ACTIVE SHIPPING CONTAINERS

VS

PASSIVE SHIPPING CONTAINERS

Guidance on making the optimum choice to eliminate confusion, reduce risk and save money when shipping temperature-sensitive pharmaceutical products

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Active shipping containers vs passive shipping containers

Guidance on making the optimum choice to eliminate confusion, reduce risk and save money when shipping temperature-sensitive pharmaceutical products

Temperature-sensitive pharmaceuticals need to be protected from hot and cold during their journey to market and a whole industry has emerged to meet the growing demand for cost-effective cold-chain solutions. Two different classes of thermal protection exist, namely active and passive, and although there are areas where one or other is the only solution, there are a lot of situations where there can be a case for either. This paper presents an overview of both active and passive systems and provides guidance for the selection of the most appropriate solution for different protection requirements.

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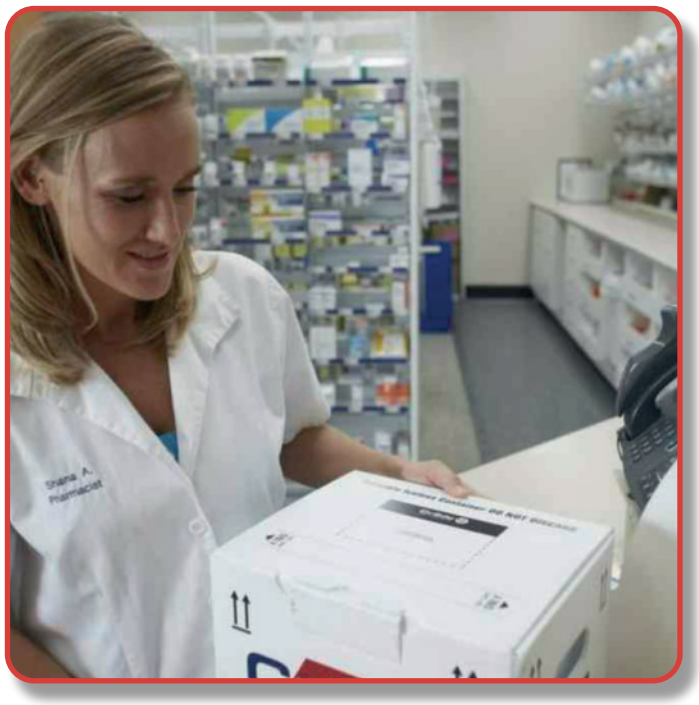
Currently worth around $1.2 trillion, global pharmaceutical industry revenue will reach an estimated $1.6 trillion by 2020[1]



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According to one recent estimate the pharma business loses upwards of $35bn per annum solely as a result of temperature excursions[2].

INTRODUCTION

Pharmaceuticals are designed to save, heal and enhance lives so it's no surprise that they need to be transported and delivered in a fully-functional condition. One of the most important criteria when it comes to maintaining the clinical efficacy of many types of drug is that of temperature. A huge proportion of pharmaceuticals need to be transported and stored within established temperature bands if they are not to have their therapeutic properties diminished or even eliminated.

It's a situation that presents enormous problems for the huge pharma industry which must ensure as far as possible that each one of the trillions of drug doses it produces annually arrive in perfect condition with millions of customers and patients right across the globe. This has resulted in the development of what is commonly referred to as the pharma 'Cold Chain' or, sometimes, the pharma 'Cool Chain'. This is the chain of actors and events that, through a highly synchronized approach, must ensure that the integrity of pharma products is maintained throughout their, often long and punishing, journey to market.

Given the highly competitive nature of the coldchain sector that has evolved to meet this need, there are many different standpoints regarding the best ways to address this physically complex issue. And, perhaps inevitably with so much at stake, much hype and ambiguity has been generated by purveyors of coldchain solutions which has only served to fuel confusion, misunderstandings and blinkered perceptions among those that are tasked with arriving at objective coldchain decisions.

One of these decisions relates to the choice of protective container in which a pharmaceutical product will be shipped. Here one of the principal dilemmas facing the product specifier seeking the optimum protection choice relates to the question of economic viability rather than technical performance; if money were not an object then there are many more or less foolproof protection systems that could be utilized. The reality, of course, is that coldchain shipping decisions are subject to the cold, hard light of budgetary reality which necessitates juggling different performance and risk criteria with the financial implications.

This paper considers the nature of the two main classes - active and passive - of shipping container system currently in widespread use for the safe transportation of pharmaceuticals and provides insights and guidance on their choice and use. It gives an overview of the key differences and the relative advantages and disadvantages of each type.

Specifiers and users of coldchain packaging will be able to use this paper as a source of reference when making fundamental choices with respect to the optimum solution for any given transport situation.

PHARMA TEMPERATURE MONITORING

The Need

The market for pharmaceuticals is large and diverse with products ranging from extremely rare research biologics that are shipped infrequently in tiny volumes to much lower value mass-market products that are systematically shipped around the world in bulk. In some cases the product will be sent by highly specialist courier service where it is kept under continuous surveillance, in other cases it will be conveyed as mere 'general cargo'.

Between these extremes are a myriad of different distribution scenarios. In some instances the distribution process is relatively direct, but in most situations the pharma-distribution model involves multiple third-parties all of which need to dovetail together closely in order to ensure that the integrity of the cold chain is maintained.

