

COLD CHAIN SHIPPING CONSIDERATIONS

WHAT ARE PASSIVE SHIPPERS
AND HOW DO THEY WORK?

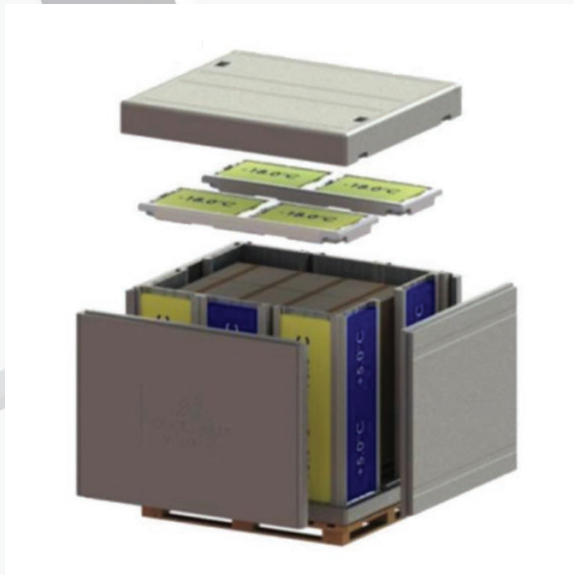


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INTRODUCTION & OVERVIEW

The maintenance of cold chain product integrity across the entire supply chain demands rigorous processes and cold chain expertise of the highest calibre—from packaging, handling, storage & distribution of temperature sensitive Investigational Medicinal Products (IMP), all the way to the investigator site. These eBooks outline industry trends and reviews how Fisher Clinical Services solutions are meeting the challenges of the cold chain distribution of clinical trial supplies all over the world.

COLD CHAIN INDUSTRY TRENDS provides an industry overview and a framework for discussion. The importance of a robust supply chain is addressed. It includes planning recommendations for biopharmaceutical companies preparing to scale up to global vaccine trials.

COLD CHAIN SHIPPING CONSIDERATIONS takes a deep dive into passive shipping options and how they work, with information on the advantages and disadvantages of various coolants.

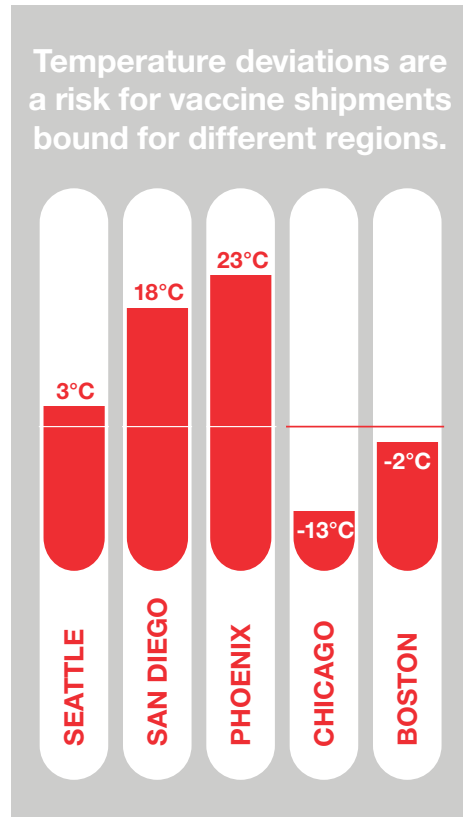
EVALUATING & QUALIFYING TEMPERATURE MANAGED SHIPPERS provides insight into how we qualify shipping options with a case study example of a 'return and reuse shipper pilot' which delivered very positive results.

MANAGING TEMPERATURE EXCURSIONS provides top tips on the best course of action to take, and provides summary recommendations for Sponsors on how to handle cold chain or temperature sensitive IMP across the supply chain, up until delivery to the investigator site.



ADDITIONAL SHIPPING CONSIDERATIONS FOR COLD CHAIN

Double-digit growth in vaccine trials taking place in every corner and climate of the globe sharply raises the logistical stakes, requiring meticulous packaging and constant temperature monitoring of product shipped to clinical sites.



In reality, temperature deviations are as much of a risk for vaccine shipments bound for different regions of the United States as they are for those en route to a different hemisphere. Consider, for example, the weather differences in cities like Boston, Phoenix, Chicago, San Diego and Seattle on a single day.

