regulations have led to a need for temperature control during the shipment of small molecule drugs previously shipped under uncontrolled ambient conditions. In this article, we will explore the additional considerations you must take when shipping a temperature-controlled product.

What is deemed a temperature-controlled product?

A temperature-controlled product can be split into five categories:

- Controlled Room Temperature (CRT) +15°C to +25°C
- Refrigerated +2°C to +8°C
- Frozen -15°C to -25°C
- Ultra Cold <-80°C
- Cryogenic <-140°C

Each product must be processed and stored within its specific temperature range to ensure that it remains active and safe. These temperatures are determined through vigorous stability studies during the early phases of product development and must be maintained throughout the supply chain.

How to choose the correct shipping system

Let's look at temperature controlled packaging. The key requirement is to maintain the product at its desired temperature for the whole duration of shipping.

- What is the duration of the product's journey from your depot to it's final destination (clinical site or a regional depot in another part of the world)? Does your chosen packaging maintain temperature for the full duration of transit...including a safety margin to allow for unplanned delays?

- What are the minimum/maximum numbers of packs you will be shipping? Temperature-controlled packaging comes in multiple sizes – choosing the wrong size may at best result in paying excessive courier fees to 'ship fresh air' and at worst could negatively impact shipper performance and result in a high number of out-of-spec shipments. Having a good idea of the size of packaging to be used can also allow for more accurate estimates of courier fees and shipper costs.
- Phase-change materials vs expanded foam shippers. While expanded foam/gel pack shippers can be suitable for short transit times and can be inexpensive, our experience is that incorporating phase change materials are the best choice for most shipments we handle. Also, these shippers have a better external dimension to payload ratio, and additional shippers' costs can be offset by reduced courier fees.
- Single use or re-usable shippers? As the need for temperature-controlled shipments increases, so too does the environmental impact of clinical trial distribution. Temperature-controlled shippers are bulkier than uncontrolled corrugated boxes, meaning fewer shippers/journey and an increased carbon footprint. In addition, if all shippers are single use, what happens to these once a product is delivered – are they disposed of in an environmentally friendly manner? Environmental impact aside – is it reasonable to leave these to our clinical sites to dispose of. Re-usable shippers can help address this problem, but there are other considerations:

    - Have you considered reverse logistics? How will you retrieve shippers from clinical sites? For some countries, is return to a central location even possible or is a local return point preferable?
    - Are your shippers clearly designated as re-usable, and do they include clear instructions (in a language the recipient will understand) on how to return them? Despite re-usable shippers being in common use these days, lost shippers remain a challenge.
    - Your source of re-usable shippers is also a key consideration. If you choose to buy your own shippers, bear in mind that you will need to acquire a significant safety stock to ensure you don't run out of shippers while awaiting return of your inventory. As an alternative to ownership, Premium couriers can provide re-usable shippers, and may also manage reverse logistics, although using courier-provided shippers may tie you into using higher-priced couriers in countries where lower cost couriers provide an equally good service. While expensive, this may be preferable and more cost-effective than buying and managing your own shipper inventory. Rental arrangements, including a shipper retrieval and reconditioning service can be a good option, as they allow freedom to select your own outbound couriers, while removing the need for building you own inventory.

- For large and high value shipments, especially those crossing customs borders, we usually recommend the use of active shipping containers. These are more expensive and can be leased from most couriers but for long transit times and an increased risk of customs delays the additional cost associated with these is minimal compared to the value, or risk to continuation of supply, of the product they contain.

Temperature tracking

Temperature monitoring systems have advanced significantly over the years. Some of our team can still recall paper-based chart recorders that not only took up valuable real estate in shippers, but were also expensive and notoriously unreliable. With the advent of small single use and multi-use temperature monitors, the ability to track shipment temperature throughout a journey became a reality…just in time for the introduction of GDP regulations that made it a necessity. Retrieval of early devices of this type to allow data downloads could be problematic for global clinical trials. This was solved over a decade ago by the addition of USB connections to these devices, that allowed the recipient to download data and send this to the sender/

Sponsor for analysis. Technology has continued to move forwards, and we are increasingly seeing the use of real time monitoring. These devices track shipment location, temperature, orientation (important for LN2 shipments) during transit. As the cost of these comes down as a result of wider adoption, we expect real time tracking to become 'the norm' in clinical trial distribution. While USB monitors allow data analysis more quickly than was possible when we had to wait for temperature monitors to be physically returned, we are unable to address excursions until shipments have been received at clinics. Real time monitoring gives us the opportunity to identify issues and implement remedial actions while the product is still in transit, minimising patient impact.