All temperature-sensitive pharma medications have different chemical and biological compositions and this means they are all potentially affected in different ways by the application or removal of heat. In practice this variability has largely been overcome from a transportation and storage perspective through the use of defined 'temperature bands' or 'temperature ranges' to which products with different prescribed temperatures limits can be assigned. These temperature bands, and any allowable temperature excursions from them, are generally derived from stability data from product tests (see Stability Data).

However, it is interesting to note that the main regulatory authorities do not refer directly to these bands in their guidance documentation. Good Distribution Practice (GDP)Regulations from the EU, for example, simply state that products must adhere to the temperature restriction on the outer packaging or as otherwise described by the manufacturer[3]. In the event of a temperature deviation during transportation the regulations require both the shipper and the recipient parties to be notified and for investigatory and handling measures to be triggered.

Products sensitive to high temperature can deteriorate by receiving thermal energy that will[2]:

- Decrease active ingredient content through transformation of degraded components (oxidative, hydrolyzed and others), some of them with possible toxic properties. The longer the time and the higher the temperature of exposure to the out-of-range conditions, the higher the amount of degradation products.

- Depreciate formulation properties, for example coloration of some components, dissolution rate modification, or separation of emulsions.

A high proportion of temperature-sensitive pharmaceuticals are required to be conditioned and maintained at temperatures between 2°C and 8°C (the 'Cold Chain') to ensure that they lose none of their potency during travel.

Another group of products must be maintained at 'Controlled Room Temperature' and this normally relates to a temperature band between 15°C and 25°C (the 'Cool Chain'). However, as noted above, there is nothing legally sacrosanct about these bands. Some particular products, need to be kept at, or between, very specific temperatures, particularly biologics that have to be kept below their biologically-active temperature thresholds.

Good Distribution Practice (GDP)

Moving pharma products from A to B has the potential to affect the efficacy and quality of a product or even to render it ineffective or, at worst, dangerous, so it is is important that adequate controls are in place to control risk.

The significance of these extremes of temperature is not lost on the pharmaceutical industry which is having to meet ever-more stringent regulations relating to the temperature control of its products during the storage and distribution steps.

Ultimately, it's all about patient safety and the temperature control issue in particular has been pushed to the fore by the recent extension of the European GDP to cover those finished pharma products that require continuously controlled room temperature (CRT) freight conditions.

One recent industry study (4) suggests that around 87% of pharma companies manufacture products in this CRT category and for the majority of these producers it is the dominant part of their overall production.

Some Biologic Temperature Thresholds[4]

- Whole Blood & Red Blood Cells: 1-6°C
- Plasma & Cryoprecipitated AHF: -18°C or colder
- Other Biologics: up to -60°C
- Platelets: Gentle Agitation: 20°-24°C
- Granulocytes: 20°-24°C
- Biologics: Thrombolytic agents, hormones, maemotopoietic growth factors, interferons, enzymes, monoclonal antibodies: 2-8C
- Other Biologics: -60C

Qualification and Validation

The prevailing GDP laws provide guidance of course, but they are risk-management focused rather than prescriptive. It is down to the pharma manufacturer, often in partnership with its logistics providers and product suppliers, to develop and test appropriate validation measures in order to prove that their distribution arrangements are under control. This involves establishing the critical control points in the distribution chain and qualifying each individual step.

However, the terms "Qualification" and "Validation" are often misunderstood or confused when it comes to good coldchain practice. The words are often used interchangeably and indeed both relate to the process of proving that a process or equipment is 'fit for purpose'. Certainly the most important thing of all is to ensure that something is fit for purpose rather than get bogged down in semantics.

However, the International Conference on Harmonisation (ICH) provides the following definitions[5] which are mirrored in the latest EU GDP guideline[3]:

Qualification

The action of proving and documenting that equipment or ancillary systems are properly installed, work correctly, and actually lead to the expected results. Qualification is part of validation, but the individual qualification steps alone do not constitute process validation.

Validation

A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting pre-determined acceptance criteria.

This means in practice that all components or equipment used in a 'validated' coldchain must be individually 'qualified'.

Coldchain Route Qualification

Regulatory obligations make it necessary for producers to validate cold chains and qualify their associated shipping lanes to demonstrate that the necessary controls are in place to ensure product and, ultimately, patient safety.

In order to provide the necessary evidence that such stipulations are being met, pharmaceutical equipment is subject as a requirement of Good Distribution Practice (GDP)[3] to validation and qualification protocols (See Good Distribution Practice) in order to demonstrate its fitness for intended purpose. These validation exercises are designed to provide shippers and regulators with a high degree of assurance that the transportation arrangements in place can meet consistently all the requirements placed on it. In the case of shipping containers, a product needs to be 'operationally and performance qualified' as part of an overall validation process.

This means that all coldchain packaging systems, vehicles and storage facilities, together with all attendant methodologies and operating procedures, need to be approved and performance-validated through a rigorous programme of pre-testing, field trials and ongoing data capture. Transportation validation is part of the overall pharmaceutical quality control process. It is essentially a systematic approach to collecting and analyzing the necessary data to give reasonable assurance and documented evidence that a specified coldchain system and protocol will consistently operate as expected within specified parameters.

Temperature Profiling

Guidance from regulatory authorities such as the Parenteral Drug Association (PDA) advises the need to "anticipate the ambient temperature variations and duration to which a product may be exposed during transportation"[6]. Such 'temperature profiling' is another tool for ensuring that disparate products can be risk-controlled and managed in the multitudinous environments they might encounter along the distribution chain. Temperature profiles are designed to accurately reflect the expected temperature conditions on a given route and form the basis for the design, configuration and qualification of temperature-controlled shipping systems. Different profiles may be compiled to reflect different exposure conditions, for example summer and winter, or an 'all-season' profile may be preferred. An example of a typical temperature profile can be seen in Fig 1.