That is why every precaution must be taken to ensure safest passage from hour 1, or pack out, through delivery. Fluctuating variables—such as potential customs delays, cancelled flights and inclement weather—are part of the process. Consider a vaccine shipment originating from the Thermo Fisher Scientific facility in Basel, Switzerland. This shipment will experience temperatures ranging from 4°C to 25°C or 39°F to 77°F during the 24- to 48-hour journey to a destination such as Pretoria, South Africa.

SELECTION OF CONTAINERS

1

Sponsors are demanding more robust systems & have an increased awareness of the cost of disposal & the problems caused by packaging waste build-up at the clinical sites.

LATEST ADVANCES IN TEMPERATURE MONITORS

2

The Universal Serial Bus (USB) port monitors offer welcomed advantages—cost effective & small; effective placement close to clinical supplies; immediate & clear visibility of data.

ADHERENCE TO REGULATORY STANDARDS

3

It is critical to meet the strict standards of Good Manufacturing Practice (GMP), Good Distribution Practice (GDP) & Good Clinical Practice (GCP) to ensure quality & control.

CROSSING BORDERS

4

Requires careful preparation, checking & maintenance of study-related documents, a clear understanding of regulations & meticulous record keeping.

COMMISSIONING SPECIALIZED PROVIDERS

5

Gives reassurance that high quality standards are being met as high cost IMP is transported across continents, often into remote locations and sometimes Direct-To-Patient.

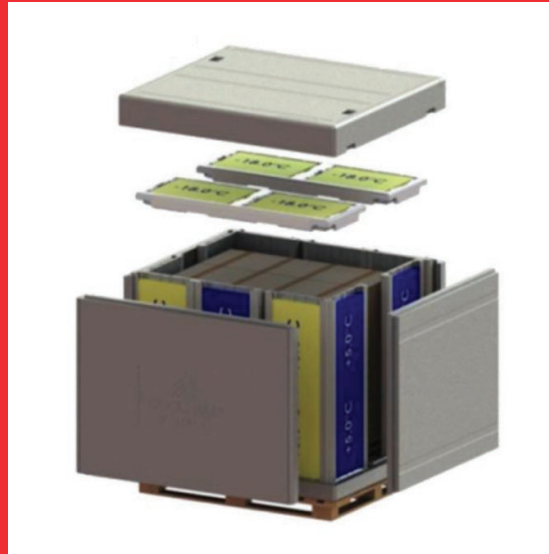
TEMPERATURE CONTROL PACKAGING

There are 3 different classes of temperature control packaging: Active, Passive and Hybrid.



ACTIVE

Active Containers utilize various mechanical cooling/heating methods to provide thermal protection to the payload. Most often the systems require some 'plug-in' time to charge the battery prior to use and may need to be plugged-in during use or at key 'touch points'.



PASSIVE

Passive packaging systems are insulated shipping containers that rely on fixed, non-mechanical cooling elements to keep the temperature of the contents within specified acceptable temperature ranges against the temperature fluctuations of the outside ambient environment.



HYBRID

Hybrid systems blend the technology from the active containers and Phase Change Materials (PCM) passive systems into one. The active element of the system charges a 'PCM battery' that is used when the system is not plugged into a power source during use. A passive shipper that is a mix of water-based and PCM coolants is often labeled as a 'passive hybrid.'

PASSIVE SHIPPING OPTIONS—HOW THEY WORK

This next section covers passive shipping options and how they work, giving detail on heat transfer, insulation materials, coolants, phase change materials and latent heat.

1. Heat Transfer

There are three (3) types of heat exchange that can occur during the use of passive shippers. This is where the ambient temperature affects the internal product temperature. It should be noted from the below diagram, that all three types of heat exchanges make for an extremely challenging and complex environment to model and to predict how a shipper will perform for a given shipping lane.

