Best Practice Guidebook

Packaging Design and Qualification in Temperature Controlled Logistics

ColdChainIQ
Temperature Control Logistics & Quality Network

14TH COLD CHAIN GDP & TEMPERATURE MANAGEMENT LOGISTICS GLOBAL FORUM

A ruined shipment of temperature-controlled medicine can cost much more than lost revenue – it can cost lives.[1] Navigating routes to patients efficiently and cost effectively with temperature sensitive materials is a labor intensive task, and one which hinges on the investment in trustworthy equipment. Investment in packaging design and qualification is a critical part of the tool kit.

Active vs. Passive Industry Spend Snapshot

Active

Rise in spend seen with active packaging

46% of respondents stated that investment had increased in 2015.

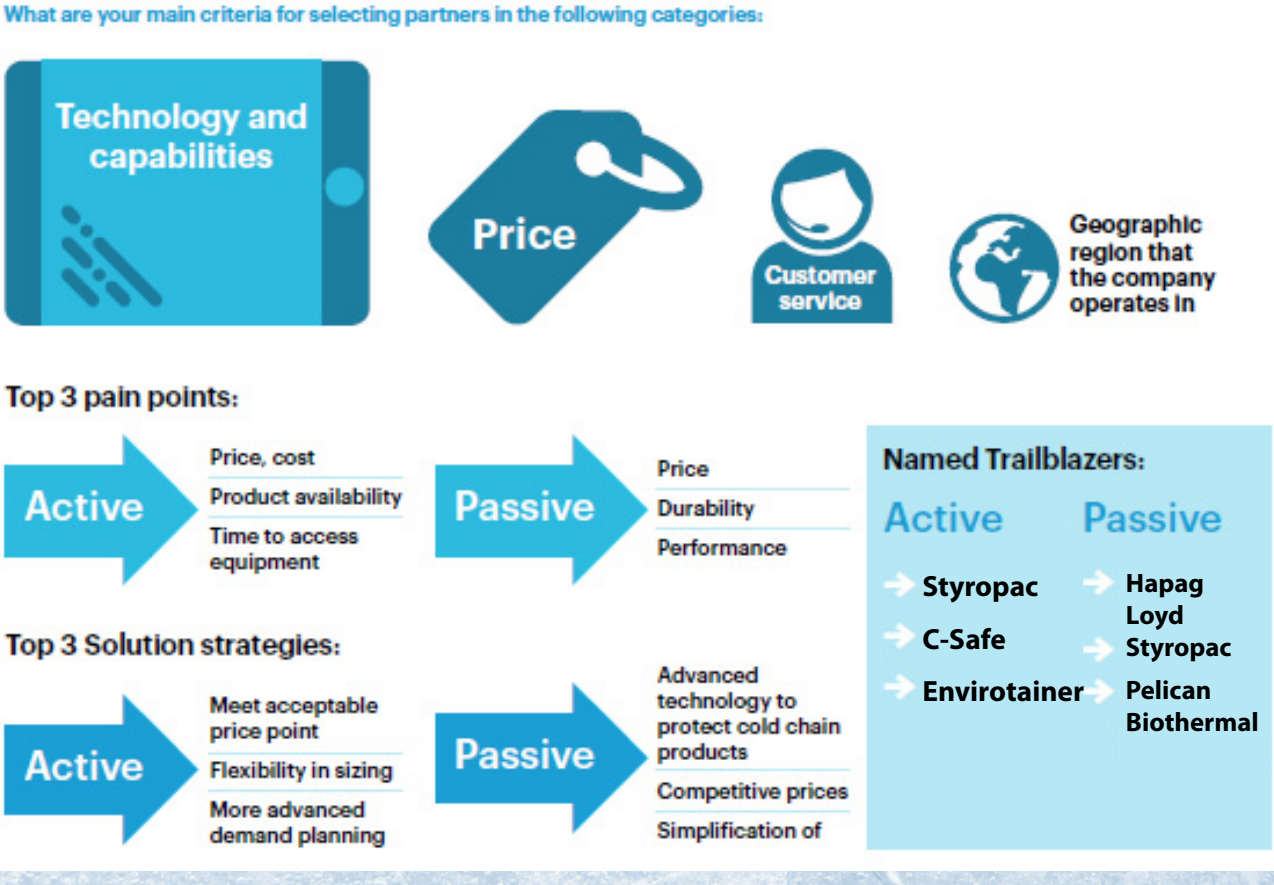
Passive

Stability in spend seen in the passive market

47% of respondents note that investment stayed the same over 2015.