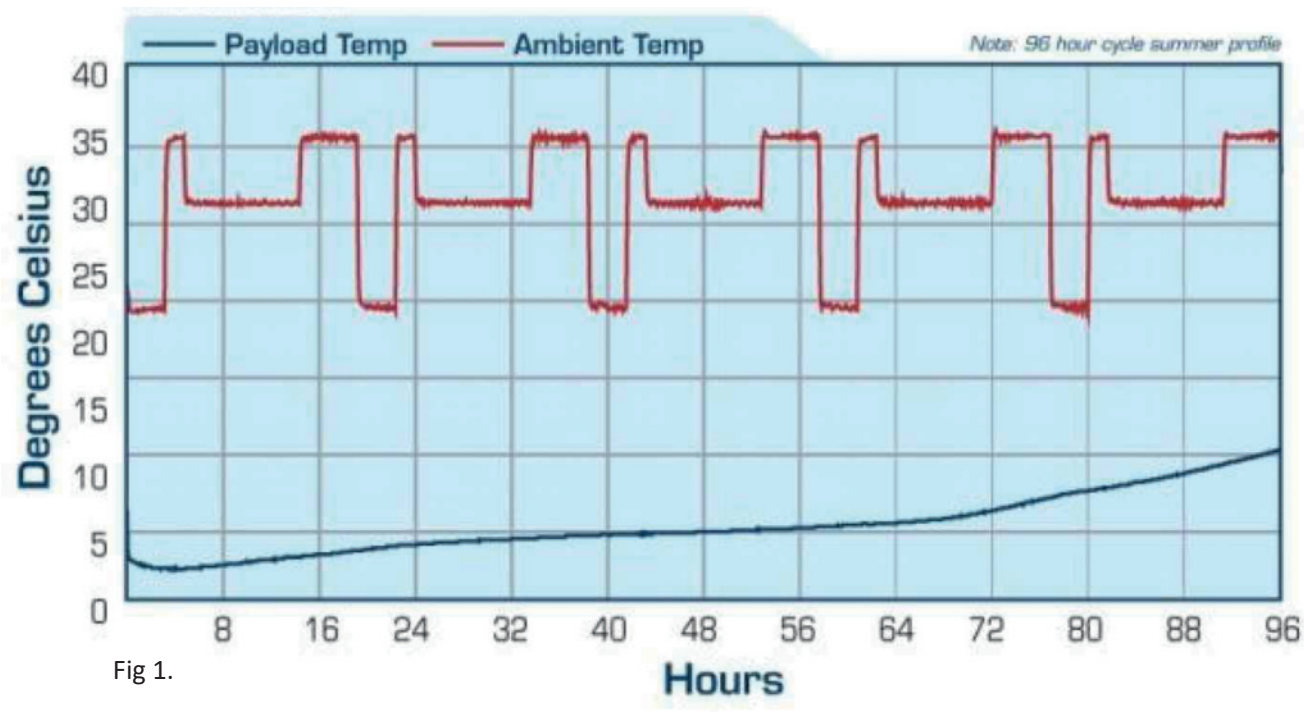


Fig 1.

However, such profiles can be produced from a wide range of sources, both static and dynamic, may contain assumptions which require robust substantiation and are not, in themselves, the subject of regulatory oversight, so it is essential that they are

Stability Data

Stability data is normally proprietary to the pharmaceutical manufacturer who will use this information to determine whether a temperature excursion will have a detrimental effect on the product concerned. It will be the ultimate arbiter when a decision is taken as to whether to condemn a violated consignment. However this data is rarely shared because the legal requirement for shipping conditions is normally based on the external label data and shippers understandably do not want any 'safety margin' implicit in stability data to be exploited by logistics providers.

It should be noted that there are a number of moves afoot to re-assess current temperature bands in the light of better understandings of product stability and the acquisition of better stability data[7]. Some parties argue that some relatively stable products, although reliable data is available, are being forced into unnecessarily restricted storage conditions.

If so, then there are likely to be many cases of perfectly safe and useable pharma products triggering costly and time-consuming recording and investigational procedures and potentially a lot of product being being needlessly discarded. Others point to the fact that current CRT levels are arbitrary and it would make sense from a cost and procedural basis to widen this to, say, 2°C - 25°C. Only time will tell.

rigorously formulated. In particular they must capture the likelihood of temperature extremes, which due to their unpredictability, infrequency and lack of measurability may not feature in relatively unsophisticated or so-called 'standard profiles. Such standard profiles sometimes form the basis for a container design. However, they should never be relied on for the validation of a shipping lane because they will often rely heavily on such assumptions and be of limited value with respect to guarding against the type of extremes that are likely to cause dangerous thermal excursions.

For example, in the past, many pre-qualification tests for thermal packaging have ignored the important phenomenon of solar radiation exposures on the basis that it was a) of limited consequence and b) unlikely to be encountered. These are both wildly erroneous assumptions and yet, when conducting risk analyses and undertaking performance tests, many have relied on temperature profiles based on simple bracketed ambient temperature readings. It is just such uncontrollable and unpredictable factors that mean that it is not possible to simply rely on historical 'meteorological office'/NWA data when compiling temperature profiles.

