THERMO KING

WHITE PAPER

ACTIVE VS. PASSIVE REFRIGERATION:

SELECTING THE IDEAL TEMPERATURE-CONTROLLED SOLUTION FOR YOUR PHARMACEUTICAL COLD CHAIN

WHAT ARE ACTIVE AND PASSIVE TEMPERATURE-CONTROLLED SYSTEMS?

According to the World Health Organization (WHO), **active systems** are defined as "actively powered systems using electricity or other fuel source to maintain a temperature-controlled environment inside an insulated enclosure under thermostatic regulations." Examples of an active system would be refrigerators, temperature-controlled trucks, or temperature-controlled ocean and air containers.

The other side of temperature control in the pharmaceutical cold chain is through **passive systems**. The WHO defines this as "systems which maintain a temperature-controlled environment inside an insulated enclosure, with or without thermostatic regulation, using a finite amount of pre-conditioned coolant in the form of chilled or frozen gel packs, phase change materials, dry ice or others." Passive systems can be single-use or reusable boxes or packages.*

*Source: World Health Organization - Annex 9 (https://www.who.int/medicines/areas/quality_safety/quality_assurance/ModelGuidanceForStorageTransportTRS961Annex9.pdf?ua=1)

There are pros and cons to each system, so the industry is reluctant to recommend one system over the other. This has to do with the context for your cold chain. Both systems can be effective as long as the external conditions are optimized for their use. Both systems have much to offer, but if the wrong system is implemented it could put your patient's safety at risk, reduce your margins, or damage your brand's reputation.

PASSIVE SYSTEMS

Single-Use

Single-use passive systems are the most cost-effective solution for low value, small parcel, and high volume medicines being delivered directly to end consumers with limited ability to collect packaging for reuse. The ideal use case may be delivering medicine to a patient's home, hospital, or clinic where they have one-off package delivery, compared to a consistent delivery from one shipper. For example, an insulin manufacturer could not expect that they would be able to retrieve packaging from home deliveries for reuse either from a logistical or financial perspective.

PRO:

- It's cost-effective

  In the use case mentioned above, a single-use passive system is the most cost-effective way to deliver a package to the end-user when the manufacturer cannot collect packaging for reuse, especially for high volume medicines that are small parcel and not highly valuable products.

CON:

- Climate change implications

  Lane validation is required to know what the typical external temperature the product will be exposed to on average, but many logistics professionals need to keep in mind the extreme ambient potential as climate change is a growing challenge. While lane validation helps with average temperatures along a certain route, there are increasing days of extreme temperature being seen due to climate change. For instance, from 1981 to 2010, Phoenix saw an average of 116 days above 95°F (35°C). Over the next 20 years, Phoenix is expected to see 137 days above 95°F and 150 days above 95°F in the 20 years following. On the cooler side, in January 2019, the polar vortex showed winters are getting colder. In Canada, they experienced temperatures below -40°C. Many passive systems may not have been designed to withstand these extreme temperatures and could have left pharmaceutical companies unable to transport the products.*

  Passive systems are not a "smart technology" and are unable to respond to unexpected changes in hot or cold temperatures, unlike active systems. Therefore, this could increase the complexity and cost of this system because they will need to be fortified for changes in geographic temperatures.

- Need for lane validation to inform design and testing strategy adds upfront costs

  With most pharmaceutical products, lane validation is a risk mitigation must, but with passive systems, there must be intensive lane validation or use case tests using trucks and trailers along expected delivery routes. This will ensure that packaging can withstand the expected temperatures typical along the routes. Understanding if the length of the journey is within the limits of the package, with at least a day of margin in extreme cases, will reduce risk.

  These tests can help to reduce risk of losing product before it gets to the patient, but it takes time. It also adds cost to the project for the manufacturer.

- Lengthy package designing and testing can increase upfront costs

  Intensive packaging design and testing on the system must be done to ensure that the packaging can handle the ambient or outside temperatures. The length of time during the journey by road or air, or both to get the product to the patient is also critical. And it adds cost to a system that might not be able to sustain long-term conditions to keep products safe.

  With the inability to reuse packaging, it's not sustainable due to the high waste. In this situation, the end-user will be forced to throw out the package.

- These systems only cool - they do not heat

  It's no secret that many pharmaceutical products have maximum and minimum stability temperature requirements to maintain viability. Specifically, about 32% of pharmaceutical cold chain products have freeze restrictions**, which means they need systems that cool and heat, which passive systems are unable to provide with gel packs or dry ice, for example.

** Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5821242/

CLIMATE CHANGE. REAL IMPLICATIONS.

There are increasing days of extreme temperature being seen globally due to global warming.