Respondents ranked the temperature controlled logistics spend priorities:

1. Cold Storage
2. **Active Containers**
3. **Passive Containers**
4. 3PLs
5. Sea Freight
6. Airlines
7. Data Loggers



Stats taken from the 2016 Cold Chain Investment Trends Research

Active vs. Passive Industry Spend Snapshot

Respondents noted with both active and passive containers – the final decision on the system of choice is kept internally with the end user rather than entrusting the selection to their 3PL. (59% for active and 67% for passive.)

Mark Edwards, Managing Director of Modalis Ltd., expressed surprise at individuals seeing large investments for active containers due to a number of reasons. Firstly due to the improved performance of passive solutions. Secondly, due to the temperature-controlled growth fuelled by 15-25° products being captured in the latest GDP guidelines and these CRT products cannot typically withstand the cost of active solutions.

Cold Chain IQ columnist Alan Kennedy noted: "With many Big Pharma companies seemingly intent on focusing on their core businesses it is illuminating to see the proportions of players that directly specify the containers used. This inability or unwillingness to offload these decisions is symptomatic of a supply chain that is far from being integrated."

Active Containers

Best practice qualifications and considerations

Selection matrix considerations in evidencing long term to short term costs

Deploying a selection matrix can compare and analyze attributes which are critical to your firm's projects to verify decision making – which is integral especially for leased solutions. Categorizations made through generating data internally can consider the following:

Temperature accuracy: Active shippers have the highest temperature accuracy in comparison to hybrid and passive shippers. They also provide the best flexibility when exposed to a temperature profile that does not match the qualification profile.
Size availability: When compared to passive shippers, active and hybrid shippers, due to their increased complexity and cost, have a narrower selection of payload sizes, which can cause complications in packaging efficiency. This demands added planning to ensure the availability of the container is well timed.
Ease of use: Active and hybrid shippers are easy to set up, but may need maintenance in transit, depending on the length of the shipment.
Cost: The increased size, weight and complexity of active and hybrid shippers make them typically very costly. This cost translates through to extended freight payments.
Hazard: Active shippers may use lithium batteries.[2]
Eco-impact – Consider the footprint active solutions are likely to produce. Alongside being compliant and controlling costs, life science companies are expected to reduce the environmental impact of their cold chain.

Volumetric efficiency

Both active and hybrid shipping systems quite often demand less distribution flexibility due to their reusability which requires a closed distribution loop. One cost reduction tactic to apply in planning phases is to evaluate the payload volumetric efficiency – leveraging innovative techniques and metric calculations to maximize container utilization. This involves the identification of where moves can be consolidated and packaging can be downsized. This will reduce the cost per unit based on packaging spend and also in freight savings as less space is occupied.[3]

Don't just validate but qualify your process

In regards to thermal packaging qualification, testing for the BLA submission should demonstrate that the selected thermal shipping systems provide adequate thermal protection for the entire manufacturing process including shipments to the distribution centers. The recommended critical-to-quality attributes are temperature range and allowable exposures and duration. Qualification of the shipping system to maintain thermal and payload integrity during the distribution process requires several components:

- Component qualification (i.e. gel packs in passive systems) or installation qualification (i.e. factory acceptance testing for the C-SAFE refrigerated pallet system)
- Operational qualification in a controlled environment (i.e. testing laboratory)
- Performance qualification with multiple field tests to confirm suitability for use.

For the cold chain industry, process qualification means that operators can have the confidence that shipping processes will consistently get the temperature-sensitive products they transport to their intended destinations intact. [19]

Passive Containers

Best practice qualifications and considerations

Size: Bulk passive shippers

In regards to looking at reusing or recycling insulation materials to increase cost savings and sustainability, Beth Ruland, Associate Director of Global Packaging at Bristol Myers-Squibb, noted that it's productive to examine the components and temperature control material being utilized as well as contemplating larger passive units for use which are reusable.

Bulk passive units provide the benefits of no power source dependence and a wider choice in payload volume sizes. These strengths allow pharma firms to be more efficient with the packing of shipments and avoid incurring over-spend from ill-fitting containers.

Congruency in SKU management

SKU refrigerants which are compatible with a selection of passive solutions will reduce the need for the excessive management of SKUs at different levels – a resource drain that can translate into delays or potentially missed shipments. Although, beneficial, this SKU congruency is hard to achieve as most passive systems are designed as unique entities.