Conduction

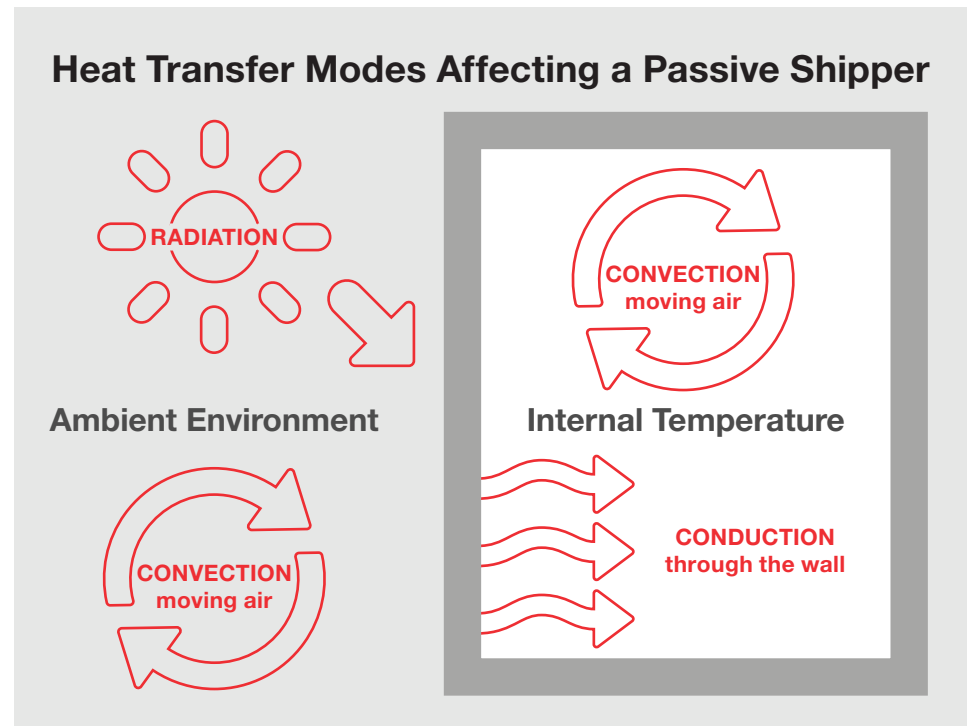
Transmission of heat through a solid object (e.g. shipper wall) where the temperature of the two sides are different. Heat travels from the hotter side to the cooler side

Convection

Transmission of heat by the movement of hot air over the cooler wall of the shipper when placed in the airflow.

Radiation

Transmission of heat from the ambient environment by electromagnetic waves (e.g. heat from hot tarmac or sunlight).



PASSIVE SHIPPING OPTIONS—HOW THEY WORK

2. Insulation Materials

There are various containers available now for the transportation of temperature sensitive clinical supplies. Insulation material and the type of coolants have a large bearing on the performance of the passive shipping system and its ability to maintain the desired temperature range.

Expanded Polystyrene Solutions (EPS) and Extruded Polystyrene Solutions (XPS) are both rigid, closed cell, thermoplastic foam materials. EPS is produced from solid beads of polystyrene. Expansion is achieved by virtue of small amounts of gas contained within the polystyrene bead. Additional insulation properties can be gained by additives such as Neopor. EPS with Neopor is commonly called Technical Insulation Foam (TIF).

Phase Change Materials (PCM) function by storing and releasing energy to reduce temperature fluctuations. While this technology is costly, it generally shows superior performance compared against traditional water-based coolants and it can be tailored to specific shipping temperatures. Shipments being controlled within +2°C to +8°C can be put into refrigerated conditions without the risk of low excursions.

Vacuum panels are examples of another technology—superior insulating properties within the walls of shipping boxes. While the additional insulation enhances safety, the downside is that the VIP panels need to be formed in a block or panel. The panels need to be linked together and the seam where the panels meet tends to diminish the insulation properties. Shippers with VIP insulation tend to be lighter and smaller with additional payload space.

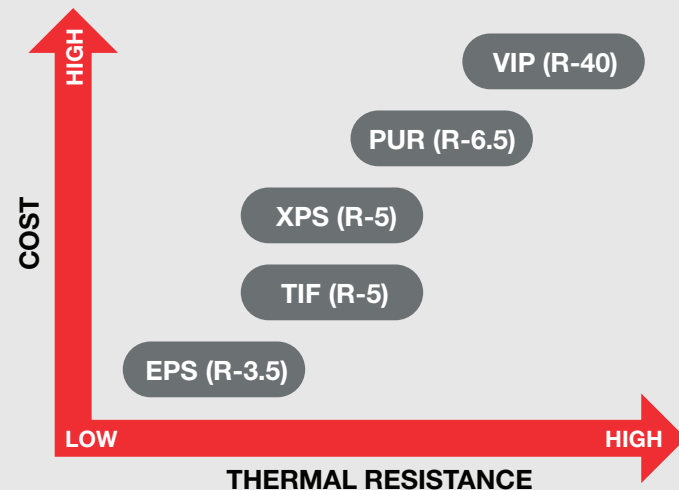
Insulation Material Performance:

The performance of the insulation material depends on the materials' thermal resistance or 'R' value. This is the ratio of the temperature difference across an insulator and the heat transfer through it. The higher the number the better the insulation materials effectiveness in resisting heat transfer. Generally, materials that have a higher R value are more expensive, but can withstand external ambient temperatures for longer duration.



You more often than not get what you pay for in terms of performance.

Relationship Between Cost and R Value



PASSIVE SHIPPING OPTIONS—HOW THEY WORK

3. Coolants

The cooling element for passive parcel shippers generally consist of frozen and/or chilled packs known as ‘Coolants’ and are constructed from a varying range of materials.

A

The coolants are ‘pre-conditioned’ to get the coolant within the desired state (e.g. solid or liquid) depending on the shipping temperature requirements

B

The coolants are then ‘conditioned’ to get the coolant to a usable temperature range (e.g. to prevent cold shock)

If the coolants do not need to be conditioned prior to use this is often referred to as a ‘zero bench time’ coolant (i.e. straight from freezer to shipper).

Common Coolants:

- Gel & water polyethylene bags in polyethylene sleeves supported by sponge or floral foam
- Gel & water filled bricks in cardboard sleeves
- Hydrocarbon based PCM in high density polyurethane shells

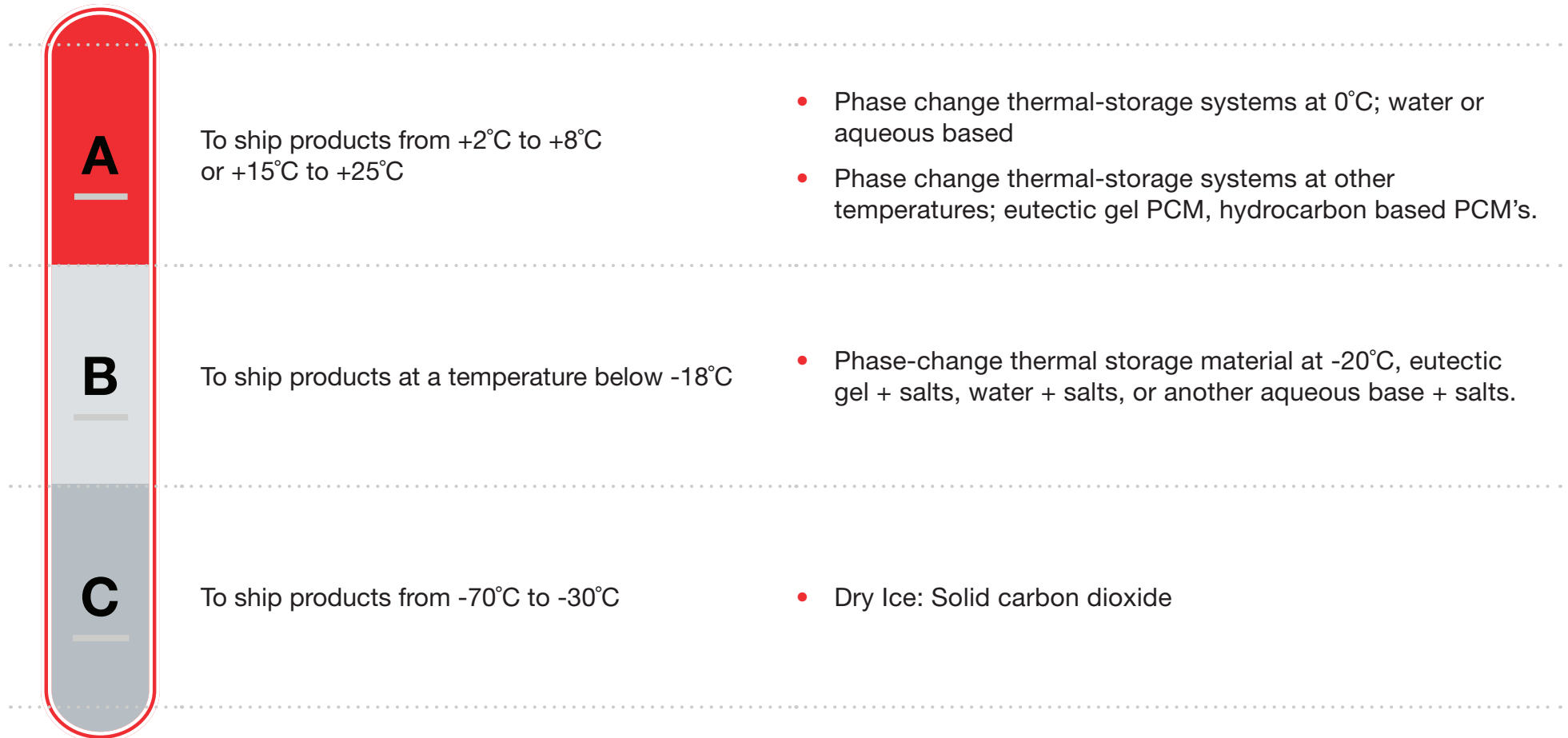


Note: Within the industry, Phase Change Materials (PCMs) are generally referred to as coolants other than water based coolants. PCMs are generally tailored to change phase within the shipping temperature limits. The more refined the PCM, the narrower the phase change temperature range and the higher the cost

PASSIVE SHIPPING OPTIONS—HOW THEY WORK

3. Coolants

Coolants are available for different temperature requirements.



PASSIVE SHIPPING OPTIONS—HOW THEY WORK

3. Coolants

Configuration