Regardless of the technology used, the infrastructure required to manage temperature excursions remains critical. For example, if an out-of-spec shipment is received at a clinical site, what is our process to inform the site whether the material is safe to use? How long does this process take? Who needs to be involved? How are we collecting and using the data to improve our processes and minimize the risk of this happening again? Tracking technology is advancing, but are our processes to manage newly available data keeping up?

Shipping route

Looking at your shipping route is very important as sometimes the cheapest route is not always the best as it can be the longest. While couriers should be able to advise on the best shipping routes for particular types of shipments, we recommend maintaining your own data on performance using different routes – pricing is only one factor; timeliness and the incidence (hopefully minimal) of out of temperature specification shipments should also be considered. We have also seen variations in the time to clear customs at different airports, even within the same country. Courier/clearing agent performance can also be inconsistent between shipping routes.

Airline and airport facilities also influence the suitability of shipment routes for some products. For example, does your chosen airline provide temperature control services and are these available at your destination airport? Finding a route that provides both the best combination of cost and quality is key.

As clinical trials globalise and account for a growing share of the airfreight market, airlines are increasingly paying attention to value-added services beyond simple transportation. For example, middle eastern airlines are investing in value-added services as their countries seek to become major transportation hubs for services to Asia and Africa. Similarly for Africa, Ethopian

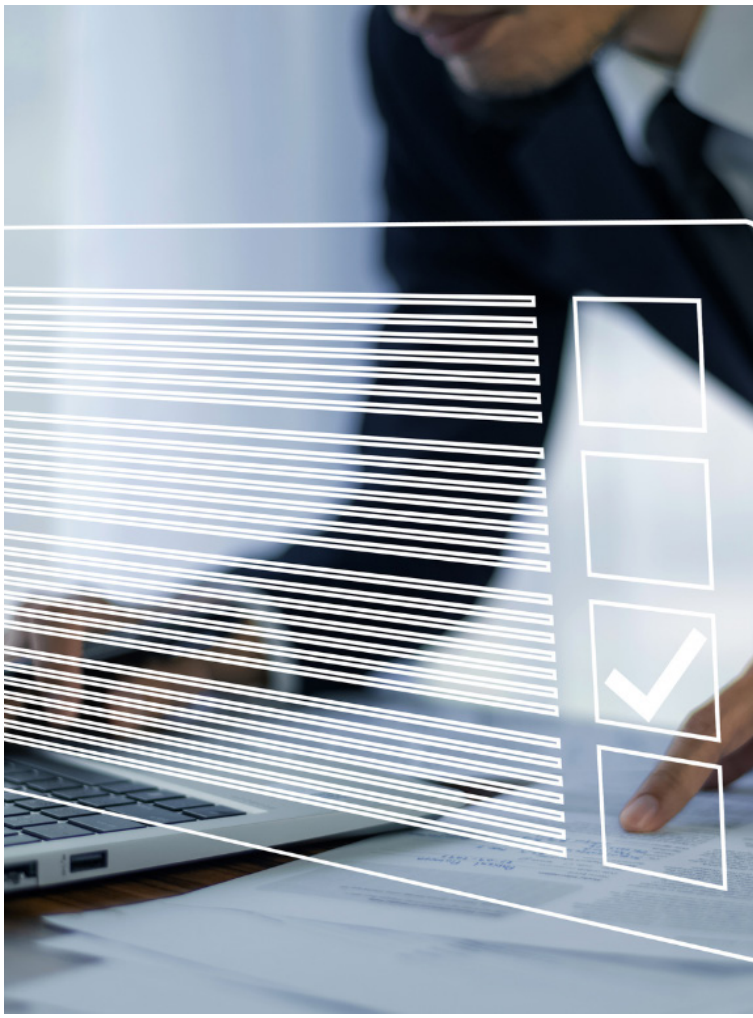
Airlines was the first African airline to achieve CEIV certification (ethiopianairlines.com), so can provide a secure route to Sub-Saharan Africa. Using an African hub can reduce the final leg of a treatment's journey to the clinic, providing a valuable safety margin that can reduce the risks associated with less infrastructure at the destination.