Ease of Use

As passive shippers require pre-conditioning and specific assembly processes – look for systems that are user friendly in terms of the packing process they require. Alternatively look to train and re-train your system handlers to aid success.

Failures

Passive shippers have a lower amount of components liable to fail during transit in comparison to active and hybrid systems. However, the awareness of potential failures with passive systems will assist with qualification. These potential failures include:

- The permeation of packaging material – This occurs due to a lack of compatibility with the phase change materials (PCM) used. This could escalate to the PCM physically eroding neighbouring packaging materials.

- Leaking – PCMs are difficult to maintain and require more robust seal types in comparison to the water based refrigerants.
- Conditioning – Challenges and added costs can be encountered when the PCM being applied needs conditioning to the intended temperature range. [4]

Tailored testing approach

Craig Vermeyen, Principal Engineer of Cold Chain Packaging at Shire, explained that sometimes modifying existing industry standards and incorporating other industry guidance can result in a more appropriate level of testing for your specific application.

For example, with physical integrity testing, a number of studies have been performed that show that packaging is often dropped from a higher height than accounted for within standard industry test methods. In response to this, he has increased the drop height on his testing so he was confident the boxes would be robust enough to fully protect

expensive and critical shipments. A similar method was applied to the thermal profiles from ISTA 7D. These were amended to what Craig's product was likely to experience in the field. These modifications resulted in a more severe test for certain winter conditions, and a less severe test for certain summer conditions. This was accomplished through the elongation and/or shortening of certain portions of the ISTA standard profiles for shipment durations longer than 48 hours.

Avoiding the Pitfall of Overspending

Kevin Kohleriter, President of The MarketBurst Group outlines the following best practices for packaging design to avoid loss through over engineering your temperature controlled packaging.

- During your packaging and design stages look for industry data that will help you optimize your spend on packaging. Technical reports, like those issued from the PDA can help save time evaluating shipping lanes (See Technical Report 58).

- With changes in weather patterns or when entering new markets, try conducting a temperature profile study that evaluates seasonal changes and their effects on your products. This will also evaluate both the packaging and the carriers.

- Determine the fiscal impact of packaging to the product itself. Over-engineering comes at price. Look at the transport process duration (24-hr; 48-hr), carrier type, container weight, packaging methods, insulated material, and shipping lanes as factors that can all be evaluated when determining the cost of the container.
- Have you tested for damage boundaries to understand what your product can withstand? If not, testing product stability can help determine where and when damage can occur so that you can use data recorders set to the right parameters or adjust packaging as needed. [3]

Collaboration between stakeholders in the supply chain will also be instrumental in ironing out packaging inefficiencies. For those in sourcing, understand that a cheaper container may provide savings in the material expenditure category but it may increase the shipping cost category. Work with the packaging expert to rank suppliers based on the impact to the logistics landed cost.

A note to the carrier or freight forwarder: work to capture the difference between actual and dimensional weight. Report the shipping charges linked to these packaging inefficiencies and offer to collaborate with your client to find a packaging solution. If you believe there is no advantage to this collaboration because you may be shrinking your invoicing, you may be soon in a RFP process for carriers or freight forwarders. You want a healthy and organic revenue that comes from the collaboration of the supply chain links. [5]

Considerations Specific to Temperature Profiles

Cold Chain 2-8°C

Frozen

CRT/Ambient 15-25°C

Frozen

Lack of phase change materials

Carolyn Williamson, Scientist II at Bristol-Myers Squibb noted that there is a healthy availability of phase change materials for 2-8 degrees but a lesser amount for frozen temperatures and cryogenic requirements. She added, "Unless you are able to be at -20, if you want to be -40 or colder you will end up in the dry ice world."

Dewers & non hazardous status

Carolyn Williamson said, "The advantage of using [dewers] is that you can ship with non hazardous status. You need to be able to maintain the temperature but the paperwork and the difficulty of logistics [are both] reduced when you are able to say there is no liquid nitrogen present."
She noted that dewer lifespan is highly dependent on handling: dents and rough care can severely shorten their duration so a maintenance programme is vital.

Cool Chain 2-8°C

Decline of water-based bricks.

Despite being more economical, water based bricks are now being exchanged for the use of phase change materials. This market trend is being seen due to water bricks not sufficiently providing the duration required for international shipments of products that require strict 2-8 degree temperature control.

Look for requirement support from your freight forwarders

Beth Ruland noted that pharma firms are looking to universal shippers to provide more cold chain abilities as freight forwarders.