ACTIVE CONTAINERS

"Key benefits include unprecedented independent temperature reliability, large payload capacity and product stability over long spans of time and distance"[12]

PROS

- Suitable for large, regular, fixed loads to serviced destinations
- Stable temperatures can be maintained for prolonged periods
- Unlimited protection and transit times when power source available and utilized (compressor models)
- Dry-ice air-freight models can typically operate for 100 hours or more
- Inbuilt heating capability (compressor models) provides full thermal modulation and protection against low temperatures
- Can be simpler to fill since they do not require complicated packouts or coolpack segregation
- Generally perceived as physically more secure than passive equivalents since the units are of solid materials and lockable
- Active sea-freight reefer containers have a high load payload capacity which can be very cost-effective
- Eco-friendly due to their re-usable status although there are 'sunk-carbon' costs associated with consumables e.g. batteries
- Easy handling at airport due to ULD design

CONS

- Needs constant power supply and batteries need to be periodically recharged
- Limited product protection in the event of a catastrophic power failure or battery expiration
- Inflexible in use due to need for power/fuel/ice availability which imposes tight restrictions on handling and shipping
- Dependable cold chain integrity is at the mercy of a complex array of electro-mechanical equipment
- Human intervention during transit can be necessary (esp. for dry ice replenishments, recharge hook-up etc.)
- The units need to be periodically temperature-calibrated for accuracy
- Units typically require one working day to recharge back-up batteries
- Limited sizes available. Typically active Unit Load Devices (ULDs) are available in either a ca. 2m³ size (designated 'RKN') accommodating a one U.S. or Euro pallet or a 6.4m³ size (designated 'RAP') which takes up to 4 U.S. pallets/5 Euro pallets
- Some larger active units are restricted to wide-bodied aircraft which limits use or can result in convoluted routings
- Reliance on local service centers for troubleshooting/maintenance etc.
- Cold weather temperature-control performance may be affected by battery degradation
- Availability generally restricted to high-traffic lanes where local service/collect/deliver hubs are available
- Can be very expensive for small payloads due to fixed container dimensions and high pivot weight
- In a dry ice container, there can be thermal shock issues if proper air-flows are not maintained
- The use of ULDs can create handling difficulties when moving goods beyond airport boundaries

PASSIVE CONTAINERS

"In a well-defined lane, a passive system, because it is a simpler system to operate and maintain, actually reduces your risks as long as you can effectively manage duration and variability."[13]

PROS

- Suitable for long-haul routes with variable load sizes and changing route patterns
- Can be the least risky in short, high-traffic lanes since they are simple in use and require little or no intervention
- Highly flexible - can be scaled, configured and optimised to meet requirements from single doses to multiple pallets
- Offers a variety of sizes for not just bulk and can be used for aircraft, trucks and sea containers
- Obtainable in both reusable and single-use types to suit user preferences
- Available in durable 'pallet-compatible' designs making them highly competitive for bulk shipping
- Not relying on a power source, there is no possibility of a technical malfunction or power failure during transit
- Appropriate for many CRT-range and high-volume generic products where expensive active solutions are unthinkable
- Broad selection of solutions from multiple suppliers with different technologies and systems
- Wide choice of vendors provides for a high security of supply
- Collapsible full-pallet shippers are available for air-freight which save time and reduce return logistics
- No need to develop custom solutions; suppliers have a wide range of solutions, some modular, straight off the shelf
- Both re-usable and single-use products are available to suit different operational and environmental objectives
- A refrigerated 'hold' feature can provide unlimited storage time in a conditioned environment, fridge, customs etc.
- Products available with a wide range of standard autonomy times such as 24, 72, 96 and 120 hours. Can be extended in customs via a refrigerated hold capacity for some systems
- No upper or lower cooling limits, the energy is depleted depending on ambient conditions

CONS

- Finite limit to protection without human intervention (refrigerant top-ups, external cooling)
- Frozen refrigerant materials must be cooled and pre-conditioned and this can require refrigeration facilities fitted with containing temperature isolation compartments for different conditioning requirements
- The variety of passive shipping options means that suitable SOPs required plus appropriate operative training
- Seasonal pack-outs with modular packaging may be used to reduce costs but this increases complexity and introduces scope for excursions perhaps due to 'unseasonable' weather or poor changeover timing
- Depending on the insulation materials involved there may be a gradual loss of performance over time
- Generally perceived as less secure and tamper-resistant than metal- or composite-shell active containers

Definitions

The following are the definitions given by the US Parenteral Drug Association (PDA) the leading global provider of science, technology and regulatory information and education for the pharmaceutical and biopharmaceutical community.

Active Temperature Controlled System:

Actively powered system that uses electricity or other fuel source to maintain a temperature controlled environment inside an insulated enclosure under a thermostatic regulation (e.g. cold room, temperature-controlled truck, refrigerated ocean or air container)[9]

Passive Temperature Controlled Packaging:

Transportation systems that maintain a temperature-controlled environment inside an insulated enclosure, using a finite amount of preconditioned coolant in the form of chilled or frozen gel-packs, phase-change materials, dry ice, or others.[10]

Pre-Qualified Containers

In some lower-risk cases, OQ tests results may be deemed sufficient to 'pre-qualify' a coldchain component product for 'off-the-shelf' operational use. These 'one-size fit all' solutions reduce costs and save time and for some specific needs can be appropriate. A situation where a pre-qualified coldchain component might be considered appropriate, for example, might involve a regular short-haul route within a single climatic zone using a reliable logistics partner and with a known coldchain infrastructure at journey start and end.

However, a reliance on 'pre-qualified' component products brings its own risks and can lead to protection for temperature-sensitive pharma merchandise that is either under- or over-specified for a given use or situation. Operating conditions can vary enormously even within a given shipping lane.