Over the next 20 years, Phoenix is expected to see 137 days above 95°F (35°C) and 150 days above those temperatures in the 20 years following.*

* Source: http://www.impactlab.org/map/#usmeas=absolute&usyear=1981-2010&gmeas=absolute&gyear=1986-2005&usvar=tasmax&usprob=0.5

Reusable

Reusable passive containers are typically used multiple times within the pharmaceutical cold chain, often between known points along the chain to enable ease of return to begin the process again.

PRO:

- The most long-term cost-effective solution for low value, and high volume products when there are dedicated routes and stakeholders

  With the ability to manufacture assets once and then over time use the same assets, it leverages a reverse logistics program. Though complex, this can be the most cost-effective way as long as it is managed properly. The length of the reusable systems last as long as necessary to make a favorable ROI based on the upfront costs and overhead to retrieve the product.

- This can be a long-term sustainable solution that reduces packaging waste

  Depending upon how the materials are categorized, as contaminated or non-contaminated waste, determines if waste must be thrown away. If it can't be recycled, it adds to concerns about dwindling landfill space and increasing removal costs to hospitals, clinics, and third-party logistics companies. By 2025, it's expected that biologic manufacturers will be producing 112,000 tons per year of plastic waste, globally.*

  WHO has classified original containers holding pharmaceutical materials, as contaminated materials so it must be thrown away. Non-contaminated are classified as non-hazardous so it can be recyclable or compostable. Typically, 85% of all health care facilities' waste is non-hazardous waste and historically were incinerated. Now it's encouraged to be recycled if possible due to the growing trend in more sustainable solutions. By reducing the packaging that needs to be thrown away it helps reduce overall non-contaminated waste by the health care industry.

*Source: https://www.pharmamanufacturing.com/articles/2018/less-space-for-waste/

REDUCE WASTE.
USE REUSABLE PACKAGING.

By 2025, it's expected that biologic manufacturers will be producing 112,000 tons per year of plastic waste, globally.[1]

In 2020, nearly $5 billion was spent on packaging costs in pharmaceutical cold chain.[2]

Source: [1]https://www.pharmamanufacturing.com/articles/2018/less-space-for-waste/
Source: [2]https://www.pharmaceuticalcommerce.com/cold-chain-focus/2020-biopharma-cold-chain-sourcebook-forecasts-a-17-2-billion-logistics-market/

KEEP IT COLD.
KEEP IT SAFE.

Trends are showing that more pharma companies are tracking shipments with temperature sensors.

Source: https://www.pharmaceuticalcommerce.com/cold-chain-focus/2020-biopharma-cold-chain-sourcebook-forecasts-a-17-2-billion-logistics-market/

CON:

- Upfront costs and knowledge needed to outline and test reverse logistics process

  It sounds simple, but not everyone can do this within their supply chain due to the high complexity of delivery locations and stakeholders. There must be comprehensive work done upfront to outline the process and cost to recollect the systems. Consideration must be made for the viability at the beginning tied to the increase in the cost of the system, the expected life of the systems, and any potential maintenance and cleaning. If the return on investment formula is missing one of these key pieces, then the business could lose money rather than save money and reduce margins. Reusable systems can only be used for certain circumstances to be truly cost-effective.

- Possible contamination issues if leveraging a vendor network of reusable systems
  - Reusable passive systems can be owned by the end-user or third-party logistics company and leveraged within their own network. This reduces risk of cross-contamination as the company knows which products were in which system but requires more financial investment and logistics knowledge. Cross-contamination could occur when reusing systems that are rented by multiple users although it is typically done due to the advantageous pricing model and the ease of use as the reverse logistics process is handled by the vendor. In this case, without knowledge of chemicals in previous shipments, there could be adverse effects that put the product at risk unless proper cleanliness procedures are done and qualified to ensure each reusable system is safe to reuse.

- Same issues as single-use:
  - Increasing and decreasing temperatures due to climate change and passive systems are unable to respond to changes in temperature.
  - High need for lane validation to inform the design and testing strategy which adds upfront costs.
  - High need for lengthy package designing and testing can increase upfront costs.
  - These systems only cool - they do not heat.

ACTIVE SYSTEMS

Active systems typically include electrical cooling and heating systems that are continuously monitored by a computer system that manages the unit performance and maintains temperature.

PRO:

- Always working to maintain the temperature
  As it says in their name, active systems are just that – active. They are always working to maintain temperature compared to their surroundings to keep the integrity of the product. For risk mitigation, this is the best way to maintain temperature control to assure patient safety. They can adapt and are smart machines that have a controller or brain that optimizes the system for precise results to pharmaceutical needs.

- Typically have built-in telematics
  Telematics can measure the temperature of the cargo space and provide more contextual data to a trip. This data can be used to show full compliance of air temperature staying within the desired range and can potentially reduce quarantine duration, if excursions occur, due to data showing the entire trip's data and proper temperatures maintained. With growing visibility to data, active systems provide another way to feel confident in the correct transportation of your pharmaceutical products with the ability to see data of your journey and possibly even receive real-time data visibility depending on your shipper's telematics system. Some telematics systems also have smart alerts that can proactively warn of potential issues to give fleet's time to resolve them before it leads to a temperature excursion or product loss.