New seafreight regulations coming into action this summer, concerning the declaration of the gross mass of packed containers, are likely to prompt end users to rely on their providers further for compliance support. Mark Edwards notes there are no clear details as to how LCL or groupage containers will be treated but it is likely that the consolidator or freight forwarder will take care of compliance. Although, they are likely to seek documented assurance that weights are correct and have been measured in accordance with the guidelines. [6]

Validation – lobby towards global standardization for thermal profiles

Industry commentators have stressed the need for an agreed industry standard for thermal profiles used in small-parcel cold chain validation procedures. Craig Vermeyen noted that the industry needs one standard that every manufacturer adopts to improve the ability of consumers to perform a true comparison of products. He added that the existing guidance is good but there are too many different thermal profiles and testing procedures (product loads, preconditioning requirements, etc.) in use, which can create confusion.

CRT / Ambient

Collaborate with peers

The standardization of ambient temperature profiles for packaging design would enable companies to share intelligence on common transit routes and lanes rather than duplicating efforts and funding the research individually to understand requirements.

This standardization should translate to deploying an agreed definition of controlled room temperature, which currently varies globally.

Ambient profile and risk

Assess and monitor risk frequently via in house teams or electronically, as this real-time awareness will equip firms with the information needed to make the right decisions. Process mapping will also allow firms to agree contingency measures prior to the initiation of the lane.

Ambient temperature profiles can be applied to quantify the amount of risk a pharma or biotech firm wants to assume. Fairly benign ambient profiles in a qualification scheme for packaging will drive down packaging costs but could, however, introduce risk into the supply chain in the form of excursions. For instance, the development of profiles through applying confidence intervals and stripping out data, could present a firm with profiles deemed as more representative for 90% of their shipments, leaving them to assume some risk with the remaining 10%. This is a very different risk profile to a case where the firm opts to use ISTA 7D as a standard, which is seen to be one of the most challenging set of profiles out there. The allocation of a risk approach will depend on the characteristics of the product in question.

The training and re-training of staff is essential to ensure understanding and compliance of temperature requirements, as well as understanding when control is necessary and the boundary of over compliance.

CRT qualification considerations

- Acquire data on your product robustness, as this will be paramount for dealing with excursions.
- Try to accommodate various temperatures when designing product.
- Validate carrier capabilities including intervention and recovery services.

Avoid stability programme laziness

Defining stability profile and shipping requirements is seen as a key hurdle in this section of the market, due to the complexity and further expense required for additional stability studies. As a result, many in the logistics arena rely on using existing stability programs when it comes to CRT products to get the product registered, which are standard ICH studies. According to a statement from Simon White, Regional Leader, Quality Operations, Europe, Middle-East & Africa Global Supply Chain from Pfizer Global Supply, this method doesn't tend to provide the stress studies or temperature cycling studies needed to help transport processes. [7]

Remember:

- Invest in good cycling stability studies and work with a 3PL that is willing to map out the shipping lane and solution.
- Perform thermal profiles for the scientific justification of routine monitoring points and ensure all monitoring software is fully validated.
- Design packaging to your stability data, not the definition of CRT.

Perfect the margin balance

The majority of Cold Chain IQ's 2015 survey respondents planned to increase investment in their CRT supply within the next 12-18 months. However, finding cost-effective packaging solutions and transportation or distribution services were pinpointed as key challenges. This compounded cost pressure to maintain overheads is produced by the lower margins attached to CRT products.

When evaluating your packaging approach, be sure to pay attention to the total cost - a low price does not guarantee a high quality of service. Also, the less expensive price per pound often ends up costing more in the long run through transportation costs, etc.[7]

Vaccine vial size has been shown to have far reaching implications on supply chain costs. A study from the International Vaccine Access Center (IVAC) discovered that expanding the vaccine vial size decreased total costs by as much as US$0.25 per dose, which could win sizable savings if administered on a mass scale.

Best Practice Considerations with Insulation Materials

In selecting product packaging and insulation materials of choice, important considerations to factor into decisions include: the stability profile of the material being shipped, the ambient profile, the risk profile, the quantity of the shipment as well as the mode of shipping. Collaboration with packaging firms and freight forwarders in planning stages is instrumental to avoiding pitfalls on route.

The most common pitfall in selecting packaging solutions is the mistake of over-engineering. Over- or under-engineering is a possibility for all solutions depending on the conditions it is due to be exposed to. This emphasizes that the most efficient selection methods are tailored and rooted in the solid understanding of the characteristics and requirements of the product and lane at hand.