The coolant configuration is critical to the performance of a passive shipping system.

Most commonly, for a water-based passive shipping system, configurations combine chilled and frozen coolants for a +2°C to +8°C. The configuration of coolant is often referred to as the “pack out”.

To prevent a +2°C to +8°C product from localized freezing with a water-based shipper, it is important to have thermal buffering between the product and frozen coolant. This is often done by the use of insulation materials or chilled coolant placed between the frozen coolants and the product space.



A single all-year pack out is often referred to as a “universal pack out”. This is the ideal; however, it can not always be readily achieved with water-based coolants and high seasonal temperature fluctuations.



PASSIVE SHIPPING OPTIONS—HOW THEY WORK

3. Coolants

Advantages & Disadvantages of Different Types of Coolants

COOLANT MATERIALS	ADVANTAGES	DISADVANTAGES
 <p>Water-based (gel packs, gel bricks)</p>	<ul style="list-style-type: none">• Inexpensive• High latent heat• Less significant impact if coolant leaks into shipper than other materials	<ul style="list-style-type: none">• Phase changes at 0°C so there needs to be a careful balance of frozen and chilled material to maintain +2°C to +8°C (often means a 2 season pack out)• Only thermal buffering with +15°C to 20°C as no side to the cooler side. phase change occurs!• Much higher risk of excursions if shipper is handled incorrectly or if there are delays.
 <p>Hydrocarbon-based gels/salts PCM</p>	<ul style="list-style-type: none">• Phase Change Materials can be tailored to the temperature requirements (usually -20°C, +4°C, +17°C or +22°C for Hydrocarbon based PCM coolants).• +2°C to +8°C shippers can be put into cold storage without the risk of driving temperatures low.	<ul style="list-style-type: none">• Usually lower latent heat than water per kg• Relatively expensive• Can have problems with PCM leaching or leaking into shipper if PCM pouches are not well sealed.