Environmental extremes, different pharma merchandise characteristics and densities, changing loading patterns, varying payload sizes etc. are just some of the factors that can easily lead to 'out of spec' conditions. This means that 'pre-qualified' status is of limited value when it comes to the selection of coldchain components since it confers no recognized standard of quality or performance and there are no normalised test regimes to enable like-for-like comparisons between competing coldchain component products.

ACTIVE AND PASSIVE – WHAT ARE THEY AND HOW DO THEY WORK?

Passive Systems

A passive container is much like it sounds - one that has no active mechanisms or moving parts, and requires no human interaction in order to function when in use. 'Passive' packaging solutions rely on clever design and the presence of suitable insulants and energy sources in order to perform. In accordance with the Second Law of Thermodynamics the temperature inside a passive container will always be progressively warming as its cold source slowly equalizes with the external ambient on the outside so long as the external air is warmer than the set-point for the package. It is important to note that temperature-control containers are not designed to act as pre-coolers. Both active and passive containers and their contents must be temperature-stabilised in suitable cooling facilities prior to packing and transit in order to maintain the product temperature and ensure the performance of the container is not seriously compromised. Passive units are typically designed to function reliably within pre-defined temperature ranges normally ranging from about -20°C to +30°C.

Active Systems

Large active containers generally rely on well-proven compression or dry-ice cooling technologies to perform. Active containers, like their passive equivalents, are also just like they sound. These units are dynamic in nature being fitted with thermostats that are continuously monitoring the internal temperature and which trigger an active response to any deviations caused by external conditions. This makes them environmentally reactive unlike passive containers which must be designed with the built-in functionality to store and release energy in order to deal with unexpected extremes such as a sudden cold snap, solar exposures, significant time spent in shade or extended delays such as a random customs internment. Active containers are typically able to perform effectively at ambient temperatures of between at least -20°C to +40°C. This enables them to perform at all the recognized temperature bands. Some of these active units are pre-fitted with integral tracking and monitoring solutions, others support third-party equipment for location, payload condition and the ambient monitoring to ensure maximum flexibility and compatibility.[8]

The response mechanism in an active container can be of two types:

a) Eutectic (cryogenic). These derive their cooling properties from eutective cooling which invokes the principle of latent heat by employing a pre-frozen eutectic solution, in this case frozen carbon dioxide or 'dry ice' in order to cool the container as required as it gradually thaws out or 'changes state'. In this respect it is more akin to a 'passive' container but the difference remains the fact that it involves thermostat control to activate the dry ice and circulate it within the container thus cooling it down (see Dry Ice (Eutectic))

b) Vapor-compression refrigeration. These use an electrically-driven compressor to cool a refrigerant in exactly the same way as a household refrigerator. Most have radiant heating elements built in and, like their dry-ice brothers, require an AC or battery power supply to function. This heat-cool temperature management capability means that these containers provide the most reliable means of adhering to a fixed set-point temperature.

Advanced Passive Packaging Systems

Passive containers are designed to be highly configurable, and utilize a large and growing array of different insulants and phase-change coolants. Understanding the differences between the various passive materials can be very useful when comparing different systems (see R-values and comparing different insulation materials).

Dry Ice (Eutectic) Containers

Dry ice is solidified carbon dioxide which at seal-level sublimates at at a temperature of -78.5C and is available in either block or pellet form. Pellets are convenient for reservoir filling but take up considerably more space than solid block form. Although dry ice is environmentally benign it poses a number of health risks and in addition to its hazard to humans, can damage some products and/or their packaging.

It must be stored and handled correctly in accordance with prevailing Health & Safety legislation and precautions must taken against the possibility of carbon dioxide an asphyxiation in confined or poorly ventilated spaces. Dry ice adds a considerable weight penalty to a container and it can also present availability problems in some locations.

In contrast, compressor-based containers are seen as a more modern solution to active temperature control and they have the big advantage that they have heating as well as cooling properties. This is of paramount benefit in the case of most vaccines and many biologics which must not be exposed to freezing conditions under any circumstances.

R-values and comparing different insulation materials

The R-value is a measure of thermal resistance, or ability of heat to transfer from hot to cold, through materials and composites. It tells us how well a particular material insulates and the higher the R-value, the more a material prevents heat transfer. The R-value is a measure of heat-flow by conduction for a given thickness of a material.

However it does not account for temperature change through convection or through any heat radiation properties of the material's surface. The latter is an important factor in the performance of, for example, solar-protective cargo covers. The R-value of a layered composite material is simply the sum of the different values and r-values are simply scaled up or down when the thickness of the material changes.

R-values in most of the world are shown in SI units of $K \cdot m^2/W$. In the US units of $ft^2 \cdot °F \cdot hr/BTU$ are sometimes used which gives an R-value figure about 5.67 times larger than those expressed in metric units.

The backbone of any passive shipping container is the low thermally conductive insulation material that provides the first line of protection against thermal shocks from high or low ambient temperatures. In the case of passive shippers for pharma products these insulants are usually made from either partially-open-cell expanded polystyrene (EPS), fully-closed-cell extruded polystyrene (XPS), rigid polyurethane (PUR) or vacuum-insulated panels (VIP).

EPS

EPS is produced from a mixture of about 90-95 percent polystyrene and a 5-10 percent inert gaseous blowing agent. This gas forms bubbles and expands the polystyrene into a rigid foam. The result is a very low density foam matrix which, due to the interstitial gaps between the closed-cell polystyrene pellets that are used in its production, is somewhat porous and this deficiency can lead to the ingress of water vapor in humid conditions and a commensurate reduction in thermal properties. Although it is rigid, EPS is relatively weak and easily damaged although it is the lowest cost of all the insulation materials. It has low thermal conductivity values of typically 0.035 W/(m·K).