Insulation, in terms of its construction within a thermal system, can be broken down into two main categories, molded and panels.

Panels

Advantages: Collapsible and no need for tooling in assembly
Limitations: Liable to temperature loss at the box's corners.

Molded:

Advantages: Supplies the best insulation integrity, even if exposed to drops.
Limitations: Not collapsible and requires tooling.

With regards to the actual insulating materials, the following advantages and limitations are the

dominant considerations to make while operating in the temperature control market.[10]

Polyurethane (PUR)

Advantages: Higher insulation properties, is more reusable than EPS.
Limitations: Not recyclable in general, high weight.

Expanded PolyStyrene (EPS)

Advantages: Low in density and weight – more cost effective than XPS in terms of more R-value per unit spent. Malleable in shape.[8]
Limitations: Weak insulation properties and not environmentally friendly.

Extruded Polystyrene (XPS)

Advantages: Higher in R value and more resilient to moisture than EPS. Acts as an air barrier.
Limitations: Not eco-friendly due to its

production requiring HCFC.

Polyethylene foam
Advantages: Low density, very high shock and vibration absorption.
Limitations: Expensive, can have an extensive lead time to acquire.

Vacuum insulated panels [1]
Advantages: High performance and collapsibility.
Limitations: Expensive, low reusability, harder to source this technology.

Phase Change Materials (PCM)
Advantages: Some PCMs can be free of hazard issues. Holds Intelligent phase change in temperature according to desired range. Available at an accessible cost. Reliable stability on thermal cycling. Biodegradable.
Limitation: Can have material compatibility issues in regards to exterior packaging. Leak proof PCM packaging is a must, as this element is harder to contain than water base refrigerants. Challenges can be had in pre-conditioning the PCM to reach the required phase. Some custom PCMs can hold a hazardous status. [9, 2, 4]

Refrigerant Gels

Polyacrylate gels
Advantages: The cheapest option of gels, custom sizes available, a range of dimensions in supply, the material has high latent heat capacity and specific heat capacity. Lower in weight in comparison to PCM and so will contribute less to transport costs.
Limitations: Can't adapt as active systems or PCMs can in the face of unexpected temperature changes.

Phenolic foam bricks
Advantages: Various sizes available, different surface area to polyacrylate gels to allow for more catered coverage.
Limitations: More expensive than polyacrylate gels

Eutectic gels
Advantages: Various sizes available, specific temperature ranges are in supply (-1° and +23°) – good duration capabilities provided. Metallic film assists with heat preservation.
Limitations: Expensive

Water bricks / water bottles
Advantages: Ecologically sound; performance is competitive to synthetic refrigerants.
Limitations: Can't adapt as active systems or PCMs can in the face of unexpected temperature changes.

Thermal foil – wraps and blankets
Advantages: Acts a vapour barrier. The thermal control buffers external temp in a scientifically significant way. In combination with gel packs these wraps can allow for tarmac time to be extended slightly.
Limitations: Expensive, some stability profiles may need more buffering materials to accompany the thermal wraps.

Dry Ice [10]

Advantages: Reliable in temperature stability and extensive duration, can last for 3-5 days – much cheaper than liquid nitrogen. Good for frozen temperatures -78° availability.

Limitations: Health and safety considerations with handling – substantial cold temperatures when solid and with the material being an asphyxiant. Regulations must be met in the shipping of this material.

Liquid Nitrogen

Advantages: Not difficult to procure, long staying power – can last for 8–10 days on a shipment with liquid nitrogen. Can maintain temperatures of sub -80°

Limitations: Hazardous – If shipping by air considerations must be made. Also the careful handling of dewers must be applied as to not displace the nitrogen. Liquid nitrogen solutions tend not to embody larger capacities – no full pallet or larger sizes.

Cell based insulation technology – owned by SkyCell [11]

Advantages: Unique cooling technology, offers ways to save energy with lower CO_2 emissions, high net volume. Utilizes stabilising coolants, healthy payload.

Limitation: Heavy in weight which may have transport cost implications.

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- Carolyn Williamson, Scientist II, Bristol-Myers Squibb

Join us at the 14th Cold Chain GDP and Temperature Management Logistics Global Forum for more tips and methods to optimize your qualification and design of cold chain packging.

14TH COLD CHAIN GDP & TEMPERATURE MANAGEMENT LOGISTICS GLOBAL FORUM

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- **Make informed purchasing decisions** by comparing the latest cutting-edge temperature-control solutions in our expanded exhibit hall.

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