- Less rigorous upfront lane validation and packaging design should reduce upfront costs
  Due to an active systems' adaptability to the environment, there is less pressure on rigorous lane validation. While it is still a best practice, the knowledge that an active system can respond in extreme temperatures creates less need to do the same type of involved testing as with passive systems. This should reduce the upfront time and costs related to this as compared to passive system lane validation.

- For fast shipment needs, with limited ability to do lane validation or packaging testing, active refrigeration is ideal to reduce risk
  With the increase in personalized medicine and some supply chains' needs to react quickly once requests arrive, active refrigeration and its limited upfront needs can be helpful for supply chains that require fast shipment needs.

PACK-OUT.
IT'S COMPLICATED.

Up to 90% of temperature excursions can be attributed to human error, with the majority attributed to errors during pack-out.

Source: https://www.coldchaintech.com/pdf/Choosing_the_Right_Passive_Thermal%20Packaging_Solution_White_Paper.pdf

SUSTAINABLE EQUIPMENT

Refrigeration units are more energy-efficient and environmentally friendly.

- **Use refrigerants with lower GWP**
- **Run on a 5% biodiesel blend**
- **85% quieter**
- **10–20% more fuel-efficient**
- **Cleanliness procedure validation ability**

Source: https://www.inboundlogistics.com/cms/article/refrigerated-trucks-haul-more-than-just-perishables/

CON:

- Higher initial investment
  The ability to reduce risk within your supply chain and increase revenue is invaluable. Having real-time data, along with a smart temperature-controlled system that can react to temperature changes, is vital. While active systems require a higher initial investment, the comparison to passive is essentially less than a percent of the total value of high-value products like biologic drugs and personalized medicine.

- Unplanned maintenance risk
  There are always ways to reduce risk, but while it can be minimized, active systems are mechanical systems and there remains a chance of unplanned maintenance events. Redundant refrigeration like undermounts below trailers and truck boxes can be added to reduce downtime.

  More importantly, the age of the equipment of your shipper's fleet is important. You should be aware of the average age of the equipment and the oldest that is being used to haul your product. Just like a car, an older active system is more likely to break down. In general, across the refrigerated transport industry, it's not uncommon for shippers to have equipment 10 to 15 years old to optimize their costs, but they also are more likely to be hauling less precious and expensive cargo. More typical, the average age before being sold out of a fleet is 7 to 10 years for a refrigerated trailer, and for pharmaceuticals, the preferred age should be 3 to 5 years. Not only should the equipment be young but it also has to do with the degradation of the container or box which for a trailer could be a 4% degradation per year. Because the temperature control equipment is one piece of the system and the container or trailer is the other, it's important to retest systems over time as insulation degrades typically about 4% each year.

CONCLUSION

Active systems should be leveraged when you need to ship products fast through more volatile temperature geographies or have higher value loads that require more intense monitoring.

If your cold chain is in an area that has been highly impacted by climate change creating unpredictable ambient ranges with lane validation procedures, then active refrigeration is likely a better risk mitigation strategy for your cold chain to ensure the pharmaceutical product gets to the patient safely.

Another good use case for active refrigeration is for shipments where you have not been able to properly validate the lane the product will pass through and have limited visibility to the ambient temperatures, making it hard to select the right passive system.

Overall, active systems have the highest risk reduction and reduce the lengthy and costly lane validation and passive design creation and testing process due to their ability to react to changes in their environment.

The most cost-effective method would be to use reusable passive packaging systems. However, this requires a reverse logistics system, which can inherently complicate your supply chain. Be sure to understand how they reduce cross-contamination between customers' products.

Passive systems can be leveraged when you need to deliver high volume, low-value products to the patient via home delivery, have less volatile geographic lanes, and possibly have the infrastructure to leverage reverse logistics to reduce costs.

Each of these systems has an ideal case and is likely used in all pharmaceutical cold chains. Make sure you are selecting the right method, at the right time or there could be inefficiency within your supply chain that increases costs, or worse, puts patients at risk.

COLD CHAIN GROWTH

By 2021, pharma cold-chain logistics purchases will be estimated at nearly $17 billion.

Up to 95% of shipments of stem cells, blood and other specimens are shipped at or below freezing temperatures.

Source: https://www.winnesota.com/coldchain

MARKET SIZE

Between 2020 and 2024, the global spending on pharmaceutical cold chain is estimated to grow by 24% and reach $21 billion.

Source: https://www.pharmaceuticalcommerce.com/cold-chain-focus/2020-biopharma-cold-chain-sourcebook-forecasts-a-17-2-billion-logistics-market/

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