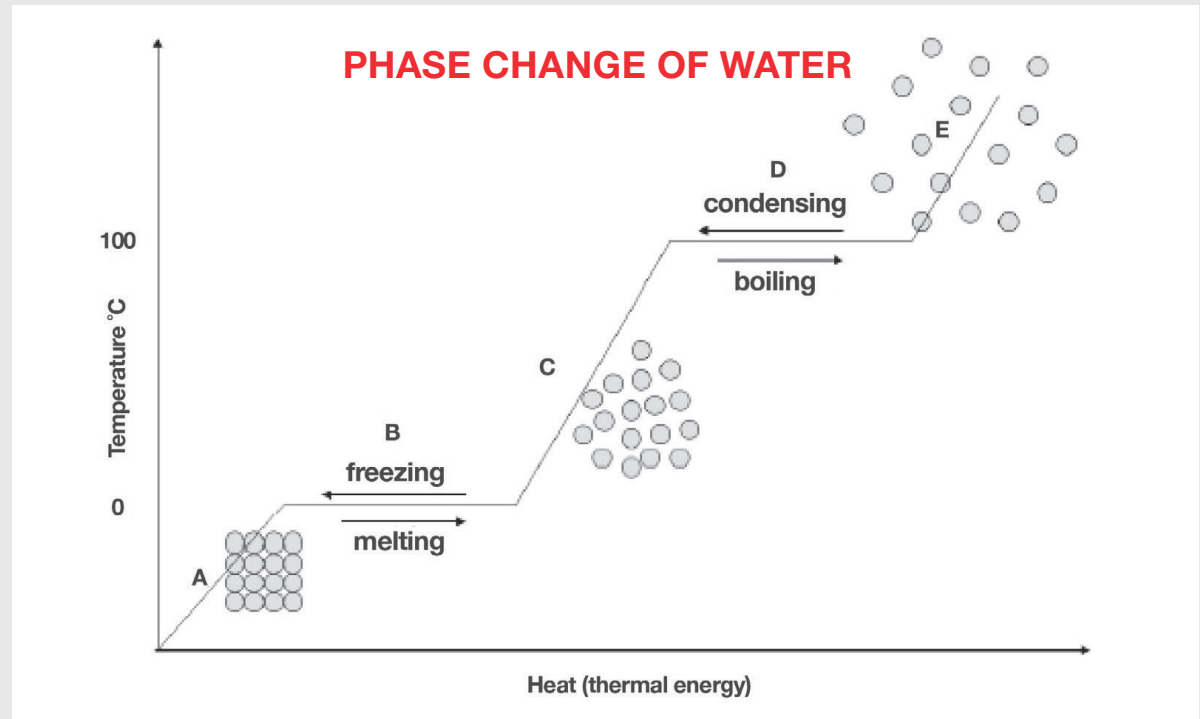
PASSIVE SHIPPING OPTIONS—HOW THEY WORK

4. Phase Change & Latent Heat

Phase-Change Material (PCM) is a substance with a high heat of fusion which, melting and solidifying at a certain temperature, is capable of absorbing, storing and releasing large amounts of heat energy. Heat is absorbed or released when the material changes from solid to liquid and vice versa; thus, PCMs are classified as latent heat storage (LHS) devices.

Latent heat is the heat released (freezing or condensing) or (melting or boiling) by a body or a thermodynamic system during a that occurs without a change in temperature.

A typical example is a change of state of matter, meaning a phase transition such as the melting of boiling of water.



The latent heat stored within the coolants is the main reason that such temperatures can be achieved within a passive shipping system exposed to fluctuating external temperatures. An illustration as to the power of latent heat is that it takes as much energy to melt 1 kg of solid ice to water at 0°C as it does to heat 1kg of water from 0°C to +80°C!