XPS

As a thermoplastic polymer, polystyrene lends itself to being extruded and molded and these are properties that are fully exploited in the production of XPS. Compared to EPS it is effectively a fully closed-cell material and it is more rigid and uniform in composition. It has a similar thermal performance to EPS.

PUR

Rigid, low-density polyurethane foams are also used to provide With a thermal conductivity of ca. 0.03 XPS is second only to VIP panels in terms of insulation efficiency. However PUR has little inherent strength and must be supported by secondary materials in order to maintain physical integrity. Furthermore, the entrapped gases in PUR which give it its excellent thermal performance can reportedly leak out over a prolonged timescale effectively resulting in a gradual deterioration in performance. This is ‘out-gassing’ phenomenon is not one that significantly affects EPS and XPS foams. Finally, PUR is the most expensive of the foam materials commonly used.

VIP

Vacuum insulated panels involve the encasement of a thin, high-performance insulant such as aerogel or molded foam, within an outer skin from which around 95% of the air is evacuated and then sealed hermetically. Vacuum-insulated panels are the most efficient insulators of all and VIP panels can be up to seven times as thermally efficient as a foam plastic alternatives. This performance comes at a cost but it should be remembered that with VIPs the thermal resistance per unit price is much less than conventional materials.

When they were first introduced VIPs were sometimes susceptible to vacuum loss over time due to air gradually infiltrating the panel and equilizing the pressure with the surrounding air. However, with modern production systems and quality control this is no longer a problem, Indeed, many VIP manufacturers are currently claiming effective life-spans in excess of fifteen years plus for vacuum panels. And unlike materials such as polyurethane foams, VIPs do not suffer from performance loss from outgassing or moisture retention.

A big benefit of VIPs for cargo protection relates to their excellent space : performance ratio. This attribute can be engineered to provide permutations of extremely low bulk protection and very long hold-out times.

Ocean Freight

Much of the 'active vs passive' debate centres around air freight where the two alternatives have their horns firmly locked, However active containers, known as 'reefer containers' are a staple resource in sea freight sector where they have a huge presence in the transportation of perishables and other temperature-sensitive products.

An ocean reefer is basically a standard intermodal container that is fitted with an integral refrigeration unit and possibly a back-up generator and another redundant refrigeration unit for the ultimate reliability with high-value, high sensitivity loads. Standard 20 foot, 40 foot and 40 foot 'high-cube' reefers are generally available with the smaller 20 foot container having a capacity around 14 times greater than a standard RKN air-freight ULD.

In the past few years an increasing volume of pharmaceutical merchandise has been shifted from air to ocean on account of the latter's perceived reliability, greater security, lower number of handling points, minimal load interference and, of course , greatly reduced cost[11].

With weight and volume not being such a big issue, and with quayside and on-board electrical power readily available, it is possible to incorporate more redundancy and features without noticeably compromising the capacity.

Interestingly, however, the use of refrigerated sea-freight reefers does not completely eliminate the need for passive protection. Passive protection is still required to cover the 'plugin-gaps' usually during loading and unloading and may also be necessary to ensure temperature integrity in the road-feeder and delivery steps when a diesel power generator is not available.

Thermal PCMs

Whenever a material undergoes a change in phase, for example during the transition of water from ice (solid) to water (liquid) to steam (gas) and vice versa, a relatively high amount of energy is either released or absorbed at a fairly uniform temperature in order for this to happen. The energy involved is known as the "latent heat of fusion."

A large proportion of passive containers use this latent heat phenomenon in order to reinforce their insulation performance and the term "phase change material" (PCM) is used to describe the temperature-modulating materials involved. PCMs when subject to warming will liquefy and absorb heat; conversely when subjected to cooling they PCMs will congeal and give off heat and, in the process, warm their immediate surroundings. PCMs can be formulated to provide a wide range of refrigerative properties.

Water- and brine-based gel coolpacks

The lowest cost and most readily available PCM is plain H2O. When water freezes it goes through a phase change, liquid to solid. The amount of energy that is removed in this change of phase is no longer the usual 4.18 joules per gram per degree Celsius (4.18 J/g·°C) but 333 J/g·°C. Plain ice or water-based gels can be supplied in flexible or rigid pouches which can be easily prepared in standard refrigeration units. These are able to provide effective protection against short-term exposures to high temperatures. The reason gels are used is simply because fluid-based versions could cause a lot of damage in the event of leakage and gels can typically withstand a high number of freeze-thaw cycles.

Eutectic PCM gel coolants

In the context of temperature controlled packaging, the term 'PCM' usually refers to materials that are not straight water based but to ones that have been specially formulated to melt or freeze at particular temperatures to suit different product requirements. Gel PCMs are usually derived from either vegetable-, salt-hydrate-, or paraffin-based sources and tend to be a lot more expensive than basic water-based refrigerants. In many cases they form part of a reusable system for reasons of cost.

PCMs need to be combined with very efficient packaging designs which will normally incorporate high performance conventional insulation materials to ensure that their full phase-change temperature properties are maintained.

Shipper's Evaluation Exercise

At a recent supply chain conference[14] one global pharma shipper presented an active versus passive decision-making model which they have developed as a guide to selecting the optimum protection system. The need had arisen following the shipper's acquisition of another vaccine business which it wished to assimilate into its existing vaccine operation.