RxSource has built a highly experienced Transportation team to handle the complexity of shipment route selection on our clients' behalf. We maintain a database of country importation requirements and preferred routes to all countries to which we ship clinical trial supplies, helping reduce transit times and the risk of delays to our clients' shipments.

Documentation

We have selected packaging that can hold our product in the appropriate temperature range, implemented technology to track temperature and an excursion management process, and selected a route to ensure secure and timely delivery to the final destination. All of this comes to nothing if we do not include complete and accurate customs documentation with our shipment.

As with all shipments, you need to ensure your documentation is correct. Check and double check your customs documentation as you don't want any unnecessary errors holding up your shipment, especially a temperature sensitive shipment. Your courier, or you must complete additional paperwork to r,equest the appropriate storage with the airline. However, even doing this doesn't mitigate the chance of your shipment not being accepted or offloaded at the last minute due to space limits; you just need to be prepared if this were to happen.



Typically, a suitable courier will have a backup plan. Ensure your courier is fully aware of the validation time of your chosen shipper. This way, if it is coming close to going beyond the validation time, they can organise for a temperature-controlled truck to take the product on the rest of its journey. As discussed previously, using the correct shipper will also help with this. An example would be a hibernating shipper. Once stored in a temperature-controlled area, it hibernates until it is needed again. This does not extend the validation of the shipper but it does prevent excursions as the shipper will keep going for longer.

We'll end this section with a tip from one of our Transportation team, who used to work as a customs officer. If the customs valuation for your shipment gives you an odd number and/or decimal points, do not be tempted to round it up! If your valuation comes to $999.93, use this value in your paperwork…and don't be tempted round it up to $1000. Apparently, customs officers' suspicions are aroused by round numbers, so if you round up you are increasing the likelihood of greater scrutiny, and potential delays, when your product passes through customs.

Other factors to consider

There will always be a risk of other factors arising that lie outside of your control.

- Adverse weather conditions. These can impact on the ability of packaging to hold products at the correct temperature, especially if shipper qualification was limited to 'typical' or 'ideal' conditions. It is worth checking whether your selected shipping system has been tested at extremes…although there will always be rare exceptions that nobody has tested for. Adverse weather can also lead to flight cancellations and delays – not just as a result of the ability of air traffic to safely take off and land, but also as a result of staff being unable to commute to the airport.
- Unexpected environmental conditions. Who can remember when an Icelandic volcano grounded transatlantic flights to western Europe? While this initially caused panic, the clinical supplies industry and our courier/airline partners were able to quickly develop alternative shipment routes to minimise the impact on this on clinical supply chain. This did add time to certain shipping routes, hence our recommendation above to select shippers that cover your planned transit time plus additional contingency time.
- Force Majeure events such as war, and industrial disputes can also impact on the reliability of airfreight.

Final thoughts

Transporting clinical trial products around the globe will always come with risks. The recommendations in this paper will help minimise the impact of these – but will never eliminate every eventuality. Establishing back-up plans is essential, but surprises we have not planned for still occur. Who (honestly!) had a plan already in place for the Icelandic volcano? I suspect we all have plans to cover us the next time this, or similar events, happen in the future. However, none of us have crystal balls that will enable us to pre-empt every potential event that could impact on our clinical supply chains. Our job as clinical professionals is to make sure we minimise risks that we can control, so that when the unexpected does happen we can continue to reliably supply patients.

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7 years+ Industry Experience

2+ years with RxSource

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