GLOBAL CLINICAL SUPPLY DISTRIBUTION FACILITIES

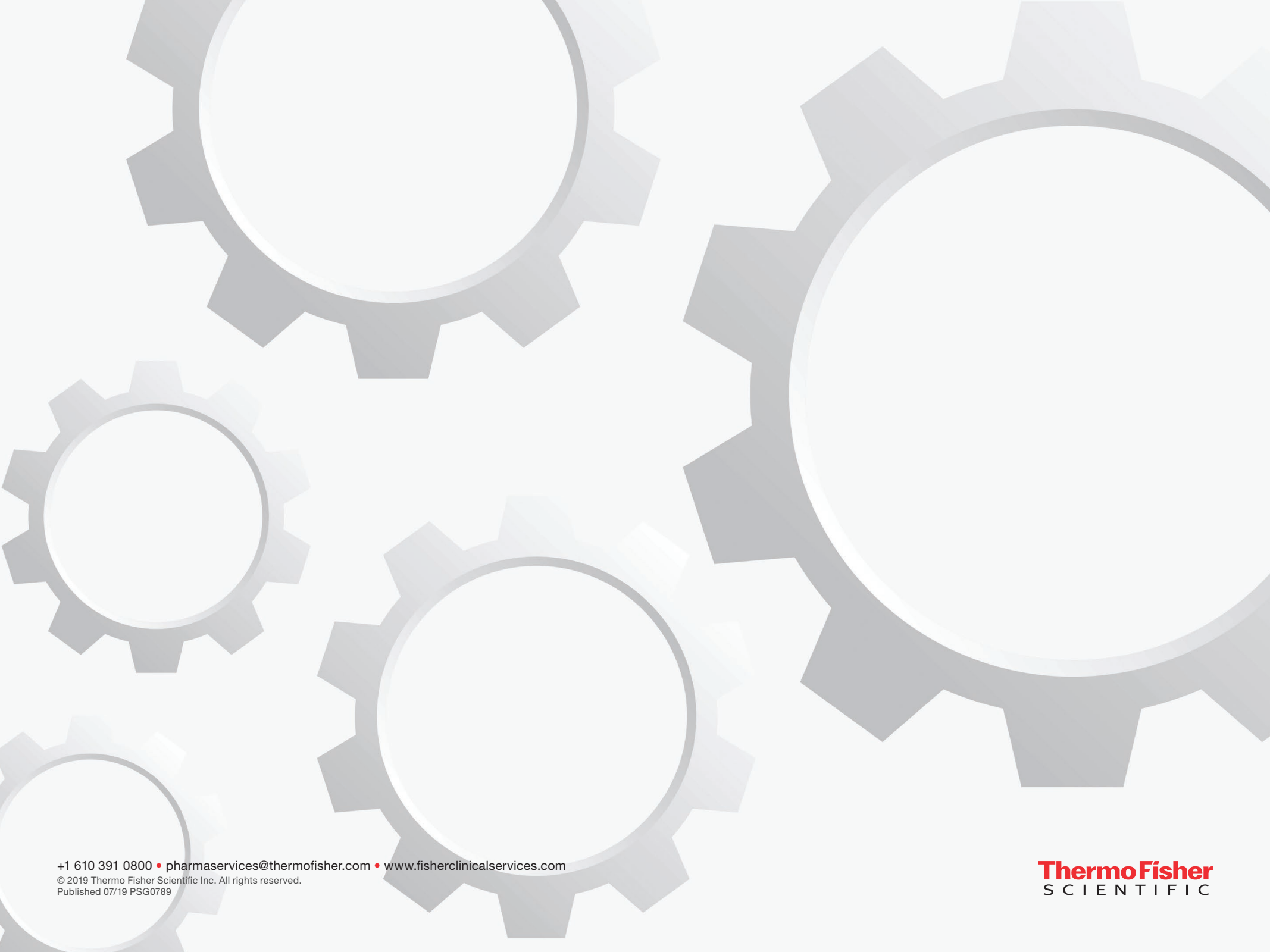


ABOUT US

With unwavering commitment to service, science and process engineering, Thermo Fisher Scientific is powered by people with an exceptional commitment to quality, deeply instilled ethics of personal responsibility and unrivaled expertise.

Thermo Fisher Scientific is the world leader in serving science, with revenues of more than \$24 billion and approximately 70,000 employees globally. Our mission is to enable our customers to make the world healthier, cleaner and safer. We help our customers accelerate life sciences research, solve complex analytical challenges, improve patient diagnostics, deliver medicines to market and increase laboratory productivity. Through our premier brands—Thermo Scientific, Applied Biosystems, Invitrogen, Fisher Scientific and Unity Lab Services—we offer an unmatched combination of innovative technologies, purchasing convenience and comprehensive services.

Fisher Clinical Services, by Thermo Fisher Scientific, are a comprehensive suite of market leading global clinical supply chain services. With a network of cGMP facilities strategically located across the globe to support the conduct of clinical trials, we offer worldwide support for all aspects of clinical supply management including comparator, co-medication and ancillary supply sourcing, packaging, labeling, storage and distribution through to returns and destruction. With more than 30 years of experience exclusively focused on clinical trials, we can offer guidance and full logistics support across all types of clinical programs and projects.



+1 610 391 0800 • pharmaservices@thermofisher.com • www.fisherclinicalservices.com

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Published 07/19 PSG0789

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