The active vs passive issue arose when it became apparent that the shipper concerned had acquired a vaccine business which had always relied on active container systems to provide the necessary product protection. The question to be answered was "is there a 'right' answer when it comes to choosing between active and passive for temperature controlled distribution?"

An examination of the relevant operational and non-operational selection criteria together with an analysis of the fixed, variable and intangibles costs relating to specific shipment characteristics and destinations led the shipper to a novel 'TCO evaluation model' and the conclusion that, in fact, there are no definitive 'one size fits all' solutions. By feeding in the costs associated with a particular shipping lane, the operator is able to view the financial 'break-even point' between different active and passive options as an aid to arriving at an optimal result.

As a consequence the shipper concerned is now following a two-pronged approach using both active and passive protection for their vaccines, combining maximum flexibility with the lowest overall cost.

OTHER CONSIDERATIONS

When looking at protective packaging for pharma products two additional factors that might be considered are, firstly, the benefits of employing scientific modeling techniques and, secondly, the pros and cons of using re-usable shipping containers.

Modeling

The problem with considering all the different active/passive product features and benefits is one of time and cost. Considering them all in the context of real-life temperature profiles, which in themselves can be very complex, time consuming and expensive to develop, becomes a major, if not impossible, task. This is where modeling comes in. A typical cargo will be exposed over several days or weeks to varying ambient and flash temperatures whilst travelling in multiple transport modes via several transportation hubs and operators. There will be unavoidable delays, equipment malfunctions, exterior exposures, weather impacts, door openings and many other unforeseeable events that can impact the transportation. Modeling allows all these variables to be dynamically simulated and tested without the need to conduct live tests in real world conditions.

Although a physical route qualification exercises will probably still be required, a modelling strategy can greatly support and accelerate the technical decision-making process and minimise the scope for costly failures. Such a risk-based approach allows the consideration of more packaging options, the determination of the 'what if' consequences for different product combinations and the likely impacts of different events during transportation process. Simulations, of course are abstractions of reality and are only as good as the underlying assumptions and interactions, the quality of the mathematical and the quality of analysis. By necessity they are always a simplification of the real world and if a reliance is being placed on them, they need to be carefully built from a full understanding of the physical realities of pharma transportation.

Single-use vs Re-usable Shippers

Passive shippers can be either single use or multi-use. Re-usable containers are often, but not necessarily always, the most environmentally-friendly or cost effective solution. The high cost of high performance passive shippers can make reusable systems rational in financial as well as in environmental terms but re-use requires careful planning of the reverse logistics programs and perhaps a collapsible product design in order to succeed.

While re-usable containers might seem at first sight to be the most responsible, environmentally-efficient solution, things are not always so simple in practice. Although there may be an intuitive desire to 'do the right thing' and reuse where possible - the so called 'moral imperative' - not all pharma packaging justifies being returned and re-used. Re-use can be very inappropriate in some cases where the safety, cost and environmental criteria just don't stack up.

The long-distance return-logistics involved with re-usable covers can quickly wipe out any perceived environmental benefit while the possibility of product damage and contamination increase significantly. Multi-use containers need to be periodically inspected, cleaned, maintained, repaired and tested and it can be very difficult to maintain 100% availability even with a continuous control regime in place. When it comes to cost, the economics of re-using shippers cargo covers can sometimes be hard to justify. There are many "hidden" and not-so-hidden costs as well as operational challenges associated with re-using shipping containers such as the need for a high degree of visibility since without a financially viable means of tracking it can be very difficult to maintain the degree of control needed in order to match supply and demand.

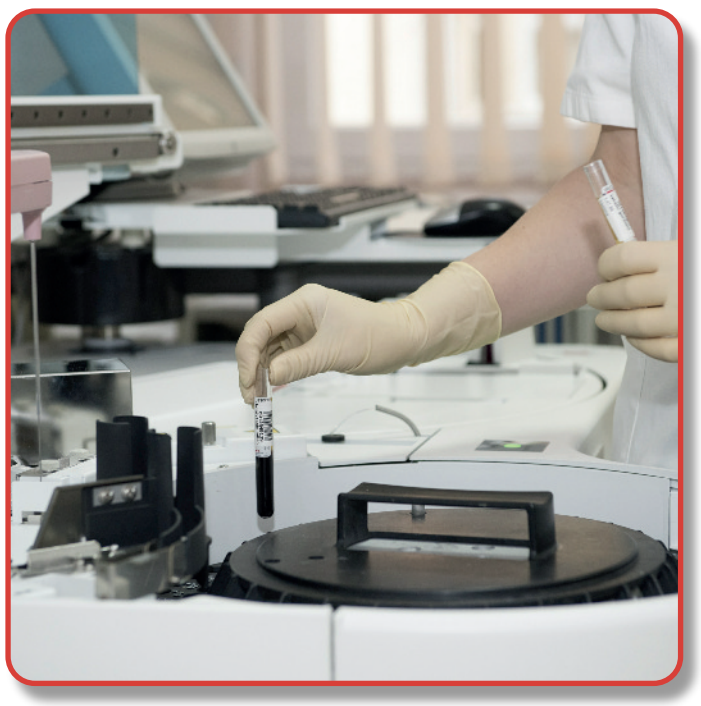
Environmental considerations

Nonetheless studies have shown that a well-managed re-use programme can provide significant environmental benefits over the long term. One study[15] showed that “the average single-use approach emits 1,122 tonnes of CO_2 compared with 241 tonnes with the reusable approach over the functional unit. This is roughly a 75 % difference in global warming potential between the two approaches.”

The study further estimated that choosing a reusable logistical approach relative to the single-use approach over a course of 30,000 shipments would reduce environmental impacts by the following percentages:

- Global warming emissions: 78 %
- Acidification emissions 66 %
- Eutrophication emissions: 67 %
- Photochemical ozone emissions: 86 %
- Human toxicity emissions: 56 %
- Post-consumer waste: 95 %

It can be seen that the reusable logistical approach imposed a significantly smaller environmental burden in all impact categories measured.



Seven critical factors to evaluate as part of the packaging solution selection process[16]

1. Performance needs, such as payload volume, temperature range and duration needed.
2. Ease of pre-conditioning/pack out, universal or seasonal.
3. Quality, specifically as it relates to regulatory needs, validation testing requirements and product tolerance level.
4. Pricing considerations, such as packaging cost, payload volumetric efficiency, packaging weight and total freight costs, as well as end-to-end shipping lane analysis.
5. Safety, including temperature data monitoring, shipment track and traceability.
6. Sustainability, considering single use versus reusable, closed-loop reverse logistics services.
7. Total cost of ownership.

A BASIS FOR DECISION

Total Cost of Ownership

A decision to use a particular technology and then a particular product usually involves the determination of the total cost of ownership (TCO) combined with flexibility and scalability considerations. Specifiers must consider the distribution model, the product value, the ease and cost of replacement, the achievable duration values, the insulation material and thickness, typical thermal mass of shipments together with more subjective factors such as vendor attributes, flexibility requirements, attitude to risk, familiarity with technology and sustainability considerations.

The TCO is the operational life-cycle or 'service life' of the product and includes all the overtly tangible costs incurred by the asset owner or user. This is not quite the same as 'whole-life costing', or 'cradle-to-grave' (C2G) costing as it is sometimes termed. A C2G cost analysis extends the TCO to include all the costs and consequential impacts borne by third-parties that relate to the product's use. These are the environmental and social costs which can be manifest all the way from raw material extraction, through usage to disposal to long-term post-disposal consequences.

Note that by considering TCO it is not being suggested that any longer-term environmental and social effects should be ignored. Simply that, due to their frequently intangible nature, and the often sketchy understanding of their full impact, it makes sense to assess these impacts separately, on a qualitative basis if necessary, and then rationally factor them into any subsequent decisions.

TCO = Initial Cost + Ownership Costs + End-of-Life Costs - Residual Value

Specifiers and buyers must always keep in mind the 'real costs' of using an unsuitable packaging product. These costs can completely overshadow the initial purchase price although they may be difficult to quantify financially at the outset. The cost of a product failure or the financial consequences of using an inappropriate product should always be factored in to a product value analysis. Selecting an unsuitable product which subsequently fails in the field will result not only in expensive product loss but, potentially, lost time, lost business, repeat shipment cost, investigational costs, significant administrative/reporting hassle, reputation loss and an official regulatory default. In other words, a 'cheap' solution can work out very expensive indeed.

Active containers, and to an increasing extent, passive containers, are often based around operating leases rather than outright ownership. Apart from minimising capital requirements and keeping the expenditures off the balance sheet, this largely transfers the headaches relating to availability, flexibility, maintenance, storage, obsolescence, disposal etc. to a third party. On some high-traffic routes, active containers are available on a one-way lease which eliminate return charges.

Risk Management

Historically, many shippers have opted for active container shipment simply in order to mitigate risk with the minimum of effort and some users continue to perceive active containers as a virtually foolproof solution. However, a reliance on batteries, external power sources, dry ice supplies and the associated manual interventions mean that passive containers have continued to gain round as their performance

steadily improves and their greater flexibility is embraced. Furthermore, many of the relatively stable Controlled Room Temperature (CRT) drugs, packaged consumer products and their generic equivalents do not merit the cost or restrictions associated with active protection.

The Future

The trend to biologics is creating additional environmental considerations - light, shock, vibration etc. - that need to be factored in to packaging considerations while the proliferation of low-cost generics, the rapid expansion of geographic markets, changing distribution models, and a growing global regulatory oversight will ensure that the demand for both active and passive pharma protection will continue to grow at a rapid pace. At the same time downward market cost pressures will necessitate tomorrow's packaging solutions to be more efficient and reliable than ever before.

As passive technology advances it is increasingly encroaching on the ground that was once the sole preserve of active protection and it is fair to say that for many pharmaceutical products especially those of a small-molecule variety, the flexibility, availability and affordability of a passive container will keep it as the solution of choice. However with an expanding support network and with the growth in highly sensitive, narrow temperature spectrum, biological medicines we are unlikely to see the demise of active containers any time soon. And it must not be forgotten that when it comes to choosing a temperature-management technology, the best cold-chain solution is never just about the product. The resources, expertise, experience, customer-focus, reliability and commitment of the supplier is just as important.

SUMMARY

With the huge range of variables involved – different products, shipping lanes, climates, storage infrastructures, handling competencies etc. there is no single or perfect solution to the safe shipment of temperature sensitive medicines. Both active and passive container have their advantages and disadvantages and in many cases it will be necessary to employ more than one solution to ensure that temperature requirements can be maintained across a broad spectrum of products and distribution objectives.

So for the foreseeable future there will continue to be a growing demand for both active and passive shipping containers for pharma products and the key will be in ensuring the most appropriate solution for the risks concerned. Indeed, in the face of ever more complex transportation challenges, by having access to these two technologies the pharma shipper is getting exactly what it needs - choice.

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